Universitat Autònoma de Barcelona

DEPARTAMENT DE PSICOLOGIA CLÍNICA I DE LA SALUT

FACULTAT DE PSICOLOGIA. UNIVERSITAT AUTÒNOMA DE BARCELONA

ESTUDIO DE LA RELACIÓN ENTRE LA VARIABILIDAD ANATÓMICA REGIONAL DEL CEREBRO MEDIDA CON RM 3-D Y LOS ESTILOS COGNITIVOS Y RASGOS DE LA PERSONALIDAD.

TESIS PRESENTADA POR

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Para la obtención del grado de Doctor por la Universidad Autónoma de Barcelona (UAB)

Directores

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Universitat Autònoma de Barcelona, 2011

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El **Dr. Joan Deus Yela**, profesor agregado del Departamento de Psicología Clínica y de la Salud de la Facultad de Psicología de la Universidad Autónoma de Barcelona (UAB), y el **Dr. Jesús Pujol Nuez**, Coordinador de la Unidad de Investigación en Resonancia Magnética (RM) de CRC-Mar Corporación Sanitaria del Hospital del Mar,

DECLARAN

Que como directores han supervisado la presente tesis doctoral, titulada '*Estudio de la relación entre la variabilidad anatómica regional del cerebro medida con RM 3-D y los estilos cognitivos y rasgos de la personalidad*', realizada y presentada por Doña Anna López Sala. Asimismo, informan y hacen constar que esta tesis cumple los requisitos académicos y científicos necesarios para ser defendida con el objetivo de obtener el grado de Doctora.

Firma,

Dr. Joan Deus Yela	Dr. Jesús Pujol Nuez
Departamento de Psicología Clínica y de la salud	Unidad de Investigación en RM
Facultad de Psicología	CRC-Mar del Hospital del Mar
Universidad Autónoma de Barcelona	Corporación Sanitaria

Bellaterra, Mayo de 2011

Al Nando,
pel temps no compartit

Als meus fills,
que me'ls estimo amb bogeria

I a tu, Jordi,
que des de València m'animaves

Agradecimientos

En primer agradezco a mis padres la educación, genética y apoyo que me han dado.

En segundo lugar a todos los coautores que han hecho posible que pueda defender este trabajo, en especial a Carlos Soriano y a Narcís Cardoner.

En tercer lugar agradecer a los voluntarios que participaron, muchos de ellos amigos míos, por el tiempo que dedicaron en los diferentes estudios.

Y por último a mi director y codirector. El azar hizo que me cruzara con Joan y a partir del primer encuentro fueron surgiendo diferentes proyectos hasta llegar al actual. A lo largo del camino me ha apoyado profesionalmente y lo considero y lo consideraré una piedra importantísima en el inicio del forjado de mi carrera profesional. Y finalmente la pieza más importante de este trabajo ha sido la figura de Jesús. Para mi ha sido un modelo a seguir del cual he aprendido actitudes y aspectos de la ciencia y del saber que difícilmente encontraré en otra persona. Estaré eternamente agradecida de todo el tiempo y dedicación que me ha ofrecido.

Gràcies a tots!

Durante toda la vida, el ser humano está sometido a un constante proceso de aprendizaje y memoria. El dictado del Oráculo de Delfos "conócete a ti mismo", bien pudiera hoy cambiarse, a la luz de las neurociencias actuales, por aquel otro de "hazte a ti mismo".

"El cerebro es un mundo
que consta de numerosos continentes inexplorados
y grandes extensiones de territorio desconocido"
Santiago Ramón y Cajal

Nobel Prize acceptance speech words:
"the great pleasure and feeling in my right brain
is more than my left brain can find the words to tell you."
Roger W. Sperry

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Prefacio

Esta tesis, presentada para poder obtener el grado académico de Doctor por la Universidad Autónoma de Barcelona (UAB), es el resultado de diferentes trabajos llevados a cabo durante los últimos 8 años en la Unidad de Investigación de Resonancia Magnética (RM) de CETIR *Grup Mèdic* y de *Corporació Sanitària* CRC-Mar en colaboración con el Departamento de Psicología Clínica y de la Salud de la Facultad de Psicología de la UAB. Durante dicho período la presente doctoranda ha obtenido el Diploma de Estudios Avanzados (DEA) cursando el programa de doctorado de Neurociencias del Departamento de Biología celular de la Facultad de Medicina de la UAB.

Los presentes artículos que configuran la tesis doctoral expuesta han sido publicados en revistas internacionales en el ámbito de las neurociencias, con un índice de impacto (IF) global de 20,933 en su año de publicación (de 2002 a 2009) y un IF de acuerdo al índice actual publicado de 21,970 (ISI of Knowledge, Journal Citation Reports 2009):

La siguiente tabla muestra los estudios que conforman la presente tesis y su correspondiente IF, en el año de su publicación y de acuerdo al IF actual.

Objetivo	Título	Autores	Revista	IF año publicación	IF actual 2010	Nº de citaciones
Neuroanatomía de la cisura de Silvio y lenguaje						
Analizar las asimetrías volumétricas en las principales divisiones anatómicas de la región cerebral lateral (perisilviana) y su contenido de sustancia blanca relativo.	The lateral asymmetry of the human brain studied by volumetric magnetic resonance imaging.	Pujol J, López-Sala A, Deus J, Cardoner N, Sebastian-Gallés N, Conesa G, Capdevila A.	Neuro image	(2002) 5,624	5,739	38
Caracterizar las anormalidades estructurales en niños disfásicos a través de un análisis *voxel-wise*.	Age-Related brain structural alterations in children with specific language impairment	Soriano-Mas C, Pujol J, Ortiz H, Deus J, López-Sala A, Sans A.	Human Brain Mapping	(2009) 6,256	(2009) 6,256	1
Neuroanatomía de la circunvolución cingulada anterior y personalidad						
Investigar la posible relación entre la variabilidad interindividual de la morfología de la circunvolución cingulada y los estilos de comportamiento.	Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality	Pujol J, López A, Deus J, Cardoner N, Vallejo J, Capdevila A, Paus T.	Neuro image	(2002) 5,624	5,739	70
Investigar la posible relación entre la variabilidad interindividual de la morfología de la circunvolución cingulada anterior y alexitimia.	Alexithymia correlates with the size of the right anterior cingulate	Gündel H, López-Sala A, Ceballos-Baumann A, Deus J, Cardoner N, Marten-Mittag B, Soriano-Mas C, Pujol J.	Psycho somatic medicine	(2004) 3,429	4,236	37
			TOTAL	**20.933**	**21,970**	**145**

IF: Índice de Impacto

Glosario de Abreviaciones

CA	Circunvolución Angular
CC	Circunvolución Cingulada
CCA	Circunvolución Cingulada Anterior
CFM	Circunvolución frontal medial
DTI	Imágenes con Tensor de Difusión (*Diffusion Tensor Imaging*)
RM	Resonancia Magnética
RM 3D	Resonancia Magnética en 3 Dimensiones
SB	Sustancia blanca
TEDL	Trastorno Específico del Desarrollo del Lenguaje
VBM	Morfometría basada en el estudio de vóxels (*Voxel based morphometry*)

Resumen

El proceso de hominización probablemente ha implicado una serie de cambios morfológicos cerebrales. El grado de desarrollo anatómico de regiones cerebrales funcionalmente relevantes, caracterizadas por su gran variabilidad interindividual y por la existencia de una marcada asimetría hemisférica, podría estar relacionado con las diferencias individuales en los estilos cognitivos y rasgos de la personalidad. Hay numerosos estudios que exponen las diferentes asimetrías morfológicas hemisféricas interindividuales. Los hallazgos más replicados son las asimetrías en áreas laterales de los hemisferios cerebrales y en la región cingulada anterior. A pesar de ello, un menor número de estudios se han centrado en estudiar la relevancia y significado funcional de dichas asimetrías y la variabilidad interindividual, aunque sí han aportado datos que han explicado, parcialmente, la relación entre volumen y estructuras cerebrales y funciones superiores.

El presente trabajo pretende investigar el significado funcional de la variabilidad anatómica de dos regiones cerebrales que son característicamente asimétricas y que tienen especial relevancia en la modulación de la conducta del ser humano. Por un lado se ha medido el volumen de la región perisilviana, como región paradigmática que sustenta el lenguaje, y por otro lado se ha medido la superficie medial de la corteza cingulada para investigar su correlación con los estilos de comportamiento. Se han desarrollado 4 estudios bajo estas dos líneas de investigación.

Con el primer estudio, el objetivo fue buscar el mejor correlato anatómico concordante con los porcentajes conocidos de la dominancia cerebral para el lenguaje. En los últimos años, se

le otorga a la sustancia blanca un papel más relevante. Se objetivó que el volumen global medido con Resonancia Magnética (RM) en 3D de la región perisilviana de ambos hemisferios no diferiría. En cambio, el volumen regional de la representación de cada lóbulo difería en los dos hemisferios. Especialmente, el volumen relativo de sustancia blanca tenía porcentajes más altos en las regiones frontales, temporales y parietales izquierdas. En el hemisferio derecho, el porcentaje más alto de sustancia blanca se ubicaba en la región témporo-parieto-occipital. Consecuentemente, el parámetro anatómico que mejor explica la lateralización del lenguaje es la asimetría del volumen relativo de sustancia blanca localizado en la región perisilviana temporal y frontal.

En la misma línea de estudio, y aplicada a niños con trastorno específico del desarrollo (TEDL) del lenguaje y utilizando mediciones mediante la morfometría basada en vóxels (VBM), se buscaba encontrar un patrón característico de esta entidad. Se ha observado que los niños con TEDL presentan un aumento de volumen global de sustancia blanca y sustancia gris y una distribución de volúmenes relativos diferentes al grupo control. Los mecanismos de compensación y la modulación dinámica temporal a que está expuesto el cerebro pueden explicar estas anormalidades a nivel estructural.

En la segunda línea de investigación, se pretendía analizar la variabilidad interindividual de la superficie de la circunvolución cingulada anterior en participantes voluntarios sanos. En el primer trabajo, se constató que un mayor tamaño de la corteza cingulada anterior derecha, en ambos sexos, se relacionaba con una disposición temperamental hacia el miedo y un sufrimiento anticipatorio. Adicionalmente, una mayor prevalencia de estos rasgos en mujeres se puede relacionar con un mayor tamaño de esta región. El rol de la mujer a lo largo de la historia puede explicar esta diferencia anatómica entre géneros.

Finalmente, en el último trabajo se buscó la relación entre la alexitimia y la superficie de la corteza cingulada anterior derecha. Se objetivó que niveles altos de alexitimia correlacionaban con una mayor superficie de la corteza cingulada anterior derecha y se interpretó como una buena estrategia de adaptación del ser humano ante posibles situaciones problemáticas.

1. Introducción

El cerebro es un órgano complejo compuesto por más de 100.000 millones de neuronas interconectadas (Williams y Herrup, 1988; Pakkenberg y Gundersen, 1997) que le confieren la gran capacidad de procesar estímulos y elaborar respuestas que caracterizan la conducta de los seres superiores. Todavía está muy extendida la noción de que se desconoce el funcionamiento del cerebro como órgano en los aspectos más básicos. La mayor parte del conocimiento de la psicología humana se ha adquirido bajo este supuesto, con diseños de investigación que consideraban al cerebro como "la caja negra" (Skinner, 1977; Ormorod, 2005). No obstante, los avances técnicos y científicos de los últimos años han proporcionado instrumentos que permiten la observación directa del cerebro en el sujeto 'in vivo'. Estas "ventanas" de la caja negra permiten descubrir cómo el cerebro ejerce su papel rector sobre el resto del organismo y genera las manifestaciones de la conducta humana.

El cerebro está estructuralmente constituido por dos hemisferios que son en su mayor parte simétricos. Ambos contienen similares surcos y circunvoluciones que configuran una anatomía muy parecida. Desde un punto de vista filogenético, la configuración bihemisférica del cerebro es muy antigua y es uno de los aspectos elementales del desarrollo neural (Palmer, 2004; Wolpert, 2005; Oros, Steuber, Davey et al, 2009). La existencia de dos hemisferios resulta eficiente para los procesos perceptivos y motores. Estas funciones básicas se llevan a cabo con el acoplamiento del hemisferio derecho y el izquierdo y así, por ejemplo, el ser humano logra deambular accionando estructuras motoras bilaterales, percibir el campo visual completo con la participación de ambos lóbulos occipitales o percibir los sonidos del entorno con la activación de los dos lóbulos temporales (Kandel, Schwartz, Jessel, 2000). Dicha configuración bihemisférica supone también cierto grado de duplicación de estructuras o redundancia que potencialmente sirve de “reserva anatómica” o suplencia en caso de daño cerebral o alteraciones del desarrollo.

Pero, si se analiza con más detalle el hemisferio izquierdo y el derecho, se puede observar que existen también regiones con marcadas asimetrías estructurales, tanto en el cerebro humano como en otras especies animales (Gannon, Holloway, Broadfield et al, 1998; Pilcher, Hammock, Hopking, 2001; LeMay, 1976; Aboitiz, García, Bosman et al, 2006). Las asimetrías más relevantes se localizan en la región “perisilviana”, o parte más lateral del cerebro, y en la corteza frontal medial. Es interesante el hecho de que estas regiones que presentan diferencias anatómicas entre los hemisferios de un individuo, además, presentan relevantes diferencias anatómicas entre distintos individuos. Efectivamente, en estas regiones coincide una variabilidad interhemisférica, o asimetría, con una relevante variabilidad interindividual. Este hecho, replicado en numerosos estudios (Snelson y Gamse, 2008), suscitó el interés para investigar la relevancia y significado de la variabilidad interindividual de estas regiones cerebrales asimétricas. Intuitivamente, la capacidad de adaptación y sobre todo la emergencia de funciones complejas en el ser humano podrían explicar la evolución asimétrica de determinadas regiones cerebrales y su variabilidad interindividual. No obstante, actualmente, existen pocos estudios que relacionen el grado de desarrollo morfológico de estas regiones con las manifestaciones conductuales de los individuos. En esta tesis se pretende estudiar el cerebro de participantes voluntarios sanos y determinados grupos de pacientes con un método anatómico cuantitativo *in vivo* para caracterizar las variaciones morfológicas de estas estructuras asimétricas y establecer su relación con funciones cognitivas básicas y rasgos de la personalidad.

En la esfera cognitiva, la función por antonomasia del ser humano es su capacidad verbal. Se puede inferir que los neandertales ya poseían un protolenguaje, que se fue elaborando y perfeccionando a lo largo de más de 2 millones de años (Mithen, 2005; Henshilwood, d'Errico, Marean et al, 2001; Krause, Lalueza-Fox, Orlando et al, 2007). Esta adquisición funcional estuvo asociada a un gran desarrollo cerebral específico de la especie humana. Desde el siglo XIX se conoce, a través de estudios lesionales, la implicación directa del hemisferio izquierdo en las funciones verbales (citado en Springer, Deutsch, 1997). En el siglo XX se estudiaron las diferencias anatómicas de los hemisferios cerebrales y se resaltó la asimetría de la región perisilviana (Galaburda, 1995). Esta incluye la parte lateral de la corteza frontal, parietal y temporal que limita con la cisura de Silvio y que cubre el lóbulo de la ínsula de Reil. A nivel ontogenético es sabido que esta asimetría está presente ya en el tercer trimestre de gestación, entre la 29ª-31ª semana de gestación intrauterina. Este hecho es importante pues indica que la asimetría perisilviana es un elemento primario de la configuración estructural cerebral y que está determinado genéticamente (Chi, Dooling, Gilles, 1977; Witelson, Kigar, 1973). Filogenéticamente también se han observado asimetrías perisilvianas en ciertas especies (LeMay, 1976, 1985).

En referencia a la evolución de la dimensión emocional de la especie humana destaca el gran desarrollo de los mecanismos de control conductual que favorecen la agrupación social (Morgan, 1971). El ser humano aprende a modular sus emociones básicas, a controlar algunas conductas reflejas y a procesar y analizar los sentimientos. El procesamiento y control emocional se efectúa en el contexto de la históricamente llamada esfera "límbica", que implica estructuras cerebrales primarias, y mediante su íntima conexión con los sistemas neurales evolucionados o neocorticales (Tucker, Luu, Pribram, 1995; Morgane, Galler, Mokler, 2005). Una parte relevante de los procesos cerebrales que intervienen en la modulación emocional y en la conducta adaptativa implica, de la misma manera que la aparición del lenguaje en el ser humano, regiones cerebrales marcadamente asimétricas como la porción anterior de la cara medial de los hemisferios. Esta región cerebral está ocupada mayoritariamente por la parte anterior de la circunvolución cingulada (CC) y por la circunvolución frontal medial (CFM) (o aspecto medial de la circunvolución frontal superior). La corteza cingulada anterior (CCA), que contiene corteza "límbica" y corteza de transición (límbico-neocortical), es la estructura paralímbica más asimétrica de esta región y tiene un papel importante en la integración de la emoción con la cognición. La corteza cingulada anterior interviene en la modulación de los aspectos más importantes de la conducta y ejerce influencia sobre las respuestas motoras, funciones cognitivas de atención y lenguaje, afectivas y viscerales (Bush, Luu, Posner, 2000; Devinsky, Morrell, Vogt, 1995; Paus, 2001).

El objetivo específico de este trabajo es contribuir a elucidar el significado funcional de la variabilidad anatómica de dos regiones cerebrales clásicamente asimétricas en relación a dimensiones conductuales básicas de la esfera cognitiva y emocional. Por un lado, se pretende contribuir a una mejor caracterización anatómica de la asimetría de la región perisilviana como supuesto fundamento del desarrollo del lenguaje, función paradigmática de la esfera cognitiva humana. Por otro lado se pretende caracterizar la asimetría de la corteza cingulada anterior y su relación con aspectos básicos de la personalidad, directamente relacionados con el control de la conducta y la modulación emocional.

1.1. El cerebro

1.1.1. Hominización y mayor volumen cerebral

La evolución biológica y los cambios culturales (Gould, 1997) han provocado unas transformaciones morfológicas en el homínido que lo han ido esculpiendo durante unos 5 millones de años hasta llegar al hombre moderno. Uno de los aspectos más destacados de la evolución humana u hominización es que va acompañada de un aumento continuado del peso del cerebro. Según la clasificación de Rosenzweig y colaboradores (1999), se pasó de los 450 gramos del *Australopithecus* a los 1400 gramos del *Homo Sapiens*. Y más significativo, si cabe, es el factor de encefalización, o relación estandarizada entre el peso del cerebro y el peso del cuerpo, siendo el del ser humano actual el más alto (Martin, 1984; Jerison, 1973). Esta evolución del cerebro de los homínidos fue provocada principalmente por la combinación de unas variables ambientales, unos cambios culturales (Gould, 1997) y la evolución biológica (selección natural). El aumento del volumen cerebral no fue aleatorio, sino que probablemente sobrevino por la aparición de nuevas habilidades cognitivas propias del ser humano. Esta especialización produjo una reorganización interna (Oxnard, 2004; Preuss, 2001) provocando unas asimetrías funcionales y estructurales.

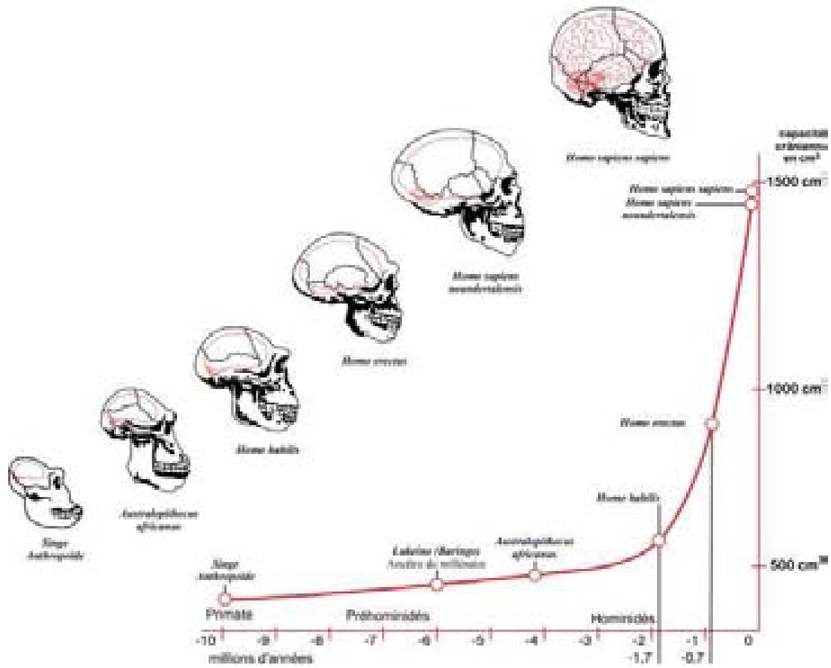

Figura 1. Refleja el aumento del volumen craneal a lo largo de la historia del hombre. Imagen extraída de Le Journal Du Net (2010).

1.1.2. Avances técnicos y científicos

En la actualidad, existen varios métodos para el estudio de la morfometría cerebral. Las técnicas más utilizadas se basan en la resonancia magnética (RM). Para los estudios morfológicos o anatómicos, la RM se puede adquirir, analizar y representar en 3 dimensiones (RM 3D). Estos estudios permiten la cuantificación del tamaño de regiones específicas de interés, así como la segmentación y la cuantificación de los distintos componentes de las estructuras cerebrales (e.g., separar y cuantificar la sustancia blanca y la sustancia gris), o la medición de la extensión y grosor del manto cerebral. Muchos de estos procesos de análisis se basan en la llamada morfometría basada en vóxels (VBM -‘*Voxel Based Morphometry*’-), que supone el proceso global de la anatomía cerebral dividida en pequeñas (1-2 mm^3) unidades anatómicas llamadas “voxel” que contienen información sobre la composición tisular y el volumen de la parte del cerebro que representan (Ashburner, Friston, 2000; Good, Johnsrude, Ashburner et al, 2001a). Otro método de interés para la caracterización tisular cerebral es la llamada imágenes con Tensor de Difusión (DTI –'*Diffusion Tensor Imaging*'-), que permite la identificación de vías o conexiones de sustancia blanca en base a información sobre la orientación de las fibras nerviosas (Pierpaoli, Jezzard, Basser, 1996; Le Bihan, Mangin, Poupon et al, 2001).

1.1.3. El cerebro actual, globalmente simétrico y con asimetrías regionales específicas

La simetría bilateral respecto a un plano sagital que divide al cuerpo en derecha e izquierda es una constante en la inmensa mayoría del reino animal. Los animales 'simétricos' son más complejos y muestran un mayor grado de encefalización (Dewel, 2000). A pesar de que se trata de una simetría aproximada y que afecta a la apariencia externa más que a la anatomía interna, tiene enormes repercusiones funcionales, como por ejemplo las posibilidades de movilidad, control de los movimientos corporales y de las percepciones sensoriales.

Una inspección pormenorizada de muchos individuos, sin embargo, revela que existen pequeñas diferencias entre las estructuras de izquierda y derecha. El cerebro humano y el de la mayoría de mamíferos presentan asimetrías hemisféricas. Aunque los dos hemisferios son parecidos en volumen y peso, la distribución de sus tejidos los diferencia de forma significativa en algunas regiones concretas. Entre las más conocidas asimetrías estructurales se encuentran las '*petalias*' (Yakovlev, Rakic, 1966) o también denominadas improntas cerebrales en el cráneo. Esta asimetría se caracteriza porque el lóbulo frontal derecho es mayor que el izquierdo y el lóbulo occipital izquierdo es mayor que el derecho, produciendo la sensación de que se han desplazado los dos hemisferios, el derecho hacia delante y el izquierdo hacia atrás (Holloway, De La Coste-Lareymodie, 1982; Lancaster, Kochunov, Thompson et al., 2003; LeMay, 1976; Watkins, Paus, Lerch et al, 2001). Este patrón recibe el nombre de 'torque' y se encuentra en los homínidos modernos y, además, puede asociarse a la evolución de las habilidades lingüísticas. Evidencias antropológicas sugieren que seres de la subfamilia de los *Hominae* mostraban similares petalias (Holloway, De La Coste- Lareymondie, 1982). Estudios más recientes del equipo de William Hopkins han mostrado mediante RM las mismas petalias en chimpancés (Hopkins, Marino, 2000; Hopkins, Taglialatela, Meguerditchian et al, 2008). No hay evidencia de este patrón en otra especie de primates a excepción de los grandes simios. El patrón parece tener que ver con las especializaciones hemisféricas en los humanos, ya que se correlaciona con el grado de dominancia de la mano derecha. En el caso de los seres humanos, se constata que las personas con una alta dominancia de la mano derecha tienden a presentar ese torque con más claridad, mientras que una parte de los zurdos muestran un patrón más simétrico, hasta el punto de que muchos de ellos carecen de la petalia frontal derecha (Leask, Crow, 2001).

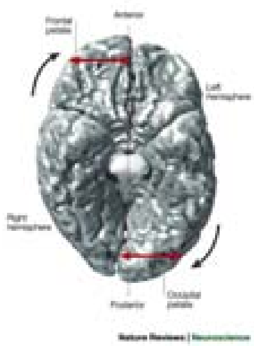

Figura 2. Muestra de las "*petalias*" en el cerebro humano. Imagen extraída de Toga y Thompson, Mapping brain asymmetry. Nature Reviews Neuroscience 2003; 4, 37-48.

Otras asimetrías clásicamente reconocidas son la del ángulo de la cisura de Silvio, más agudo el del hemisferio derecho que el del izquierdo (Cuningham, 1892 citado en Geschwind, Galaburda, 1985 a, b, c; Geschwind, Levitsky, 1968; Steinmetz, Volkmann, Jäncke et al, 1991; Witelson, Kigar, 1992; Foundas, Faulhaber, Kulynych et al, 1999), en relación con un mayor *'planum temporale'* izquierdo (Geschwind, Levitsky, 1968; Steinmetz, 1996; Dorsaint-Pierre, Penhune, Watkins et al, 2006; Watkins, Paus, Lerch et al, 2001); y mayor circunvolución cingulada y caudado derecho que izquierdo (Watkins, Paus, Lerch et al, 2001).

Tabla I. Tabla resumen de las diferencias anatómicas y los correlatos neuropsicológicos del hemisferio derecho e izquierdo.

Asimetría anatómica		**Correlato neuropsicológico**
las '*petalias*' - polo frontal - polo occipital	 D>I D<I	 habilidades lingüísticas y grado de dominancia de la mano derecha
ángulo de la cisura de Silvio	D<I	habilidades lingüísticas
'planum temporale'	D<I	habilidades lingüísticas
circunvolución cingulada	D>I	integración de la emoción con la cognición y en el control del habla/vocalización
caudado	D>I	

D: derecho; I: izquierdo

1.1.4. Desarrollo cerebral (ontogénesis)

El peso del cerebro del niño recién nacido es aproximadamente de 350 gramos. (Sneou, 1976). El tamaño total del cerebro hacia los 6 años de edad es aproximadamente el 90% del tamaño adulto (Reiss, Abrams, Singer et al, 1996; Giedd, 2004). Este aumento de volumen es debido en gran parte a un aumento de la sustancia blanca (Rivkin, 2000). El grosor aparente de la corteza y su volumen siguen un curso de U invertida con un período de aumento en el inicio de la infancia y un subsiguiente adelgazamiento cortical en la adolescencia (Bourgeois, Rakic, 1993; Huttenlocher, Dabholkar, 1997; Shaw, Kabani, Lerch et al, 2008; Ostby, Tamnes, Fjell et al, 2009; Jeringan, Trauner, Hesselink et al, 1991; Reiss, Abrams, Singer et al, 1996; Giedd, Blumenthal, Jeffries et al, 1999; Sowell, Thompson, Holmes, 1999; Sowell, Thompson, Rex et al, 2002; Lenroot, Gogtay, Greenstein et al, 2007; Wilke, Krägeloh-Mann, Holland, 2007; Shaw, Kabani, Lerch et al, 2008). Pero no existe una reducción real de la sustancia gris hasta muy avanzado el envejecimiento. En realidad, la mielinización constante de los axones en el cerebro a lo largo de toda la vida incluye también la porción axonal intracortical y genera una aparente reducción de su espesor sin que exista pérdida neuronal durante la mayor parte de la vida adulta (Yakovlev, Lecours, 1967).

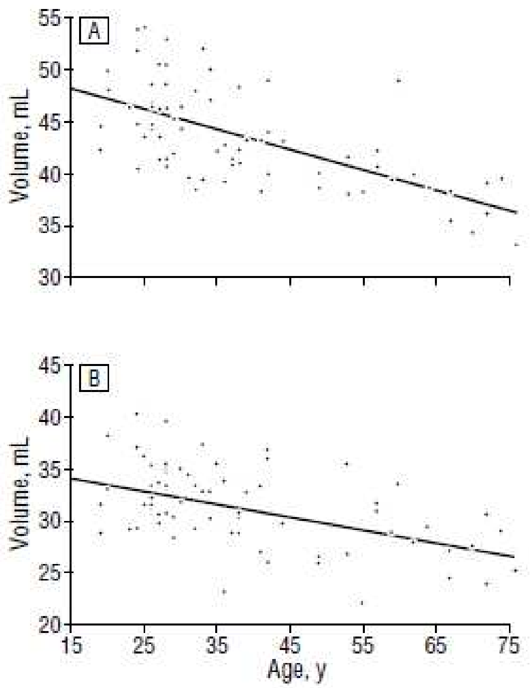

Figura 3. Regresión del volumen de sustancia gris en el lóbulo frontal (A) y temporal (B) dependiente de la edad en una muestra de 70 hombres adultos. Imagen extraída de Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-Related Changes in Frontal and Temporal Lobe Volumes in Men. A Magnetic Resonance Imaging Study. Arch Gen Psychiatry. 2001;58:461-465

El volumen de la sustancia blanca presenta un aumento generalmente lineal a través del final de la infancia y adolescencia, con pequeñas diferencias de pendiente entre los diferentes lóbulos (Giedd, Blumenthal, Jeffries et al, 1999; Paus, Collins, Evans et al, 2001; Sowell, Thompson, Rex et al, 2002; Giedd, 2004; Lebel, Walker, Leemans et al, 2008). El volumen aumenta, debido al aumento de la mielinización durante la adolescencia y la edad adulta, hasta llegar a un pico hacia la cuarta o quinta década de la vida y entonces se produce una caída paulatina (Bartzokis, Beckson, Lu et al, 2001; Sowell, Peterson, Thompson et al, 2003; Walhovd, Fjell, Reinvang et al, 2005; Ostby, Tamnes, Fjell et al 2009; Reiss, Abrams, Singer et al, 1996; Giedd, Blumenthal, Jeffries et al, 1999; Sowell, Thompson, Rex et al, 2002; Lenroot, Gogtay, Greenstein et al, 2007).

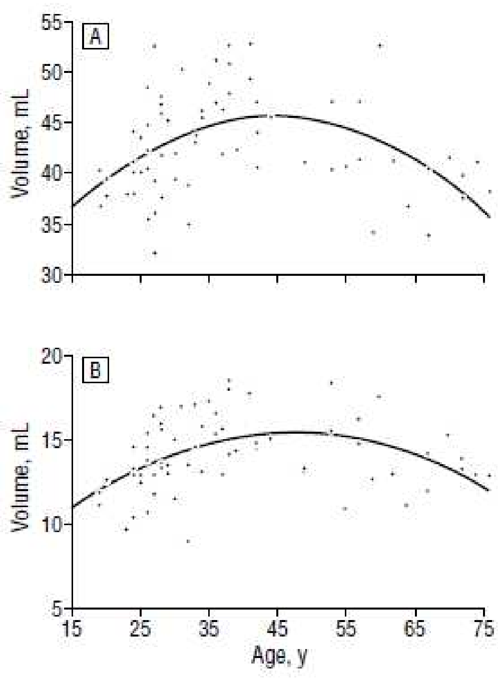

Figura 4. Regresión del volumen de sustancia blanca en el lóbulo frontal (A) y temporal (B) dependiente de la edad en una muestra de 70 hombres adultos. Imagen extraída de Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-Related Changes in Frontal and Temporal Lobe Volumes in Men. A Magnetic Resonance Imaging Study. Arch Gen Psychiatry. 2001;58:461-465

1.1.5. Relevancia funcional de la sustancia blanca

El papel de la sustancia blanca en la mediación de las funciones superiores es menos reconocido que el de la sustancia gris. No existen mapas de sustancia blanca parecidos a las áreas de Brodmann de la corteza cerebral. No obstante, en las últimas décadas, la sustancia blanca paulatinamente ha ido ganando más atención como un componente esencial de las redes neurales que sustentan la cognición y el procesamiento emocional. Por ejemplo, datos recientes indican un aumento selectivo del volumen de sustancia blanca prefrontal en humanos comparado con los primates no humanos, mientras que el volumen de la sustancia gris no es significativamente diferente (Schoenemann, Sheehan, Glotzer, 2005). En general, cada vez se va consolidando más la idea de que la sustancia blanca tiene un papel esencial no sólo en determinar la velocidad de conducción neuronal, sino que la complejidad de las conexiones de las redes funcionales cerebrales es un factor determinante en la modulación de los comportamientos más elaborados de los humanos. Los estudios del equipo de Katerina Semendeferi demuestran que el tamaño del lóbulo frontal humano no es proporcionalmente mayor que el de los grandes simios. En cambio, sugieren que las ventajas que ofrecen los lóbulos frontales al ser humano están basadas en una mejor interconectividad y en diferencias en regiones corticales específicas (Semendeferi, Lu, Schenker et al, 2002). Precisamente, en las zonas de asociación, donde la mielinización acontece en último lugar (Parazzini, Baldoli, Scotti et al, 2002), son las que presentan una densidad menor. Esto es interpretado como una cualidad que facilita su mayor interconexión y complejidad en la formación de las redes neuronales, siendo fundamental para el desarrollo de la conducta simbólica humana. Según se ha sugerido, la densidad celular decrece al ir ascendiendo filogenéticamente, aumentando paralelamente el número de sinapsis o redes neuronales de la corteza, siendo los humanos los que presentan mayor proliferación (Lenneberg, 1976). Al aumentar la superficie de la corteza, el número de neuronas es mucho mayor, compensando con creces esta disminución filogenética de la densidad neuronal y, a su vez, se facilita su interconexión para formar redes neurales, factor importante como base de la conducta humana.

Por otro lado, hay varios estudios que muestran ejemplos de la plasticidad de la sustancia blanca experiencia-dependientes. Bengtsson y colaboradores (2005) observaron una correlación entre las horas practicadas por unos pianistas y el nivel de mielinización altamente organizada que se detectaba en los tractos corticoespinales y el cuerpo calloso. Carreiras y colaboradores (2009) exponen los cambios detectados, mediante el estudio con VBM, en sustancia blanca en jóvenes guerrilleros de Colombia que iniciaban programas de aprendizaje de lectura respecto a personas analfabetas. Los que aprendieron a leer presentaban más sustancia blanca en el '*esplenium*' del cuerpo calloso y más sustancia gris en la circunvolución angular (CA) bilateralmente, corteza occipital dorsal, temporal media, supramarginal izquierda y circunvolución temporal. Otro estudio con DTI, que apunta en la misma dirección, es el de Tamnes y colaboradores (2010). Estos autores encuentran que con independencia de la edad, las habilidades verbales y manipulativas están relacionadas con la microestructura de la sustancia blanca, predominantemente en el hemisferio izquierdo. Lebel y Beaulieu (2009) sugieren que la lateralización del fascículo arqueado, estudiada mediante la DTI, mantiene una relación con las habilidades cognitivas. La lateralización izquierda extrema se asoció a mejores resultados en pruebas de vocabulario expresivo, mientras que los que presentaban una lateralización izquierda moderada realizaban mejor tareas de procesamiento fonológico.

Por otro lado, las lesiones focales en la sustancia blanca son el origen de síndromes clásicos neurocomportamentales. No obstante, las afectaciones difusas de la sustancia blanca están ganando peso como factor causal en un gran número de entidades neuropsiquiátricas y en el ámbito de las demencias (Filley, 2010). Así, hay estudios que constatan un aumento global de volumen de la sustancia blanca en sujetos autistas (Herbert, Ziegler, Deutsch et al, 2003). Dicho resultado ha sido replicado en diversos estudios controlando el volumen cerebral, el grado de macrocefalia y variables demográficas relevantes (Bigler, Abildskov, Petrie et al, 2010). Todo ello apoya la teoría de la importancia de un hiperdesarrollo cerebral o mielinización aberrante en la etiopatogenia del autismo, siendo éste posible que sea mucho más marcado en la población infantil que en la adulta (Carper, Moses, Tigue et al, 2002; Courchesne, Karns, Davis et al, 2001).

1.1.6. Diferencias entre hombres y mujeres

Los hombres y las mujeres difieren en habilidades cognitivas, rasgos de comportamiento y en el riesgo de padecer diferentes trastornos psiquiátricos. A nivel anatómico, la diferencia macroscópica más marcada es el tamaño del cerebro. El cerebro de los hombres es más grande que el de las mujeres. La diferencia está presente en adultos (Gur, Turetsky, Matsui et al, 1999; Goldstein, Seidman, Horton et al, 2001; Nopoulos, Flaum, O'Leary et al, 2000), en niños (Reiss, Kesler, Vohr et al, 2004) y en recién nacidos (Gilmore, Lin, Prastawa et al, 2007). Los hombres tienen un 10% más de volumen cerebral total (Peters, 1991). Este aumento de volumen se observa en la sustancia blanca y gris. Las diferencias en ambos volúmenes globales se mantienen incluso después de tener en cuenta las diferencias sexuales de tamaño de cerebro (Gur, Gunning-Dixon, Bilker et al, 2002) y de covariarlas por la altura y peso (Peters, Jäncke, Staiger et al, 1998; Skullerud, 1985; Ankney, 1992; Jerison, 1973).

A parte del mayor volumen cerebral del cerebro del varón, hay otras variables morfológicas que los diferencian de las mujeres. El estudio de Kovalev y colaboradores (2001), con 380 adultos, demostró que el cerebro de los hombres era más asimétrico que el de las mujeres (Kovalev, Kruggel, Gertz et al, 2001). En el cerebro masculino existen más asimetrías morfológicas a nivel global y local (Yücel, Stuart, Maruff et al, 2001). Por otra parte, los trabajos que utilizan el método VBM muestran diferencias entre los hombres y las mujeres en cuanto a volúmenes regionales y concentración de sustancia gris (Good, Johnsrude, Ashburne et al, 2001b). Vasileiadis y colaboradores (2009) observaron en una muestra de niños y niñas pretérmino que las niñas presentaban un menor volumen cerebral. En cambio, el índice de surcos corticales (*cortical folding area*) era mayor en las niñas que en los niños. Todos estos datos ponen de relieve diferencias, ya en edades muy tempranas, entre los dos géneros.

Se ha observado que el desarrollo evolutivo de la sustancia blanca entre ambos géneros no es paralelo. Así, si bien a los 12 años, el volumen de sustancia blanca en chicos y chicas es similar, a los 18 años los chicos tiene un 9% más en el lóbulo frontal y un 25% más en el lóbulo occipital (Perrin, Leonard, Perron et al, 2009; Perrin, Hervé, Leonard et al, 2008). Además, con la edad el volumen de la sustancia blanca aumenta suavemente en las mujeres y de forma brusca en los hombres. Los trabajos de Perrin y colaboradores (2009) presentan evidencias sobre el rol del receptor andrógeno que media el efecto de la testosterona en la sustancia blanca. Esta hormona afecta más al calibre axonal que al grosor de la capa de mielina. Durante la adolescencia masculina, la testosterona actúa a través del receptor andrógeno aumentando el volumen de la sustancia blanca. Asimismo, los trabajos de Paus y colaboradores (2010) apuntan en la misma dirección. El volumen de sustancia blanca absoluto y relativo es mayor en adolescentes masculinos que femeninos. El receptor andrógeno modera el efecto de la testosterona en relación al volumen de la sustancia blanca y sustancia gris.

1.2. Lenguaje

1.2.1. Diferencias anatómicas

Existen muchos datos acerca de las asimetrías cerebrales relacionadas con las regiones que sustentan las funciones lingüísticas. Ya en 1968, Geschwind y Levitsky demostraron un mayor tamaño del '*planum temporale'* izquierdo, corteza situada posteriormente a la circunvolución auditiva de Heschl, en comparación con el derecho (ver figura 5). Dicho dato ha sido replicado posteriormente (Habib, Robichon, Lévrier et al, 1995). Estudios más recientes (Dos Santos Sequeira, Woerner, Walter et al, 2006) defienden que la magnitud de esta asimetría no viene determinada únicamente por la lateralización del lenguaje, sino que depende de la combinación entre ésta, la preferencia manual y el género.

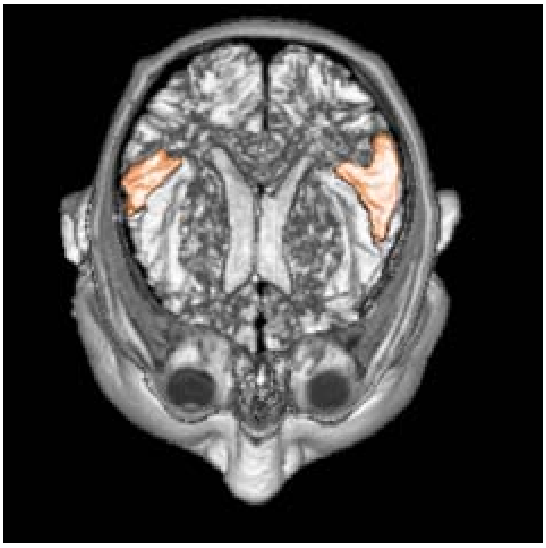

Figura 5. Visualización, en un plano axial, del p*lanum temporale*. Imagen cedida por el Dr Pujol

También se han identificado asimetrías en las áreas 44 y 45 de Brodmann (área de Broca en el hemisferio izquierdo), con mayores volúmenes en el hemisferio izquierdo (Amunts, Schleicher, Ditterich et al, 2003; Annett, 1970; Falzi, Perrone, Vignolo, 1982; Foundas, Leonard, Gilmore et al, 1996; Foundas, Eure, Luevano et al, 1998; Geschwind, Galaburda 1985). Trabajos recientes (Dubois, Benders, Lazeyras et al, 2010) han detectado asimetrías en las regiones perisilvianas ya en el tercer trimestre de gestación. Lebel y Beaulieu (2009) han referido una asimetría del fascículo arqueado con DTI. Aproximadamente un 10% de los individuos presentaban una lateralización derecha y un 34% una marcada lateralización izquierda. Sus resultados son consistentes con los estudios volumétricos del '*planum temporale*' que demuestran que mientras la mayoría de la población está lateralizada a la izquierda, aproximadamente un 9-12% de los diestros presenta una asimetría del '*planum temporale*' a favor del hemisferio derecho (Dos Santos Sequeiro, Woerner, Walter et al, 2006; Pujol, López-Sala, Deus et al, 2002; Steinmetz, 1996). La lateralización del fascículo arqueado está presente en el inicio de la infancia y se mantiene constante a través de la adolescencia y edad adulta. Otros estudios (Rademacher, Caviness, Steinmetz et al, 1993; Penhune, Zatorre, MacDonald et al, 1996) también muestran asimetrías de la circunvolución de Heschl siendo el del hemisferio izquierdo más grande que el del derecho (Warrier, Wong, Penhune et al, 2009). Anderson y colaboradores en 1999, proponen que el aumento de sustancia blanca en la región temporal superior posterior explica la ventaja del hemisferio izquierdo para procesar las señales acústicas rápidas y variadas que conllevan los sonidos del lenguaje. En la misma línea, Tallal y colaboradores (1993) propuso que el hemisferio izquierdo estaba especializado en procesar señales acústicas con rápidas variaciones temporales y que esto podría marcar la habilidad de este hemisferio para ser la base del lenguaje. Como ya ha demostrado la física (Joos 1948 citado en Zatorre, Belin, Penhune, 2002) un sistema no puede ser bueno de forma simultánea en resolución temporal y espectral. Zatorre y colaboradores (2002) sugirieron que la corteza auditiva izquierda se especializa en el análisis temporal mientras que la derecha se especializa en el análisis espectral. Con un estudio funcional se ha demostrado una lateralización a favor de la circunvolución de Heschl izquierda para la velocidad de cambio de estímulo y una lateralización a favor de la circunvolución de Heschl derecha para la información espectral. Warrier y colaboradores (2009) postulan que los elementos básicos para el lenguaje son cambios acústicos rápidos y los elementos básicos para la música son la información compleja de frecuencias.

Con todos los datos que se disponen, se puede inferir que el desarrollo del lenguaje en la especie humana ha ido modulando el cerebro a lo largo de millones de años. Esta modulación ha supuesto una especialización regional que ha provocado la aparición de las asimetrías anatómicas anteriormente mencionadas.

1.2.2. Base funcional

El lenguaje y la preferencia manual han sido, desde hace mucho tiempo, los dos factores principales en toda discusión sobre la dominancia cerebral. A partir de las aportaciones de Broca en 1861 y Wernicke en 1874 (Broca, 1861; Wernicke, 1874), y de otros autores previos a dicha época, se empezó a tener datos objetivos sobre la lateralización del lenguaje en el hemisferio izquierdo. Éste es el dominante para el lenguaje en la mayoría de las personas diestras (Crystal, 1994). Este hecho se manifiesta de modo más notorio en los casos de afasia, en los que un daño cerebral adquirido en el lado izquierdo del cerebro puede causar un trastorno del lenguaje. Muchos estudios funcionales actuales han constatado la lateralización del lenguaje en le hemisferio izquierdo (Branch, Milner, Rasmussen, 1964; Zangwill, 1967; Rasmussen, Milner, 1977; Dapretto, Bookheimer, 1999; Binder, 2000; Price, 2000; Zatorre, 1989). Se acepta que en un 96% de los sujetos diestros y en un 76% de los sujetos zurdos el lenguaje se localiza básicamente en el hemisferio izquierdo (Pujol, Deus, Losilla et al, 1999).

1.2.3. Lenguaje y patología

El ejemplo paradigmático de una alteración del lenguaje sin una lesión cerebral adquirida es la disfasia del desarrollo, considerado como un tipo de Trastorno Específico del Desarrollo del Lenguaje (TEDL) (Deus, Junqué, Pujol et al, 1997). La definición más común de esta entidad es una definición por diagnóstico de exclusión. Es decir, es todo retraso o enlentecimiento en el desarrollo del lenguaje que no pueda ser puesto en relación con un déficit sensorial, motor, deficiencia mental, trastornos psicopatológicos, privación socioafectiva ni con lesiones cerebrales evidentes (Rapin, 1982; Rapin, Allen, Dunn, 1992; American Psychiatric Association: DSM-IV 1994; Deus, Junqué, Pujol et al, 1997). El fenotipo lingüístico del niño disfásico es muy heterogéneo. Una de las clasificaciones más utilizadas es la de Rapin y Allen (Rapin, 1996). Como es un trastorno del desarrollo, su naturaleza es dinámica y puede inscribirse en diferentes subtipos a lo largo del desarrollo del niño.

Las causas neurobiológicas se desconocen. Raras veces los trastornos específicos del desarrollo del lenguaje se asocian a lesiones cerebrales demostrables por neuroimagen. En general, la neuroimagen de estos niños es informada como normal aunque hay algunos trabajos que señalan alteraciones sutiles del sistema nervioso central (Guerreiro, Hage, Guimarães et al, 2002; Trauner, Wulfeck, Tallal et al, 2000). El hallazgo más replicado es la falta de asimetría a favor de la región perisilviana izquierda (De Fossé, Hodge, Makris et al, 2004; Gauger, Lombardino, Leonard, 1997; Herbert, Ziegler, Deutsch et al, 2005;

Jernigan, Hesselink, Sowell et al, 1991; Leonard, Lombardino, Walsh et al 2002; Leonard, Eckert, Given et al, 2006; Leonard, Eckert, 2008; Plante, Swisher, Vance et al, 1991). Jernigan y colaboradores (1991) compararon 20 niños disfásicos con 12 niños normales, apareados por edad, sexo y preferencia manual. En el grupo patológico se observó una disminución volumétrica significativa de las regiones correspondientes a la corteza prefrontal anterior izquierda y de la corteza parietal superior del lado derecho. Los trabajos que describen alteraciones volumétricas son muy heterogéneos. En niños con diagnóstico de dislexia del desarrollo también se ha descrito una disminución de la asimetría en el '*planum temporale'* (Larsen, Hoien, Lundberg et al, 1990).

Uno de los pocos trabajos con VBM es el de Jancke y colaboradores (2007). Estos autores constataron que los niños con disfasia del desarrollo presentaban una densidad de sustancia blanca disminuida en redes neurales del lado izquierdo que incluían la corteza motora primaria, la premotora dorsal, la premotora ventral y el plano polar de la circunvolución temporal superior. Los resultados apuntan a una anomalía anatómica en las redes audio-motrices en el hemisferio dominante para el lenguaje. A pesar de que muchos autores defienden que la adquisición fonológica interactúa con la adquisición del control motor para el habla, el hecho de que los trastornos del lenguaje tengan asociado problemas motrices es controvertido.

Uno de los pocos estudios con RM funcional es el de Hugdahl y colaboradores (2004). Los resultados del estudio permiten concluir que los individuos con diagnóstico clínico de disfasia del desarrollo muestran una actividad reducida o hipoactividad en áreas cerebrales que son críticas para el procesamiento del habla y para la conciencia fonológica.

Una teoría que explicaría la disfasia es la de Geschwind y Galaburda (1985). Estos autores defienden que los dos hemisferios empiezan teniendo originariamente las mismas potencialidades. Pero uno de ellos, generalmente el derecho, sufre una pérdida neuronal en área del lenguaje, dejando que su homólogo sustente las funciones lingüísticas. Los patrones atípicos van asociados a una limitada involución del hemisferio derecho más que una limitación del desarrollo del hemisferio izquierdo (Josse, Tzourio-Mazoyer, 2004). Se conoce, a partir del trabajo de Chi y colaboradores (1977), que el desarrollo de ambas regiones perisilvianas no es estrictamente sincrónico. Se realiza más precozmente en el hemisferio derecho. Por dicha razón puede suponerse que un determinado agente etiológico podría interferir en el proceso morfogenético en un hemisferio cerebral y no en el otro. En la patología que nos ocupa, ocurriría una tala excesiva del hemisferio derecho.

1.2.4. Diferencias género

Varios estudios sugieren diferencias en las asimetrías cerebrales asociadas al lenguaje entre hombres y mujeres. Se ha mencionado que el cerebro del varón, en general, puede estar más lateralizado o ser más asimétrico que el de la mujer (Shaywitz, Shaywitz, Pugh et al, 1995).

El grupo de Good y colaboradores (2001b) observó en varias regiones cerebrales una asimetría de la sustancia gris y de la sustancia blanca más marcada en hombres que en mujeres. Específicamente, la existencia de una asimetría del '*planum temporale*' y en la circunvolución de Heschl a favor del hemisferio izquierdo. Identificaron un aumento de sustancia blanca, y disminución de sustancia gris, en el hemisferio izquierdo comparado con el hemisferio derecho en una porción lateral del lóbulo frontal y temporal.

Otros trabajos aportan datos funcionales donde se observa que las funciones lingüísticas están más fuertemente lateralizadas en los hombres que en las mujeres (Springerl, Deutsch, 1998; Josse, Tzourio-Mazoyer, 2004; Hécaen, Ruel, 1981).

1.3. Temperamento

1.3.1. Bases neuroanatómicas: la circunvolución cingulada

La circunvolución cingulada (CC) es una estructura prominente de la cara medial del cerebro que cubre dorsalmente el cuerpo calloso. Por sus características citoarquitectónicas, proyectivas y funcionales, en la CC se pueden diferenciar dos regiones: una anterior y otra posterior. La anterior es más ejecutiva y la posterior es más evaluativa (Vogt, Finch, Olson, 1992; Vogt, Nimchinsky, Vogt et al, 1995; Paus, Petrides, Evans et al, 1993; Bush, Luu, Posner, 2000; Pujol, Vendrell, Deus et al, 2001). La CCA limita dorsalmente con las áreas mediales motoras, premotoras y prefrontales. La superficie de esta región es muy variable de persona a persona y también ínterhemisféricamente, es decir, del hemisferio derecho respecto al izquierdo (Paus, Tomaiuolo, Otaky et al, 1996; Yücel, Stuart, Maruff et al, 2001; Vogt, Nimchinsky, Vogt et al, 1995; Ono, Kubik, Abernathey, 1990; Ide, Dolezal, Fernández et al, 1999).

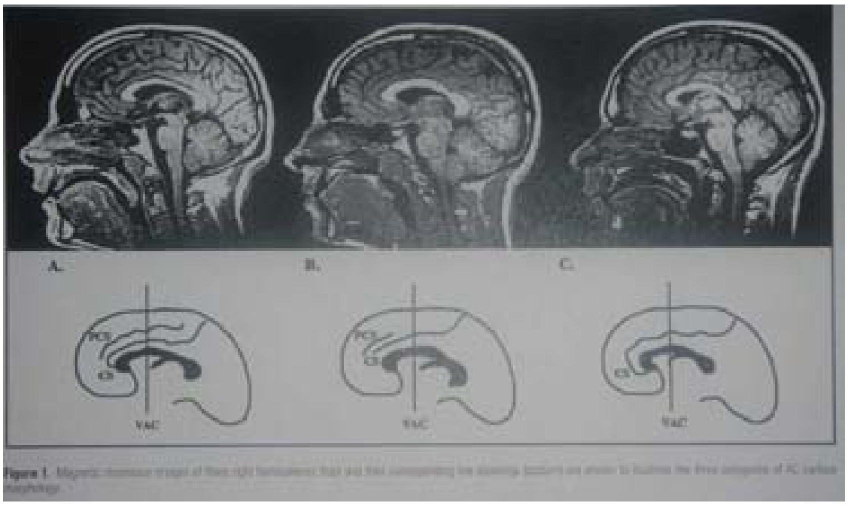

Figura 6. RM de tres hemisferios derechos (imagen de arriba) y sus correspondientes dibujos (imagen de abajo) que ilustran las tres categorías de la morfología de superficie del cingulado anterior. Imagen extraída de Yücel M, Stuart GW, Maruff P, Velakoulis D, Crowe SF, Savage G et al. Hemispheric and gender-related differences in the gross morphology of the anterior cingulated/ paracingulate cortex in normal volunteers: An MRI morphometric study. Cereb Cortex 2001; 11: 17-25.

La región paracingulada es una circunvolución que está presente sólo en un 30-60% de los casos (Paus, Otaky, Caramanos et al, 1996; Yücel, Stuart, Maruff et al, 2001) y cuando está presente se sitúa en la parte dorsal y paralela a la CC. Esta circunvolución se encuentra con más frecuencia y más pronunciada en el hemisferio izquierdo que en el derecho (Yücel, Stuart, Maruff et al, 2001; Huster, Westerhausen, Kreuder et al, 2007). Más específicamente, en el trabajo de Paus y colaboradores (1996) lo encuentran más desarrollado en un 54% de los sujetos en el hemisferio izquierdo y en un 37% en el hemisferio derecho.

1.3.2. Implicaciones funcionales de la circunvolución cingulada

La circunvolución cingulada anterior (CCA) contribuye en la conducta a través de la modulación del amplio abanico de las respuestas cerebrales (Paus, 2001; Devinsky Morrell, Vogt, 1995). Está involucrada en ajustar las respuestas de las personas al entorno (Bush, Luu, Posner, 2000). Interviene en el control emocional, en la focalización de la atención, en la resolución de problemas, en el reconocimiento de errores y en las respuestas adaptativas a condiciones cambiantes. La CCA es una estructura altamente compleja a nivel funcional que incluye: (i) módulos de procesamiento específico de información sensorial, motriz, cognitiva y emocional; (ii) integra entradas de diferentes regiones cerebrales: motivación, análisis del error y representaciones de las redes cognitivas y emocionales, (iii) actúa influenciando la actividad de otras regiones cerebrales y modulando respuestas cognitivas, motoras, endocrinas y viscerales (Yücel, Stuart, Maruff et al, 2001; Vogt, Finch, Olson, 1992; Devinsky, Morrell, Vogt, 1995; Fornito, Yücel, Word et al, 2004). Además, junto con la corteza prefrontal ventromedial (Damasio, Grabowski, Bechara et al, 2000; Rudebeck, Bannerman, Rushworth, 2008), la CCA se ha visto implicada con el comportamiento social (Devinsky, Morrell, Vogt, 1995).

Las asimetrías hemisféricas en la sustancia gris de la CC y paracingulada son consistentes con el rol propuesto para estas estructuras en la integración de la emoción con la cognición y en el control del habla/vocalización (Paus, Otaky, Caramanos et al, 1996)

La actividad de la CCA fluctúa con los niveles del arousal cortical (Paus, 2000) y con el arousal autonómico periférico (Critchley, Corfield, Chandler et al, 2000), que son más elevados en personas preocupadas y miedosas (Davis, 1997). Las lesiones en la CCA , según los estudios realizados en animales de experimentación, imposibilitan la adquisición del aprendizaje de una conducta de evitación y aumentan la presencia de un comportamiento arriesgado. En humanos, la cingulotomía anterior reduce la respuesta y la preocupación causada por los estímulos nocivos y alivia la ansiedad en pacientes con trastornos psicopatológicos (Vogt, Finch, Olson, 1992).

1.3.3. Psicopatología

Uno de los primeros trabajos que intentaron relacionar el volumen cerebral con las tendencias psicopatológicas fue el de Matsui y colaboradores (2000). Estos autores estudiaron en 59 participantes voluntarios sanos la neuroanatomía de estructuras lobares concretas mediante la RM, específicamente estudiando el volumen del lóbulo temporal y del frontal, y su relación con los resultados obtenidos en el Inventario Multifásico de Personalidad de Minnesotta (MMPI). La tendencia a la psicopatología se asoció a las medias más bajas de volumen del lóbulo frontal. Cuando la muestra se dividió de acuerdo al sexo, estas correlaciones fueron significativas en los hombres pero no en las mujeres. Los resultados sugirieron que las dimensiones de la personalidad en personas sanas podían relacionarse con los sustratos neurales que pueden servir como marcadores endofenotípicos de una disposición psicopatológica. Los efectos dimórficos sexuales fueron consistentes con las diferencias ligadas al género en las manifestaciones clínicas de los trastornos psicopatológicos y pueden sugerir una modulación hormonal de los trastornos mentales.

El trabajo de Boes y colaboradores (2008) aportó nuevos datos sobre el papel de la CCA, estudiando su volumen mediante RM, en la conducta social y agresiva evaluada mediante la Escala de Conducta Pediátrica de Achenbach y Edelbrock (1983) (CBCL) y la Escala de Conducta Pediátrica de Lindgren y Koeppl (1987) (PBS). Los autores encontraron que los chicos, en una amplia muestra en edades comprendidas entre 7 y 17 años, que tenían un menor volumen de la CCA derecha mostraban un mayor comportamiento agresivo y desafiante.

1.3.4. Evaluación de la personalidad

Hay varios instrumentos psicométricos para evaluar los rasgos o dimensiones de la personalidad normal. Destacan, entre otros, el Inventario de Personalidades de Eysenck-EPQ (Eysenck y Eysenck, 1975), el Cuestionario de Dieciséis Factores de Personalidad (16PF) (Cattell, 1970), modelo pentafactorial de los Cinco Grandes (McCrae, 1991), el cuestionario de personalidad de Zuckerman-Khulman (ZKPQ) (Zuckerman y Kuhlman, 1991) y el Invenvario de Temperamento y Carácter de Cloninger (TCI) (Cloninger, 1991, 1993, 1994). En general, no se ha buscado la relación entre estos instrumentos y la base neurobiológica de los rasgos de la personalidad. Hasta el momento, hay pocos estudios en este sentido. Uno de ellos es el recientemente publicado por el grupo De Young y colaboradores (2010). A una muestra de 116 sujetos, se les practicó una RM craneal y se les administró el NEO-PI-R (Costa y McCrae, 1992). Buscaron asociaciones entre áreas cerebrales y rasgos de personalidad y encontraron covariaciones con la extraversión, neuroticismo, amabilidad y responsabilidad. Más concretamente, la extraversión se asoció con el volumen de la corteza medial orbitofrontal, el neuroticismo con el volumen de la corteza prefrontal dorsomedial derecha y con porciones del lóbulo temporal medial, la amabilidad con el volumen de la corteza cingulada posterior y la responsabilidad con el volumen de la corteza prefrontal lateral. El quinto rasgo al que no se le encontró una asociación neuroanatómica, era el de Apertura.

Otro trabajo que correlacionó personalidad con anatomía cerebral fue el de Wright y colaboradores (2006). Estos autores encontraron que el grosor de algunas regiones específicas de la corteza prefrontal correlacionaba con las medidas de extraversión y neuroticismo. En cambio, no encontraron correlaciones con la amígdala. Los resultados sugieren que aspectos específicos de la anatomía prefrontal se asocian con rasgos concretos de personalidad.

El instrumento más utilizado para estudiar la personalidad desde una perspectiva neurobiológica es el Inventario del Temperamento y el Carácter (TCI) de Cloninger (Cloninger, 1991, 1993, 1994). El TCI se basa en la teoría psicobiológica de la personalidad de Cloninger. Esta alberga 5 planos concernientes a la adaptación humana: el plano sexual (reproducción y sexualidad), el plano material (poder y posesiones), el plano emocional (lazos afectivos y apegos sociales), el plano intelectual (comunicación y cultura) y el plano espiritual (entender qué hay después de la existencia humana).

Cloninger distingue entre temperamento y carácter. El primero se basa en la peculiaridad e intensidad individual de los afectos psíquicos y de la estructura dominante de humor y motivación. Dicho rasgo de personalidad se asienta básicamente en la herencia genética. El carácter es el rasgo de la personalidad que se modula durante la vida de la persona, por su experiencia y la cultura.

Hay cuatro escalas de temperamento que describen aspectos de la personalidad. Estos son hereditarios, no influenciables por el aprendizaje sociocultural, estables durante el desarrollo, son genéticamente homogéneos e independientes unos de otros. Son estructuralmente consistentes en diferentes culturas y grupos étnicos, inconscientemente influyen en los procesos de aprendizaje, y ya se pueden observar a principios de la niñez. Las cuatro escalas son Evitación del Daño, Búsqueda de Novedad, Persistencia y Dependencia de Recompensa. Varios estudios han demostrado diferencias significativas entre hombres y mujeres en la dimensión Evitación del Daño y Dependencia de la

Recompensa (Cloninger, Svrakic, Przybeck, 1993; Mendlowicz, Girardin, Likkin et al, 2000; Parker, Cheah, Paker, 2003; Miettunen, Veijola, Lauronen et al, 2007). Las mujeres muestran una mayor inhibición de la conducta y mayor preocupación que los hombres, así como un mayor sentimentalismo, empatía e intensidad de las respuestas recompensa dependientes.

Dichas dimensiones de temperamento se relacionan con la concentración de ciertas aminas cerebrales (Cloninger, 1994; Suhara, Yasuno, Sudo et al, 2001; Peirson, Heuchert, Tómala et al, 1999; Okuyama, Ishiguro, Nankai et al, 2000). Los datos propuestos por Cloninger (1987) son los que se exponen en la tabla II.

Tabla II. Resumen de la relación entre las dimensiones del temperamento y la concentración de monoaminas cerebrales. Extraído de Cloninger CR. A systematic method for clinical description and classification of personality variants. Arch Gen Psychiatry 1987; 44: 573-588.

Dimensiones del temperamento	Concentraciones de monoaminas cerebrales
Evitación del Daño	alta actividad serotoninérgica
Búsqueda de Novedad	actividad dopaminérgica basal baja
Dependencia de Recompensa	actividad noradrenérgica baja

El carácter se refiere a tres dimensiones que se han desarrollado plenamente en la edad adulta, influyen en la eficacia personal y social, así como en la adquisición de la conciencia. Son autodireccionalidad, cooperación y autotrascendencia. Son expresiones de los procesos cognitivos más altos y moderadamente influenciables por el aprendizaje sociocultural. El carácter, en principio, es menos hereditario que el temperamento pero hay estudios que encontraron un grado significativo de heredabilidad (Gillespie, Cloninger, Heath et al, 2003).

1.3.5. Alexitimia

Este término es relevante en el contexto de la regulación del estado del ánimo y en la investigación de sus bases biológicas. Se define como la dificultad en el procesamiento de las emociones que clínicamente se manifiesta por las dificultades en identificar y verbalizar sentimientos. Se creyó que la base neuropsicológica de la alexitimia se encuentra en una falta de conexiones corticales adecuadas entre el sistema límbico y la neocorteza (Nemiah, Sifneos, Apfel-Savitz, 1977). Las hipótesis neuroanatómicas tienen como fundamento el hecho de que el hemisferio derecho es especialmente relevante en el procesamiento de las emociones y que la expresión verbal se localiza en el hemisferio izquierdo en los sujetos diestros normales. Así, la falta de comunicación entre los hemisferios en los individuos produciría una deficiencia en la capacidad para verbalizar las emociones. Esta hipótesis fue planteada originalmente en 1949 por McLean. Este autor, observó que los enfermos psicosomáticos respondían a las situaciones emocionales con respuestas predominantemente físicas. Esto pueda deberse a que existe una alteración en la conexión entre el sistema límbico (‘cerebro visceral’) y la neocorteza cognitiva (incluyendo el ‘cerebro verbal’) de estos pacientes (Otero, 1999).

La alexitimia se ha correlacionado con rasgos de personalidad. Dos estudios han encontrado correlaciones positivas entre la alexitima y el neuroticismo y una correlación negativa con la apertura y la extraversión (Bagby, Taylor, Parker, 1994; Luminet, Bagby, Wagner et al, 1999). Lane y colaboradores (1997) hipotetizaron que la alexitimia era la ceguera para los sentimientos y lo correlacionaron con la CCA, ya que sustentaba funciones atencionales cognitivas y, posiblemente, también emocionales.

1.3.6. Diferencias de género

Un reciente estudio de Al-Halabí y colaboradores (2010) apoya la teoría de Cloninger acerca de las diferencias entre hombres y mujeres (Cloninger, Svrakic, Przybeck, 1993; Mendlowicz, Girardin, Likkin et al, 2000; Parker, Cheah, Paker, 2003; Miettunen, Veijola, Lauronen et al, 2007). El sexo femenino puntúa más alto en las dimensiones de temperamento de Evitación del Daño y Dependencia Recompensa. Una de las explicaciones a estas diferencias de género puede ser que a las 8 semanas de gestación intrauterina los niveles de testosterona en el feto del niño o de la niña ya son diferentes. Esta diferencia hormonal temprana puede ejercer influencias permanentes en el desarrollo del cerebro y del comportamiento (Hines, 2010).

2. Objetivos e Hipótesis del presente estudio

El presente trabajo pretende investigar el significado funcional de la variabilidad anatómica de dos regiones cerebrales que son característicamente asimétricas y que tienen especial relevancia en la modulación de la conducta del ser humano. Por un lado se ha medido el volumen de la región perisilviana como región paradigmática que sustenta el lenguaje. Por otro lado se ha medido el tamaño de la corteza cingulada (CC) para investigar su correlación con los estilos de comportamiento y/o dimensiones de la personalidad. Se han desarrollado 4 estudios bajo estas dos líneas de investigación.

Los objetivos generales y específicos que se han perseguido en las dos líneas de investigación se describen a continuación.

1) Estudiar las asimetrías volumétricas de la región perisilviana mediante análisis de cuantificación en un grupo de participantes voluntarios sanos y un grupo de pacientes con un Trastorno Específico del Desarrollo del Lenguaje (TEDL).

1.A.- Estudiar las asimetrías en el volumen de sustancia blanca y sustancia gris en las principales divisiones anatómicas de la región perisilviana en una muestra de participantes voluntarios sanos como potencial sustrato de la dominancia hemisférica para el lenguaje. Concretamente, se pretendía buscar el mejor correlato anatómico concordante con los porcentajes conocidos de dominancia cerebral para el lenguaje. También se midió el área del '*planum temporale*' para estudiar su relación con las medidas volumétricas efectuadas en los lóbulos cerebrales.

1.B.- Investigar la posible existencia de alteraciones en las medidas de volumen cerebral regional en una población con Trastorno Específico del Desarrollo del Lenguaje (TEDL) tipo Disfasia del Desarrollo a través del VBM. Se consideró relevante introducir un punto de vista dinámico y evolutivo para interpretar los hallazgos. Identificar hasta qué punto las potenciales alteraciones tisulares en este contexto pueden afectar diferencialmente ambos hemisferios cerebrales.

2) Estudiar la posible relación entre la variabilidad interindividual de las medidas de superficie de la circunvolución cingulada anterior (CCA) y estilos de comportamiento.

2.A.- Investigar la variabilidad de la CCA entre géneros y relacionarla con estilos específicos de comportamiento. Más específicamente, en base a las funciones atribuidas a esta región cerebral, con la dimensión de Evitación del Daño de Cloninger.

2.B.- Estudiar la variabilidad interindividual de la CCA en relación con el grado de alexitimia de participantes voluntarios sanos.

Las hipótesis de esta tesis se enmarcan en el contexto general de que el grado de desarrollo anatómico de regiones cerebrales funcionalmente relevantes caracterizadas por su gran variabilidad interindividual y por la existencia de una marcada asimetría hemisférica podría estar relacionado con las diferencias individuales en los estilos cognitivos y rasgos de la personalidad.

Hay numerosos estudios que exponen las diferentes asimetrías morfológicas hemisféricas interindividuales. Los hallazgos más replicados son las asimetrías en áreas laterales de los hemisferios cerebrales y en la circunvolución cingulada anterior (CCA). A pesar de ello, un menor número de estudios se han centrado en estudiar la relevancia y el significado funcional de dichas asimetrías y la variabilidad interindividual, aunque sí han aportado datos que han explicado parcialmente la relación entre volumen y estructuras cerebrales y funciones superiores.

Las hipótesis que se plantean para cada uno de los trabajos que configuran la presente tesis se especifican a continuación:

Hipótesis I

El volumen global, medido con RM 3D, de la región perisilviana de ambos hemisferios no diferirá. Contrariamente, el volumen regional de la representación de cada lóbulo sería diferente en los dos hemisferios. Especialmente, el volumen relativo de sustancia blanca tendrá porcentajes más altos en las regiones frontales, temporales y parietales del hemisferio izquierdo, y en el hemisferio derecho el porcentaje más alto se ubicará en la región témporo-párieto-occipital. El patrón de asimetría en el volumen relativo de sustancia blanca de la región temporal, frontal y parietal sería concordante con las proporciones conocidas de lateralización del lenguaje y de preferencia manual en sujetos sanos.

Hipótesis II

La medición neurонanatómica, mediante la técnica de análisis de imagen de VBM, mostrará patrones diferentes tanto del volumen de sustancia blanca como de sustancia gris en las regiones perisilvianas de ambos hemisferios en una serie de sujetos con diagnóstico clínico de disfasia del desarrollo respecto a un grupo control de participantes sanos. Los trastornos de lenguaje objetivados se podrán asociar a estas alteraciones estructurales.

Hipótesis III

La variabilidad interindividual de la superficie de la circunvolución cingulada anterior (CCA) en participantes voluntarios sanos se correlacionará con las dimensiones de la personalidad. Específicamente, el tamaño de la CCA derecha se relacionará positivamente con la dimensión de temperamento de Evitación al Daño del Inventario de Temperamento y Carácter de Cloninger (TCI). La evolución histórica del rol de la mujer puede justificar el mayor tamaño de la CCA derecha presente en la actualidad en las mujeres.

Hipótesis IV

Las puntuaciones de alexitimia se relacionarán con la variabilidad interindividual de la circunvolución cingulada anterior (CCA). De forma más concreta, las puntuaciones de alexitimia obtenidas a través del Inventario psicométrico del TAS-20 correlacionarán de forma negativa con la superficie de la CCA derecha.

2. Metodología

La presente tesis está constituida por un total de 4 trabajos cuyo objetivo ha sido el estudio de la asimetría neuronatómica ínter-hemisférica en participantes voluntarios sanos y en menores con diagnóstico clínico de disfasia del desarrollo y la variabilidad interindividual en relación con las dimensiones de personalidad. Para la consecución de dicho objetivo general se han utilizado diferentes metodologías de adquisición y análisis de imagen de RM, así como de instrumentos psicométricos específicos para la evaluación de los rasgos de la personalidad. La metodología específica utilizada en esta tesis se describe detalladamente para cada artículo (ver la sección de resultados). A continuación se comentarán las particularidades metodológicas de cada uno de los trabajos que configuran la presente tesis doctoral.

Trabajo 1. Pujol J, López-Sala A, Deus J, Cardoner N, Sebastian-Gallés N, Conesa G, Capdevila A. The lateral asymmetry of the human brain studied by volumetric magnetic resonance imaging. NeuroImage 2002, 17: 670-679.

En este trabajo se han medido los volúmenes de regiones cerebrales mediante la RM volumétrica o 3D. La muestra estaba constituida por 100 sujetos sanos (50 hombres, 50 mujeres), diestros, de edades comprendidas entre los 20 y 40 años, y todos ellos cursando los últimos cursos de universidad o licenciados. Se les realizó una entrevista clínica completa para descartar los participantes que presentaran indicio de un posible trastorno psicopatológico, neurológico o médico, así como historia de abuso de alcohol o consumo de drogas.

A todos ellos se les realizó una RM craneal. Las imágenes se adquirieron utilizando un aparato de 1.5 teslas (Signa, GE Medical System, Milwaukee, WI). El análisis de las imágenes se realizó con un *software* que permitió hacer la reconstrucción 3D (Advantage Windows, Version 2.0, GE Medical Systems).

Para el posterior análisis de las imágenes adquiridas se debía decidir la delimitación neuroanatómica de las regiones de estudio. La delimitación de la región lateral de cada hemisferio se realizó mediante un corte sagital que separara el opérculo frontoparietal y la ínsula. A partir de este plano, se identificaban cuatro regiones en la parte lateral del cerebro. La región frontal que quedaba delimitada por la cisura de Silvio y la cisura central. La región temporal quedaba definida por la cisura de Silvio y una línea horizontal perpendicular al tramo final de la misma cisura. La región parietal quedaba circunscrita entre la cisura central y la prolongación de la cisura de Silvio paralela al surco postcentral. Finalmente, la región témporo-parieto-occipital quedaba definida por los límites de la región temporal y parietal. Para este trabajo, se utilizaron imágenes expuestas en espejo para que no se supiera que las proyecciones provenían del hemisferio derecho o izquierdo. De cada región se obtuvo volumen de sustancia blanca y gris.

El estudio de las asimetrías se realizó para el volumen de cada región y para cada tejido en concreto. Se calculó el porcentaje de sustancia blanca relativa al volumen regional (100 x volumen sustancia blanca / volumen regional). El inverso de este porcentaje corresponde al porcentaje de la sustancia gris.

El índice de asimetría se calculó de acuerdo a la expresión 100 x (I – D)/ (I + D) (Galaburda 1987; Shapleske, Rossell, Woodruff et al, 1999), donde I y D son mediciones del hemisferio izquierdo y derecho. El rango de simetría se estableció entre los valores -10 y +10. Los valores por encima de +10 representaban una asimetría a favor del lado izquierdo, y los valores por debajo de -10 mostraban un patrón derecho.

También se midió el *planum temporale*. El surco de Heschl delimitó el límite anterior y el punto final del la cisura de Silvio o donde esta se bifurca significó el límite posterior.

Las diferencias de volumen entre los dos hemisferios fueron analizadas con un grado de confianza del 99% y tests de T de Student. Los posibles efectos de género fueron evaluados utilizando análisis de varianza (ANOVA). El volumen cerebral se incluyó en este análisis como covariable. Los índices de asimetría entre regiones se compararon con un test de χ^2. Las correlaciones de Pearson sirvieron para examinar la asociación entre volúmenes regionales y superficie del *planum temporale*. Un análisis de regresión múltiple "*stepwise*" estableció la mejor predicción del área del '*planum temporale'* a partir de las medidas de volumen regional.

Trabajo 2. Soriano-Mas C, Pujol J, Ortiz H, Deus J, López-Sala A, Sans A. Age-related brain structural alterations in children with specific language impairment. Human brain Mapping 2009, 30; 1626-1636.

En este estudio, se intentó caracterizar las posibles anormalidades estructurales en una serie de niños clínicamente diagnosticados de disfasia del desarrollo respecto a su grupo control de participantes sanos mediante la técnica de VBM. El grupo se compuso de 36 niños disfàsicos (24 niños y 12 niñas), de entre 5 y 17 años, 4 de ellos con dominancia lateral manual gráfica zurda, diagnosticados en el Servicio de Neurología del Hospital Sant Joan de Déu de Barcelona. Todos ellos presentaban alteraciones en la adquisición del lenguaje desde un inicio y un desarrollo normal en los otros ámbitos cognitivos evaluados.

A todos ellos se les realizó una RM de 1.5 teslas sin sedación. Se preprocesaron y normalizaron las imágenes mediante el software del SPM2. Se comparó el volumen de la sustancia gris, sustancia blanca y líquido cefaloraquídeo de las imágenes no normalizadas mediante un ANCOVA univariado, y se utilizó la edad y el género como covariables. Se usaron correlaciones de Pearson para analizar la relación entre la edad y el volumen de los tejidos en los pacientes y en el grupo control. Para el análisis volumétrico regional (*voxel-wise*) se utilizó el SPM2. Se compararon los dos grupos en cuanto a sustancia blanca y gris, con la edad y género como covariables.

Para buscar las relaciones existentes con la edad, se realizó una correlación de Pearson entre la edad de los sujetos y los valores de los voxels obtenidos en el análisis previo. Se realizó un test de ANCOVA, con el grupo y edad como variables independientes, para valorar las diferencias entre grupos en cuanto a volúmenes regionales y edad.

Trabajo 3. Pujol J, López A, Deus J, Cardoner N, Vallejo J, Capdevila A, Paus T. Anatomical variability of the anterior cingulate gyrus and Basic dimensions of human personality. NeuroImage 2002, 15: 847-855.

En este tercer trabajo el campo de estudio se trasladó de la esfera cognitiva a la esfera conductual. Se pretendió estudiar la posible relación entre las variaciones interindividuales de volumen de la región cingualda y los rasgos de temperamento.

La muestra de participantes voluntarios sanos de estudio fue la misma que la del primer trabajo (ver primer parágrafo del primer estudio).

Para valorar los diferentes estilos de comportamiento se utilizó la versión 9 del Temperament and Character Inventory (TCI) de Cloninger. Se eligió esta escala por su fundamento neurobiológico. El TCI está basado en 4 dimensiones para valorar el temperamento (Evitación del Daño, Búsqueda de Novedad, Dependencia de Recompensa y Persistencia) y tres para medir el carácter (Autodirección, Cooperación y Autotrascendencia). Cada una de estas siete dimensiones, a excepción de la Persistencia, contiene de 3 a 5 subescalas de nivel inferior.

En el mismo día de la administración del TCI se les realizó una RM craneal de 1.5 teslas. Se reconstruyó una imagen 3D para cada cerebro para obtener el volumen total. Por otro lado, se seleccionaron los cortes sagitales que mejor exponían la superficie medial derecha e izquierda de cada hemisferio. Cada uno de estos cortes se codificó y guardó sin relación al nombre, edad, género o hemisferio del sujeto. En una segunda fase se delimitó la región cingulada. Los surcos correspondientes delimitaban la región. La recta horizontal que pasaba por el punto medio entre las dos comisuras separaba la región cingulada anterior de la posterior.

Para este estudio, el índice de asimetría se calculó de acuerdo a la expresión 100 x (I – D)/0.5 x (I + D), donde I y D son mediciones del hemisferio izquierdo y derecho. El rango de simetría se estableció entre los valores -5 y +5. Los valores por encima de +5 representaban una asimetría a favor del lado izquierdo, y los valores por debajo de -5 a favor del derecho.

Se realizaron análisis de variancia (ANOVA) con covariables para controlar el efecto del volumen cerebral y valorar el peso del género (hombre, mujer) y el hemisferio (derecho, izquierdo) y la relación entre ellos. Los índices de asimetría entre sexos fueron comparados mediante un test χ^2. Se realizaron correlaciones de Pearson, ajustadas al volumen cerebral utilizando correlaciones parciales, para examinar la asociación entre las medidas de RM craneal y las siete dimensiones de personalidad. Cuando se detectaba una asociación significativa con las principales escalas, se realizaba una correlación para las subescalas que la componían.

Trabajo 4. Gündel H, López-Sala A, Ceballos-Baumann A, Deus J, Cardoner N, Marten-Mittag B, Soriano-Mas C, Pujol J. Alexitimia correlates with the size of the right anterior cingulate. Psychosomatic Medicine 2004, 66: 132-140.

Siguiendo la línea del tercer estudio de la presente tesis doctoral, en este último trabajo se quiso buscar la relación entre el tamaño de la CCA y la alexitimia. Los participantes voluntarios sanos de estudio fueron los mismos que en el primer y tercer trabajo.

A todos ellos se les administró la escala validada al español de la Toronto-Alexithymia Scale (TAS-20) (Martínez-Sánchez, 1996). Se utilizó la puntuación total así como las puntuaciones de tres factores: dificultad en la identificación de sentimientos, dificultad en la descripción de sentimientos y pensamiento orientado externamente. Se analizaron estas puntuaciones como dimensiones continuas.

Las mediciones de la corteza cingulada fueron las mismas que se utilizaron en el anterior trabajo descrito.

A los análisis realizados en el tercer estudio, se le añadieron: (i) un análisis de t-test para detectar diferencias de género en la puntuación total del TAS-20 y un análisis de medidas repetidas ANOVA para los subcomponentes del TAS-20; (ii) una correlación entre el TAS-20 y la superficie CCA y entre el TAS-20 y las puntuaciones del TCI; (iii) finalmente, un análisis de regresión lineal múltiple con la CCA como variable dependiente para analizar el poder predictivo de la puntuación total del TAS-20.

4. Resultados

4.1 Neuroanatomía de la cisura de Silvio y lenguaje.

4.1.1. *Artículo 1: The lateral asymmetry of the human brain studied by volumetric magnetic resonance imaging.*

NeuroImage **17,** 670–679 (2002)
doi:10.1006/nimg.2002.1203

The Lateral Asymmetry of the Human Brain Studied by Volumetric Magnetic Resonance Imaging

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Received November 12, 2001

Improvements in *in vivo* imaging methods have boosted research on brain asymmetry aimed at further establishing putative anatomical substrates for brain functional lateralization and particularly to explain left-hemisphere specialization for language. We analyzed volume asymmetries for major anatomical divisions of the lateral (perisylvian) brain region and their relative white matter content. A total of 100 healthy right-handed subjects were examined with 3D magnetic resonance imaging (MRI). The insular plane was used to limit the lateral brain, and the sylvian fissure and central sulcus to define frontal, parietal, temporal, and temporo-parieto-occipital regions. Results revealed a frontal region showing similar volumes in both hemispheres, a parietal region and a temporal region both larger in the left hemisphere, and a temporo-parieto-occipital region with predominantly right-sided asymmetry. Volume measurements of the parietal, temporal, and temporo-parieto-occipital regions complemented each other and accounted for 58% of planum temporale area variations. All study regions showed significant asymmetry for relative white matter content (percentage of white matter relative to region volume). White matter asymmetry, however, was particularly relevant for the frontal and temporal regions showing a highly frequent left-sided pattern (frontal region, 90%; temporal region, 91% of subjects). Leftward asymmetry in these two regions occurred in both genders, although hemisphere differences were significantly larger in men. Results from this MRI volume analysis of structural asymmetries in the lateral brain region complement data obtained by other methods and suggest a high occurrence of leftward asymmetry for relative white matter content in language-related regions.

INTRODUCTION

Evolution differentiation entailed a functional specialization of both brain hemispheres that has largely contributed to human advantage in the cognitive domains (Hiscock and Kinsbourne, 1995). Anatomical differences between left and right brain sides seem to be less apparent. Nonetheless, there are specific sites where hemisphere asymmetry is evident, such as the lateral brain region surrounding the sylvian fissure.

The posterior end of the sylvian fissure is frequently asymmetrical with sharper angulation on the right side (Steinmetz *et al.*, 1991; Witelson and Kigar, 1992; Foundas *et al.*, 1999). The planum temporale (superior temporal cortex behind Heschl's gyrus) and the parietal operculum are larger in the left hemisphere for most right-handed subjects (Geschwind and Levitsky, 1968; Habib *et al.*, 1995). Anatomical asymmetries have also been described for specific areas of the lateral frontal cortex (Uylings *et al.*, 2000). It seems likely that perisylvian asymmetries are involved in left-hemisphere specialization for language. It is, however, noteworthy, that the frequency of left-sided patterns reported in morphological studies is usually lower than the prevalence of left-hemisphere dominance for language (Geschwind and Levitsky, 1968; Albanese *et al.*, 1989; Witelson and Kigar, 1992; Shapleske *et al.*, 1999).

Research using volume measurements provided new insights suggesting that asymmetries may be particularly relevant for regional tissue composition (Penhune *et al.*, 1996; Anderson *et al.*, 1999; Good *et al.*, 2001). These authors proposed that greater white matter content in the left Heschl's gyrus (Penhune *et al.*, 1996) and left posterior superior temporal lobe (Anderson *et*

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1053-8119/02 $35.00

al., 1999) may account for left-hemisphere advantage in processing the rapidly varying acoustic signals conveyed in speech sounds. Paus *et al.* (1999) demonstrated an age-related increase in white matter density of fiber tracts laterally connecting left frontal and temporal lobes.

We used 3D magnetic resonance imaging (MRI) to analyze volume asymmetries for major anatomical divisions of the lateral-perisylvian brain region and their relative white matter content in 100 healthy right-handed subjects. The insular plane was used to limit the lateral brain, and the sylvian fissure and central sulcus to define frontal, parietal, temporal, and temporo-parieto-occipital (TPO) regions. Correlations of measured volumes with the planum temporale area were also investigated.

MATERIALS AND METHODS

Subjects

A total of 100 healthy volunteers participated in this study, including 50 women and 50 men aged between 20 and 40 years. Subjects were recruited in the university environment of Barcelona and were all screened to exclude a positive history of neurological, psychiatric, and serious medical disorders, as well as for alcohol and drug abuse. Right-hand preference according to the Edinburgh Inventory (Oldfield, 1971) and a normal MRI examination were required. Mean age $\pm$ SD for the final sample was 25.5 $\pm$ 3.9 years (25.5 $\pm$ 3.7 years for women and 25.5 $\pm$ 4.2 years for men). IQ estimated using the verbal part of the Kaufman Brief Intelligence Test (Kaufman and Kaufman, 1994) was 108.6 $\pm$ 6.1 in women and 108.1 $\pm$ 6.2 in men. All subjects were in final year of university or graduates. Written informed consent was obtained for each subject and the study received approval from the ethical committee of our institution.

MRI Examination

All imaging studies were acquired using a 1.5-T magnet (Signa, GE Medical Systems, Milwaukee, WI). A 60-slice 3D spoiled gradient-recalled acquisition sequence was obtained in the sagittal plane. Acquisition parameters were TR 40 ms, TE 4 ms, pulse angle 30°, field of view 26 cm, and matrix size 256 $\times$ 192 pixels. Section thickness varied according to brain size, ranging from 2.4 to 2.6 mm.

The image analysis was performed on an auxiliary workstation (SPARCstation 20; Sun Microsystems, Mountain View, CA), using commercially available software (Advantage Windows, Version 2.0, GE Medical Systems). This system enabled us to construct 3D brain models, to identify and isolate specific brain regions, and to perform volume measurements of the isolated structures. Each MRI scan series was labeled with a reference number and images were displayed with no graphic overlay so that the investigator was blind to the subject's identification, including gender, and no left/right reference appeared on the screen. In addition, orthogonal views used to assist image analysis (axial and coronal) were flipped 180° (mirror images) at random to ensure operator blindness to the brain side (the system allows flipping of orthogonal projections using the "oblique display" option).

Image processing. A 3D MRI model of each subject's head was constructed and reformatted to high-resolution 1-mm slices. Head rotations detected on axial and coronal views were corrected. Thereafter, the brain was isolated from the surrounding cerebrospinal fluid (CSF) by means of volume segmentation and standard image processing tools (erosion, "open bridges," and dilation). This procedure was visually guided by the operator. Thresholding between gray and white matter was established at this stage using the histogram of MRI intensities across the isolated brain. The minimum value between gray and white matter peaks was used to separate both tissue types.

The next step involved isolating the lateral-perisylvian region in each hemisphere. This region included brain tissue lateral to the insula and its medial limit was operatively defined by a sagittal plane separating the frontoparietal operculum and the insula (Fig. 1). Specifically, this plane passed tangentially to the most medially lying convolution of the frontoparietal operculum and corresponded to the point where Heschl's gyrus intersects with the insula. Simultaneous real-time visualization of the cutting outcome on sagittal projections served to accurately adjust the reference plane at a similar anatomical location in both brain sides.

Region definition. Four different regions were identified in the lateral brain using the two primary sulci of the convexity (Fig. 2). Anteriorly, the sylvian fissure and the central sulcus (with downward prolongation to join the sylvian fissure) delimited the frontal region. Posteriorly, the central sulcus and the sylvian fissure (with upward prolongation parallel to the postcentral sulcus) delimited the parietal region. The temporal region was defined by the sylvian fissure and a line perpendicular to the major edge of the temporal lobe crossing the sylvian fissure (horizontal ramus) at its endpoint. The major edge of the temporal lobe was defined as the anterior–posterior line that divides the temporal lobe into two parts (superior and inferior) showing similar size. The posterior limits of the temporal and parietal regions defined our temporo-parieto-occipital (TPO) region.

The process of delimiting the regions was assisted by "computer-simulated craniotomy" models (Fig. 2). These MRI models are routinely used in our center to assist neurosurgery (Pujol *et al.*, 1998) as they provide an accurate display of the lateral sulcal pattern. In this

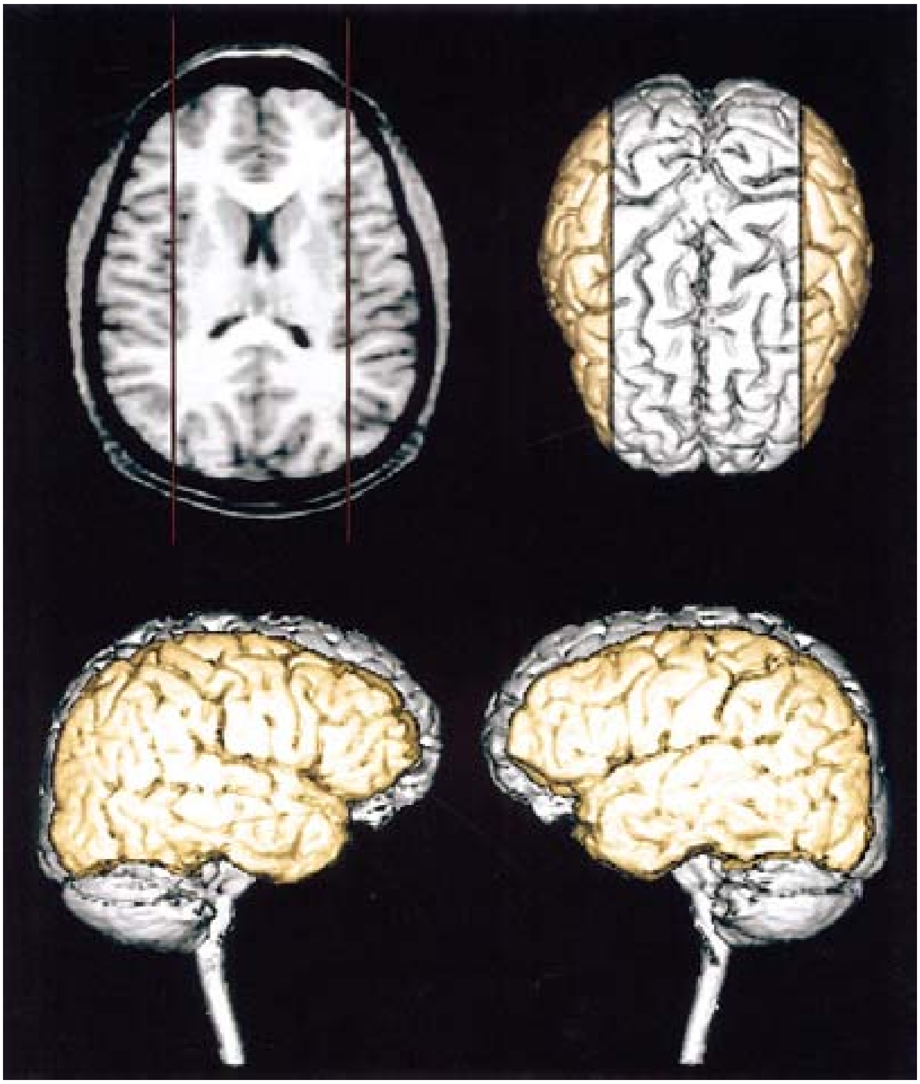

FIG. 1. The lateral-perisylvian region considered in this study (colored tissue). The sagittal plane separating the frontoparietal operculum and the insula was used to medially limit this region (top left).

study, "simulated craniotomies" were modified to project both left and right hemispheres from the left lateral view to maintain operator blindness to hemisphere (Fig. 2, bottom).

Measurements. The anatomical landmarks described above were identified on consecutive sagittal sections and each specified region was manually traced using a mouse-driven computer-guided cursor and paintbrush tools. Each region of interest was defined and separated from the rest of the tissue slice by slice. The selection of all defined sagittal sections allowed us to isolate regional parenchyma volumes including both cortex and white matter. The analysis system directly provided the volume (ml) for each isolated tissue volume. White matter volumes were obtained after applying the segmentation threshold.

Separate asymmetry analyses were performed for region volumes and for a single tissue composition measurement, namely, percentage of white matter relative to region volume (100 × white matter volume/region volume). The relative white matter content may inform as to function-related remodeling in adult brain (Pujol *et al.*, 1993; Sowell *et al.*, 2001). Evidently, this percentage is also the inverse measurement of relative gray matter content.

An asymmetry index was computed for each region volume and for each tissue composition measurement according to the expression $100 \times (L - R)/0.5 \times (L + R)$, where L and R were measurements for the left and right hemispheres. The symmetry range was established between the index values -10 and $+10$ (Galaburda *et al.*, 1987; Shapleske *et al.*, 1999). Asymmetrical cases, therefore, were those showing values below -10 (right-sided pattern) or above $+10$ (left-sided pattern).

Measurement reliability was also confirmed in blinded conditions by repeating the image analysis in

FIG. 2. Region definition. The central sulcus and the sylvian fissure were used to delimit frontal, parietal, temporal, and temporo-parieto-occipital regions of interest (central images). "Computed-simulated craniotomies" assisted identification of these anatomical landmarks (top). Left and right "simulated craniotomies" were projected from the left lateral view (bottom) to maintain operator blindness to hemisphere.

30 randomly selected MRI exams 6 weeks later. We found intraclass correlation coefficients ranging from 0.89 (right parietal region) to 0.92 (left temporal region).

Planum temporale. Correlations between measured volumes and planum temporale area were also investigated in this study. We measured the planum temporale area as defined by Geschwind and Levitsky

TABLE 1

Asymmetry Analysis for Regional Brain Volumes[a]

	Left mean (SD)	Right mean (SD)	Mean difference	99% CI of the difference	t	P
			Volume (ml)			
Whole lateral brain	194.2 (19.2)	192.5 (19.7)	1.7	−1.9 to 5.3	1.2	0.225
Frontal region	46.4 (6.7)	48.0 (7.5)	−1.6	−3.4 to 0.3	−2.2	0.028
Parietal region	36.7 (7.8)	26.7 (6.4)	10.0	7.8 to 12.1	12.1	<0.001
Temporal region	68.8 (11.4)	59.0 (10.1)	9.9	6.9 to 12.8	8.9	<0.001
TPO region	42.2 (14.6)	58.8 (11.9)	−16.6	−21.1 to −12.1	−9.7	<0.001

	Left > right	Left = right	Left < right
		Asymmetry (No. of subjects)	
Whole lateral brain	10	87	3
Frontal region	14	53	33
Parietal region	82	17	1
Temporal region	66	26	8
TPO region	8	19	73

[a] CI, confidence interval; SD, standard deviation; TPO, temporo-parieto-occipital.

(1968), using the method described by Kulynych *et al.* (1994). The anterior limit of the planum temporale was defined as Heschl's sulcus (the sulcus immediately posterior to the most anterior transverse gyrus) and the posterior limit conformed to the point where the horizontal sylvian fissure either terminates or bifurcates. Individually for each hemisphere, a line was traced across the lateral aspect of the isolated brain model following this defined lateral border. Tissue above this level was removed and a rendered view of the planum was exposed using an oblique-axial projection. Regions of interest (ROIs) of the planum temporale surface were drawn manually on these supratemporal renderings. The researcher was blind to subject data, including region volume measurements, but not to the left–right brain side during planum temporale measurement.

Statistical Analysis

Mean volume differences between both hemispheres were analyzed on the basis of 99% confidence intervals and Student t tests. Possible gender effects (women vs men) were evaluated using repeated-measures (left vs right) analysis of variance (ANOVA). Brain volume was included in this analysis as a covariate. Asymmetry index rates between regions were compared with a χ^2 test. Pearson's correlations served to examine the association between region volume measurements and planum temporale areas. A stepwise multiple regression analysis established the best prediction of planum temporale area from region volume measurements.

RESULTS

Asymmetry Analysis for Region Volumes

The mean volume of the isolated lateral-perisylvian parenchyma was similar in both hemispheres (Table 1) and represented 14.8% (left side) and 14.6% (right side) of brain volume (mean ± SD brain volume in our subjects was 1316 ± 109 ml). Asymmetrical cases were not frequent for the whole lateral brain, as only 10 subjects showed an asymmetry index greater than "+10" (leftward asymmetry) and 3 subjects smaller than "−10" (rightward asymmetry).

By contrast, relevant left–right volume differences were observed for specific anatomical regions. For the frontal region, mean volume difference between hemispheres was small, although asymmetrical cases were relatively frequent (Table 1). The parietal and temporal regions were consistently larger in the left hemisphere, both on average (Table 1, top) and in the majority of subjects (Table 1, bottom). An inverse situation was observed for the TPO region that showed larger volumes in the right hemisphere in 73% of subjects. Figure 3 illustrates the results from a representative subject.

Gender analysis. We found no gender effect in this analysis.

Correlation with planum temporale measurements. The mean ± SD planum temporale area was 630.7 ± 177.5 mm^2 in the left hemisphere and 413.6 ± 196.9 mm^2 in the right hemisphere (mean difference, 217.1 mm^2; 95% confidence interval, 174.2–260.0 mm^2; t = 10.0; $P < 0.001$). Planum temporale asymmetry index ranged from −34.6 to 81.5 (mean ± SD, 22.8 ± 24.8). A

TABLE 2

Asymmetry Analysis for Relative White Matter Content[a]

	Left mean (SD)	Right mean (SD)	Mean difference	99% CI of the difference	t	P
			Relative volume (%)			
Whole lateral brain	26.4 (3.8)	22.9 (3.6)	3.5	3.0 to 4.0	17.3	<0.001
Frontal region	23.7 (4.1)	18.7 (4.0)	5.0	4.4 to 5.6	20.9	<0.001
Parietal region	32.9 (5.1)	26.4 (5.2)	6.5	5.7 to 7.3	20.7	<0.001
Temporal region	27.8 (4.1)	21.5 (3.9)	6.3	5.6 to 7.1	21.6	<0.001
TPO region	20.2 (5.1)	25.8 (4.8)	−5.6	−6.9 to −4.2	−10.8	<0.001

	Left > right	Left = right	Left < right
	Asymmetry (No. of subjects)		
Whole lateral brain	69	31	0
Frontal region	90	10	0
Parietal region	83	17	0
Temporal region	91	8	1
TPO region	4	24	72

[a] CI, confidence interval; SD, standard deviation; TPO, temporo-parieto-occipital.

total of 70 subjects showed leftward asymmetry, 12 subjects a right-sided pattern ($\chi^2 = 41.0$; $P < 0.001$), and 18 subjects no asymmetry. When these frequencies were compared with those reported in Table 1 (bottom) for regional brain volumes, differences were not significant in the case of the temporal region ($\chi^2 = 2.4$; $P = 0.306$), but were so in the other regions (frontal, $\chi^2 = 64.4$, $P < 0.001$; parietal, $\chi^2 = 10.3$, $P = 0.006$; TPO, $\chi^2 = 93.1$, $P < 0.001$). Note that the frequency of planum temporale left-sided asymmetry was similar to the frequency of TPO right-sided asymmetry (i.e., 70% vs 73%, $\chi^2 = 0.2$, $P = 0.631$).

Pearson's correlations between region volumes and planum temporale area of the corresponding hemisphere (200 measurements, 100 subjects with two hemispheres) yielded, $r = 0.07$ and $P = 0.326$ for the frontal region, $r = 0.64$ and $P < 0.001$ for the parietal region, $r = 0.67$ and $P < 0.001$ for the temporal region, and $r = -0.57$ and $P < 0.001$ for the TPO region. Thus, we found larger planum temporale in subjects with larger parietal and temporal volumes and smaller TPO volumes.

In the stepwise multiple regression analysis performed to investigate possible combination effects, the temporal region volume entered the equation in the first step, the parietal region in the second step and the TPO region in the third and last step (multiple $r = 0.77$, adjusted $r^2 = 0.58$, $F(3,196) = 93.8$; and $P < 0.001$). The standardized β coefficient for the temporal region was 0.41 ($t = 7.3$; $P < 0.001$), for the parietal region it was 0.31 ($t = 5.2$; $P < 0.001$), and for the TPO region it was -0.21 ($t = -3.7$; $P < 0.001$). This analysis indicates that volume measurements of the three surrounding regions complemented each other and accounted for 58% of planum temporale area variations.

Asymmetry Analysis for Relative White Matter Content

Asymmetries in tissue composition were analyzed using the percentage of white matter relative to region volume. White matter percentage for the entire brain showed a mean ± SD of 33.4 ± 4.0%. Smaller values were obtained for the left (26.4%) and right (22.9%) lateral-perisylvian parts of the brain. The 3.5 percentage difference between hemispheres was highly significant (Table 2) and represents a left-hemisphere increase of 15%. Therefore, we defined a lateral brain region showing similar volumes in both hemispheres, but with different tissue composition (Tables 1 and 2).

All anatomical divisions of the lateral brain were largely asymmetrical for relative white matter content. The frontal, parietal, and temporal regions showed leftward asymmetry and the TPO region a reverse right-sided pattern (Table 2).

The frontal and temporal regions showed the most consistent hemisphere differences (see the narrow 99% confidence intervals and the highly frequent left-sided asymmetry in Table 2). Remarkably, rightward asymmetry was exceptional, irrespective of applied symmetry ranges. Indeed, just two subjects showed a greater right than left white matter percentage (asymmetry index below zero) in the frontal region and only one in the temporal region. In essence, our analysis indicates that (1) a left-sided pattern for relative white matter content is highly frequent for these two regions, (2) there is a reduced number of subjects showing little or no asymmetry (exact frequency depends on arbitrary criteria defining the symmetry range), and (3) rightward asymmetry is exceptional.

Gender analysis. ANOVA showed no significant main effect of gender for any region studied. We did,

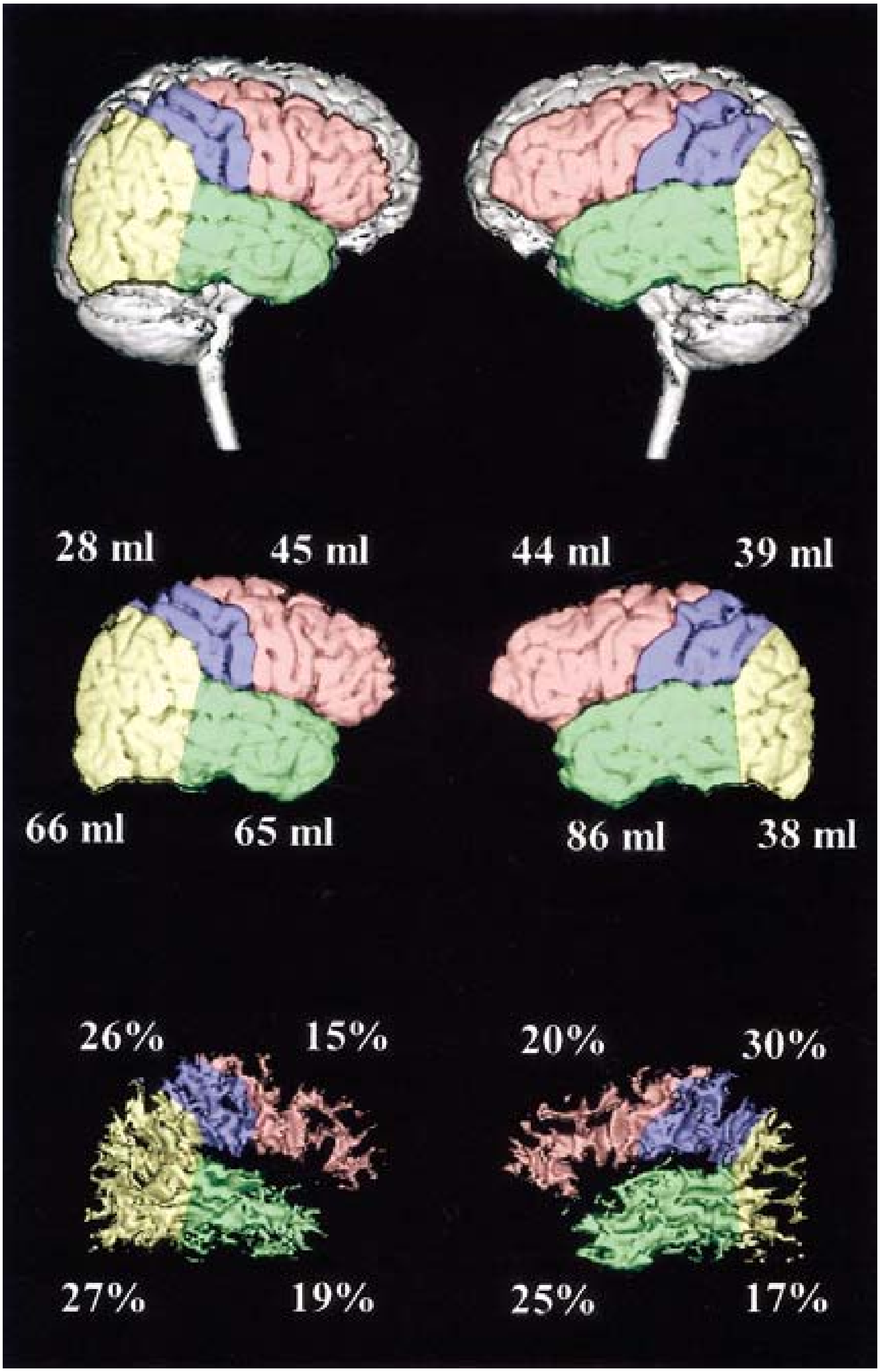

FIG. 3. Results from a representative subject showing all the asymmetries described for the entire sample. Region volumes (ml) and percentages of white matter (%) are reported for this particular case in pictures showing the regions (central images) and their segmented white matter (bottom). Observe the tendency of infrasylvian white matter to accumulate in the temporal region on the left and in the temporo-parieto-occipital region on the right hemisphere.

however, find significant gender × side interactions for the frontal ($F(1,98) = 12.3$; $P = 0.001$) and the temporal ($F(1,98) = 10.0$; $P = 0.002$) regions.

Mean ± SD left–right difference for percentage of frontal white matter was 4.2 ± 2.3 points in women (99% CI = 3.3–5.1; $t(49) = 13.2$; $P < 0.001$) and 5.8 ±

2.7 points in men (99% CI = 4.9–6.6; $t(49) = 18.1$; $P < 0.001$). Post hoc t test revealed that the difference between genders was significant ($t = 3.5$; $P = 0.001$). For the temporal region, hemisphere difference was 5.4 ± 2.4 points in women (99% CI = 4.5–6.4; $t(49) = 15.7$; $P < 0.001$) and 7.2 ± 3.1 points in men (99% CI = 6.0–8.4; $t(49) = 16.4$; $P < 0.001$). The difference between genders was also significant in post hoc t test ($t = 3.2$; $P = 0.002$). Therefore, both women and men showed a highly significant leftward asymmetry for white matter in regions directly related to language operations, although asymmetry was significantly more pronounced in men.

DISCUSSION

We used the insular plane to define a lateral portion of the brain showing similar volumes in both hemispheres. In this perisylvian area, the central sulcus and the sylvian fissure allowed distinction of a frontal region showing no relevant left–right volume difference, a parietal and a temporal region both larger in the left hemisphere, and a TPO region with predominantly right-sided asymmetry. All study regions showed significant asymmetry for relative white matter content. White matter asymmetry, however, was particularly consistent for the frontal and temporal regions, showing a highly frequent left-sided pattern.

Witelson and Kigar (1992) stated that the basic asymmetry in the lateral brain is in the position where the sylvian fissure turns up as a result of surrounding gyrus size. The asymmetry pattern observed in our study closely reflects this key morphology feature. Large parietal and temporal volumes and small TPO volumes coincide with predominantly flat sylvian fissures on the left hemisphere. The reverse pattern occurs on the right showing sharper sylvian fissure angulation.

The planum temporale is an asymmetrical part of the temporal lobe consisting of auditory association cortex. Larger growth of the left planum temporale is thought to play a role in left-hemisphere language specialization (Shapleske *et al.*, 1999). We found that planum temporale anatomical variations were mostly explained by the combination of the parietal, temporal, and TPO volumes. This finding partly conforms to the hypothesis of Binder *et al.* (1996) proposing that both the point of upward sylvian fissure deflection and the planum temporale area depend on the relative size of the perirolandic (and frontal) tissue and posterior parietal lobe. Our data support a three-way regional influence on planum morphology, involving all the structures surrounding the posterior sylvian fissure, but not the lateral frontal lobe. This correlational analysis, however, does not imply a causal and directional relationship between surrounding areas and the planum. Distant events could also influence the anatomy of this region.

It is not obvious how morphology variations in the posterior perisylvian region may comprehensively account for hemisphere functional specialization. Language is lateralized to the left in about 96% of right-handed subjects (Rasmussen and Milner, 1977; Pujol *et al.*, 1999) and functional lateralization occurs at both perception (temporal) and production (frontal) language levels. We found only 66% of subjects with a larger left temporal region and no clear asymmetry for the frontal region when analyzing total region volumes.

Anatomical asymmetries have also been investigated in the anterior speech region. Results from different studies suggest that relevant asymmetry may occur in restricted areas, particularly in the pars opercularis and pars triangularis of the inferior frontal gyrus (Albanese *et al.*, 1989; Foundas *et al.*, 1996). Authors coincide in that Broca's area anatomy is highly variable across individuals (Tomaiuolo *et al.*, 1999; Amunts *et al.*, 1999), but leftward asymmetry is probably more consistent for citoarchitecturally defined areas (Galaburda, 1980; Amunts *et al.*, 1999) than for macroscopically specified convolutions (Tomaiuolo *et al.*, 1999).

Our white matter analysis depicted an interesting new situation. Incidence of leftward asymmetry for relative white matter content in frontal and temporal regions was very high (>90%) and closer to the frequency of language lateralization in right-handers. Remarkably, reverse rightward asymmetry was exceptional. Our data are congruous with the findings obtained in the recent study by Good *et al.* (2001). They used a powerful voxel-based morphometric method to examine 465 healthy subjects and detected a left-hemisphere white matter increase (and gray matter decrease) relative to the right hemisphere in the "peripheral" (lateral) portion of the frontal and temporal lobes. Good and co-workers' study (2001) and ours may represent two very different anatomical and technical approaches to show relative white matter increase in the regions subserving language and related operations.

Tallal *et al.* (1993) proposed that the left hemisphere is specialized in processing acoustic signals with rapid temporal variations and that this enhanced ability may be the basis of dominance for speech. Penhune *et al.* (1996) demonstrated larger volumes of white matter on left Heschl's gyrus and suggested that left-hemisphere advantage for encoding the rapidly varying speech sounds occurs at the early stages of auditory perception. Anderson *et al.* (1999) observed greater volumes on the left for white matter under the planum temporale showing thicker myelin sheaths. Thus, the dominant hemisphere may also be faster in auditory cortical association operations. Our findings and data from Good *et al.* (2001) suggest a generalized phenomenon involving widely distributed left temporal and frontal areas.

White matter leftward asymmetry in the frontal and temporal regions occurred in both genders, although hemisphere differences were significantly larger in men. This is congruous with clinical, behavioral, and functional data supporting language functions as being less strongly lateralized in women (Springer and Deutsch, 1998). In women, both hemispheres may share the ability to process acoustic signals with rapid temporal variations.

Our parietal region showed frequent leftward asymmetry for total volume and its relative white matter content. This part of the brain may mediate sensory–motor interactions between the anterior and posterior speech regions (Aboitiz and García, 1997; Paus *et al.*, 1999). Functions of the anterior-inferior parietal lobe, however, go beyond the language domain and subserve, for example, primary sensory representation of face, secondary representation of whole body surface, control of precision movements, ideomotor praxis, perception of pain and visceral sensations, and evaluation of affective components of sensory information (Schnitzler *et al.*, 2000). Significantly, white matter lesions in the left frontoparietal operculum were found to be associated with the occurrence of depressive symptoms (Pujol *et al.*, 1997). The role of the inferior-anterior parietal lobe is, therefore, complex. The wealth of functional imaging studies is likely to elucidate the significance of the parietal asymmetry.

The TPO region showed a reverse pattern with relevant right-sided asymmetry. We chose to define a TPO region in our study, not only due to the lack of complete sulcal landmarks delimiting temporo-parieto-occipital boundaries (Ono *et al.*, 1990), but also because the TPO region may play a unifying role allowing multimodal interaction, as in visuospatial integration. The right hemisphere is dominant for many visuospatial functions (Mesulam, 2000). Here, once more, we found a coincidence between hemisphere dominance and the pattern of white matter asymmetry.

There are several potential factors that may contribute to the increase in relative white matter content in the dominant regions. It may be a consequence of a general larger region development (larger regions, more corticocortical and corticosubcortical connections). Increased white matter content may also reflect enlarged diameter of myelinated axons as a result of functional maturity. Alternatively, or additionally, the different hemispheric distribution of white matter could reveal a distinct connectivity pattern for each brain side, showing greater development of intratemporal connections in the left hemisphere and TPO connections in the right. It is interesting to note in Fig. 3 the extent to which the right hemisphere concentrates white matter in the TPO region and the left hemisphere in the temporal region. This type of white matter distribution was previously predicted by Aboitiz and García (1997).

Finally, we would add a methodological comment concerning tissue segmentation. We chose imaging parameters in our 3D sequence to obtain optimal signal/noise ratio without excessive loss in spatial resolution. The brain was isolated from CSF under operator guidance and intensity value histograms of MRI volumes were used to operatively segment gray and white matter. This method entails few technical restrictions and produces acceptable reliability indexes. Nevertheless, there are more sophisticated procedures using multispectral data sets, which are operator independent, or applying algorithms correcting for image nonhomogeneity and artifacts (Clarke *et al.*, 1995). We consider, however, that our whole-brain segmentation procedure should produce minimal left–right bias for tissue composition, as eventual noncorrected segmentation inaccuracies should be consistent across the two hemispheres.

CONCLUSION

We analyzed gross morphology asymmetries of the lateral brain aspect using a volumetric approach. Results expand previous descriptions of asymmetry related to the posterior sylvian fissure anatomy and provide a relevant new finding showing a highly frequent leftward asymmetry for relative white matter content in language-related regions, close to the frequency of language lateralization in right-handers. This finding may be biologically relevant in the extent to which relative white matter content expresses functional maturation of a specific region and may be of potential use for specific clinical applications. Several questions, however, are open to future research. At which stage of brain development is the reported white matter asymmetry established? Could eventual alterations of normal asymmetry be related to the occurrence of language disorders (e.g., dysphasia, dyslexia) or thought disorders (i.e., schizophrenia)? Or could an inverse right-greater-than-left white matter asymmetry predict right-hemisphere dominance for language?

ACKNOWLEDGMENTS

This study was supported in part by the James S. McDonnell Research Grant, Bridging Brain Mind and Behavior Program (2000), and the Direcció General de Recerca de la Generalitat de Catalunya (Grant Nos. 1999SGR-328 and 2000XT-43). We thank Gerald Fannon, Ph.D., for revising the manuscript and Robert Zatorre, Ph.D., for his contribution.

REFERENCES

Aboitiz, F., and García, R. 1997. The anatomy of language revisited. *Biol. Res.* **30:** 171–183.

Albanese, E., Merlo, A., Albanese, A., and Gomez, E. 1989. Anterior speech region: Asymmetry and weight–surface correlation. *Arch. Neurol.* **46:** 307–310.

Amunts, K., Schleicher, A., Bürgel, U., Mohlberg, H., Uylings, H. B. M., and Zilles, K. 1999. Broca's region revisited: Cytoarchitecture and intersubject variability. *J. Comp. Neurol.* **412:** 319–341.

Anderson, B., Southern, B. D., and Powers, R. E. 1999. Anatomic asymmetries of the posterior superior temporal lobes: A postmortem study. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **12:** 247–254.

Binder, J. R., Frost, J. A., Hammeke, T. A., Rao, S. M., and Cox, R. W. 1996. Function of the left planum temporale in auditory and linguistic processing. *Brain* **119:** 1239–1247.

Clarke, L. P., Velthuizen, R. P., Camacho, M. A., Heine, J. J., Vaidyanathan, M., Hall, L. O., Thatcher, R. W., and Silbiger, M. L. 1995. MRI segmentation: Methods and applications. *Magn. Reson. Imaging* **13:** 343–368.

Foundas, A. L., Leonard, C. M., Gilmore, R. L., Fennell, E. B., and Heilman, K. M. 1996. Pars triangularis asymmetry and language dominance. *Proc. Natl. Acad. Sci. USA* **93:** 719–722.

Foundas, A. L., Faulhaber, J. R., Kulynych, J. J., Browning, C. A., and Weinberger, D. R. 1999. Hemispheric and sex-linked differences in Sylvian fissure morphology: A quantitative approach using volumetric magnetic resonance imaging. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **12:** 1–10.

Galaburda, A. M. 1980. La région de Broca: Observations anatomiques faites un siècle après la mort de son découvreur. *Rev. Neurol.* **136:** 609–616.

Galaburda, A. M., Corsiglia, J., Rosen, G. D., and Sherman, G. F. 1987. Planum temporale asymmetry, reappraisal since Geschwind and Levitsky. *Neuropsychologia* **25:** 853–868.

Geschwind, N., and Levitsky, W. 1968. Human brain: Left–right asymmetries in temporal speech region. *Science* **161:** 186–187.

Good, C. D., Johnsrude, I., Ashburner, J., Henson, R. N. A., Friston, K. J., and Frackowiak, R. S. J. 2001. Cerebral asymmetry and the effects of sex and handedness on brain structure: A voxel-based morphometric analysis of 465 normal adult human brains. *NeuroImage* **14:** 685–700.

Habib, M., Robichon, F., Lévrier, O., Khalil, R., and Salamon, G. 1995. Diverging asymmetries of temporo-parietal cortical areas: A reappraisal of Geschwind/Galaburda theory. *Brain Lang.* **48:** 238–258.

Hiscock, M., and Kinsbourne, M. 1995. Phylogeny and ontogeny of cerebral lateralization. In *Brain Asymmetry* (R. J. Davidson and K. Hugdahl, Eds.), pp. 535–578. MIT Press, Cambridge, MA.

Kaufman, A. S., and Kaufman, N. L. 1994. *Kaufman Brief Intelligence Test (K-BIT)*. Am. Guidance Service, Circle Pines, MN.

Kulynych, J. J., Vladar, K., Jones, D. W., and Weinberger, D. R. 1994. Gender differences in the normal lateralization of the supratemporal cortex: MRI surface-rendering morphometry of Heschl's gyrus and the planum temporale. *Cereb. Cortex* **4:** 107–118.

Mesulam, M. M. 2000. Behavioral neuroanatomy: Large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In *Principles of Behavioral and Cognitive Neurology* (M. M. Mesulam, Ed.), 2nd ed., pp. 1–120. Oxford Univ. Press, New York.

Oldfield, R. C. 1971. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* **9:** 97–113.

Ono, M., Kubik, S., and Abernathey, C. D. 1990. *Atlas of the Cerebral Sulci*. Thieme, Stuttgart.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D. L., Blumenthal, J., Giedd, J. N., Rapoport, J. L., and Evans, A. C. 1999. Structural maturation of neural pathways in children and adolescents: In vivo study. *Science* **283:** 1908–1911.

Penhune, V. B., Zatorre, R. J., MacDonald, J. D., and Evans, A. C. 1996. Interhemispheric anatomical differences in human primary auditory cortex: Probabilistic mapping and volume measurement from magnetic resonance scans. *Cereb. Cortex* **6:** 661–672.

Pujol, J., Vendrell, P., Junqué, C., Martí-Vilalta, J. L., and Capdevila, A. 1993. When does human brain development end? Evidence of corpus callosum growth up to adulthood. *Ann. Neurol.* **34:** 71–75.

Pujol, J., Bello, J., Deus, J., Martí-Vilalta, J. L., and Capdevila A. 1997. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* **49:** 1105–1110.

Pujol, J., Conesa, G., Deus, J., López-Obarrio, L., Isamat, F., and Capdevila, A. 1998. Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. *J. Neurosurg.* **88:** 863–869.

Pujol, J., Deus, J., Losilla, J. M., and Capdevila, A. 1999. Cerebral lateralization of language in normal left-handed people studied by functional MRI. *Neurology* **52:** 1038–1043.

Rasmussen, T., and Milner, B. 1977. The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann. NY Acad. Sci.* **299:** 355–369.

Schnitzler, A., Seitz, R. J., and Freund, H. J. 2000. The somatosensory system. In *Brain Mapping: The Systems* (A. W. Toga and J. C. Mazziotta, Eds.), pp. 291–329. Academic Press, San Diego.

Shapleske, J., Rossell, S. L., Woodruff, P. W. R., and David, A. S. 1999. The planum temporale: A systematic, quantitative review of its structural, functional and clinical significance. *Brain Res. Rev.* **29:** 26–49.

Sowell, E. R., Thompson, P. M., Tessner, K. D., and Toga, A. W. 2001. Accelerated brain growth and cortical gray matter thinning are inversely related during post adolescent frontal lobe maturation. *NeuroImage* **13:** S1103.

Springer, S. P., and Deutsch, G. 1998. Sex differences in cognition and asymmetry. In *Left Brain, Right Brain: Perspectives from Cognitive Neuroscience* (R. C. Atkinson, G. Lindzey, and R. F. Thompson, Eds.), 5th ed., pp. 139–156. Freeman, New York.

Steinmetz, H., Volkmann, J., Jäncke, L., and Freund, H. J. 1991. Anatomical left–right asymmetry of language-related temporal cortex is different in left- and right-handers. *Ann. Neurol.* **29:** 315–319.

Tallal, P., Miller, S., and Fitch, R. H. 1993. Neurobiological basis of speech: A case for the preeminence of temporal processing. *Ann. NY Acad. Sci.* **682:** 27–47.

Tomaiuolo, F., MacDonald, J. D., Caramanos, Z., Posner, G., Chiavaras, M., Evans, A. C., and Petrides, M. 1999. Morphology, morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an in vivo MRI analysis. *Eur. J. Neurosci.* **11:** 3033–3046.

Uylings, H. B. M., Malofeeva, L. I., Bogolepova, I. N., Amunts, K., and Zilles, K. 2000. Broca's language area from a neuroanatomical and developmental perspective. In *The Neurocognition of Language* (C. M. Brown and P. Hagoort, Eds.), pp. 319–336. Oxford Univ. Press, Oxford, UK.

Witelson, S. F., and Kigar, D. L. 1992. Sylvian fissure morphology and asymmetry in men and women: Bilateral differences in relation to handedness in men. *J. Comp. Neurol.* **323:** 326–340.

4.1.2. *Artículo 2: Age-related brain structural alterations in children with specific language impairment*

Age-Related Brain Structural Alterations in Children With Specific Language Impairment

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Abstract: Previous neuroimaging studies have suggested that children with specific language impairment (SLI) may show subtle anatomical alterations in specific brain regions. We aimed to characterize structural abnormalities in children with SLI using a voxel-wise analysis over the whole brain. Subjects covered a wide age range (5–17 years) in order to assess the dynamic nature of the disorder across childhood. Three-dimensional MRIs were collected from 36 children with SLI and from a comparable group of healthy controls. Global gray and white matter measurements were obtained for each subject, and voxel-based morphometry (VBM) was used to evaluate between-group differences in regional brain anatomy. Possible age-related changes were assessed in separate analyses of younger (below 11 years of age) and older children. SLI patients showed larger global gray and white matter volumes, particularly in the younger subgroup. Voxel-wise analyses of the whole sample showed two regions of increased gray matter volume in SLI: the right perisylvian region and the occipital petalia. Age-group analyses suggested a more extended pattern of volume increases in the younger subjects, which included entorhinal, temporopolar, caudate nucleus, motor-precentral and precuneus gray matter, and white matter of the frontal and temporal lobes. Our results suggest that in the SLI brain there are enduring anatomical alterations that exist across a wide age range, as well as a distributed pattern of abnormalities that appear to normalize with development. They also suggest that the neuroanatomical basis of SLI may be better characterized by considering the dynamic course of the disorder throughout childhood. *Hum Brain Mapp 30:1626–1636, 2009.* © 2008 Wiley-Liss, Inc.

Key words: child and adolescent; specific language impairment; MRI; neuroanatomy; voxel-based morphometry (VBM)

INTRODUCTION

Specific language impairment (SLI) is defined as a failure to acquire age-appropriate language skills in children with normal opportunities to learn language, no obvious sensorial or neurological alterations, and with otherwise typical development [World Health Organization, 1992]. The language phenotype of children with SLI is heterogeneous, presenting with varying combinations of deficits in the expressive and receptive domains, as well as with literacy problems [McArthur et al., 2000]. Phonological processing is typically altered in SLI [Bishop and Snowling,

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Received for publication 2 February 2008; Revised 19 May 2008; Accepted 22 May 2008
DOI: 10.1002/hbm.20620
Published online 9 September 2008 in Wiley InterScience (www.interscience.wiley.com).

2004], with both deficits in phonological memory [Gathercole and Baddeley, 1990] and phonological awareness [Snowling et al., 2000] being reported. However, language alteration is not restricted to phonology, as impairments in morphology and syntax, and poor lexical and discourse skills, have also been described [Bishop and Snowling, 2004].

The causes and biological basis of SLI are poorly understood [Webster and Shevell, 2004]. Although there are some reports of central nervous system abnormalities [Guerreiro et al., 2002; Trauner et al., 2000], brain magnetic resonance imaging (MRI) of children with SLI usually appears normal upon visual inspection. Nevertheless, subtle structural abnormalities, such as alterations of the normal (leftward) asymmetry pattern of perisylvian language-related regions, have been consistently described in group-level morphometry studies [De Fossé et al., 2004; Gauger et al., 1997; Herbert et al., 2005; Jernigan et al., 1991; Leonard et al., 2002, 2006; Plante et al., 1991]. Reports of associated volumetric alterations, however, have been notably heterogeneous. Thus, while some authors reported left hemisphere volume reductions in the pars triangularis of the left inferior frontal gyrus [Gauger et al., 1997] and in the posterior perisylvian cortex [Jernigan et al., 1991], others have described a bilateral reduction of the planum temporale [Preis et al., 1998] or a specific volume increase of the right perisylvian region [Plante et al., 1991]. Likewise, reports of white matter alterations include decreases in motor, premotor, and temporopolar regions of the left hemisphere [Jancke et al., 2007], as well as global increases in the frontal, temporal, and occipital lobes [Herbert et al., 2004]. By comparison, medial white matter structures, such as the corpus callosum, are typically unaffected [Herbert et al., 2004; Preis et al., 2000]. There are also mixed results regarding global brain volume differences, from reductions in cerebral [Leonard et al., 2002] or forebrain volumes [Preis et al., 1998], to larger global brain volumes in SLI [Herbert et al., 2003b]. In this context, automated voxel-wise volumetric methods, such as voxel-based morphometry (VBM) [Ashburner and Friston, 2000], may be useful in characterizing morphometric alterations at a higher spatial resolution over the entire brain. Indeed, this structural analysis technique has already been applied in one study with SLI patients [Jancke et al., 2007].

Neuroanatomical anomalies in SLI might also be more apparent if the disorder were considered in a developmental context. At the behavioral level, there is some evidence indicating a dynamic nature to SLI. For example, the different phenotypes of this disorder are highly variable during children's development [Conti-Ramsden and Botting, 1999], suggesting that, at a given point in time, the precise nature of the language impairment may depend on the interaction with the normal pattern of development throughout childhood [Botting, 2005; Thomas and Karmiloff-Smith, 2002]. If this is indeed the case, coexisting anatomical alterations might also manifest developmentally, as normal brain maturation is known to occur along region-specific time courses [Lenroot and Giedd, 2006].

The purpose of this study was to investigate the existence of general as well as age-related anatomical alterations in children with SLI relative to control subjects. We used VBM to study volumetric abnormalities at a voxel-by-voxel basis over the whole brain.

MATERIALS AND METHODS

Participants

Thirty-six children with SLI participated in the study. This included 24 boys and 12 girls with an age range of 5–17 years (mean ± SD of 10.58 ± 2.80 years). Four children were left-handed, which is consistent with reports of a distribution of left-handers in SLI that is not different from the normal population [Bishop, 2005]. All children were referred to the neurodevelopmental disorders unit of Sant Joan de Déu Hospital, Barcelona, due to poor school achievement and suspected language disorder, and were consecutively included at the initial or follow-up visits. SLI was defined as a disturbance in the normal pattern of language acquisition from the early stages of development that was accompanied by a normal development in other domains, and could not be attributable to neurological conditions, sensory impairments, or environmental factors [World Health Organization, 1992].

Specific neuropsychological assessment was used to substantiate a deficit in the expressive, expressive/receptive, or high order language domains, and a normal nonverbal function. According to Rapin [1996], five children fulfilled criteria for a speech programming deficit, 18 for a phonological-syntactic deficit, and eight for a lexical deficit. The remaining five children could not be exclusively classified into one particular subgroup. Language assessment included the Spanish versions of the Peabody picture vocabulary test (PPVT) [Dunn and Dunn, 1997], the Token test for children (TTFC) [DiSimoni, 1978], and the Illinois test of psycholinguistic abilities (ITPA, four subscales administered, see Table I) [Kirk et al., 1968]. In addition, the Spanish version of the Wechsler Intelligence Scale for Children (WISC-III) [Wechsler, 1991] was administered as a general intelligence test assessing both language and non-language functions. Table I presents the scores of these assessments for the whole sample of children with SLI and split by age-group (see below). In all cases, scores more than 1 SD below the population mean were considered abnormal (indicated with an asterisk in Table I). Despite the wide age range of our sample, we chose to use the same scales in all children with SLI. In children older that 12 years, adult percentiles and normative values for 12-year-old children were used in the TTFC and the ITPA subscales, respectively. In any case, this did not affect the diagnosis of SLI, which was always established before 12 years of age.

At the initial visit a parental interview was performed to identify possible relevant conditions in the medical history of the patient and the existence of a language deficit from

TABLE I. Neuropsychological performance of children with SLI

	Mean (SD)								
	Full-scale IQ[a]	Verbal IQ[a]	Perform. IQ[a]	PPVT[b]	TTFC[b]	ITPA (AA)[b]	ITPA (AC)[b]	ITPA (AR)[b]	ITPA (GC)[b]
Whole SLI sample (n = 36)	84.58* (15.89)	74.61* (13.42)	100.48 (12.72)	39.28* (8.49)	40.43 (10.47)	36.95* (7.12)	40.74 (8.90)	43.25 (8.46)	34.92* (9.90)
Younger children with SLI (n = 19)	88.83 (18.99)	78.33* (14.81)	104.33 (14.47)	41.61 (9.62)	44.62 (10.67)	35.83* (7.18)	38.20* (6.92)	41.44 (8.31)	32.11* (7.70)
Older children with SLI (n = 17)	80.33* (12.31)	69.46* (9.49)	95.15 (7.38)	36.29* (5.82)	36.80* (9.13)	40.83 (6.16)	51.67 (9.28)	50.00 (5.61)	45.42 (11.17)

IQ, intelligence quotient; ITPA (AA), Illinois test of psycholinguistic abilities (auditory association); ITPA (AC), Illinois Test of Psycholinguistic Abilities (auditory closure), ITPA (AR) = Illinois Test of Psycholinguistic Abilities (auditory reception); ITPA (GC), Illinois test of psycholinguistic abilities (grammatical closure); PPTV, Peabody picture vocabulary test; TTFC, Token test for children.

*Score more than 1 SD below the age-adjusted population mean.

[a] IQ scores have a population mean ± SD = 100 ± 15.

[b] PPVT, TTFC and ITPA scores are presented as T scores of mean ± SD = 50 ± 10.

the early stages of development. Exclusion criteria included global developmental delay (specifically, no children with autism spectrum disorders were selected), the presence of other relevant medical and neurological conditions, sensorial or gross motor deficits, and abnormal MRI upon visual inspection. In all cases, the parents reported no perinatal problems and a normal acquisition of the autonomous deambulation (mean ± SD, in months = 12.8 ± 2.15). Objective neurological examination was normal in 23 cases and showed motor soft signs (e.g., poor motor coordination or difficulties in sequencing of complex motor tasks) in 13 subjects.

Thirty-six healthy control subjects (24 boys and 12 girls, two left-handed) of comparable age (mean ± SD age, 10.88 ± 2.83 years; range 5–17) were selected. These subjects were neurologically intact children with normal school performance whose parents agreed to participate in an ongoing study of brain development. A neurological examination and a parental interview were performed to exclude any sensorial, psychomotor or cognitive alterations, with particular interest in detecting current deficits in the language domain and possible delays in the acquisition of language function. All MRI scans were acquired without sedation. The study was approved by the local Investigational and Ethics Committee, and written informed consent was obtained from the parents of each participant.

MRI Acquisition and Processing

A 1.5-T scanner (Signa, GE Medical Systems, Milwaukee, WI) was used to obtain a sixty-slice 3D SPGR sequence in the sagittal plane (TR 40 ms, TE 4 ms, pulse angle 30°, field of view 26 cm, matrix size 256 × 192 pixels, and section thickness between 2.4 and 2.6 mm). Imaging data were processed on a Microsoft Windows platform using a technical computing software program (MATLAB 7; The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM2; The Wellcome Department of Imaging Neuroscience, London, UK).

All images were first checked for artifacts. Image preprocessing was automated with a MATLAB script (cg_vbm_optimized, see http://dbm.neuro.uni-jena.de/vbm/), which involved several processes aimed at: (a) segmenting whole brain images in native space into gray matter, white matter, and cerebrospinal fluid (CSF); (b) optimally normalizing, with linear and nonlinear deformations, each segment to a tissue specific template (during this process, images were resliced to a voxel size of 1 mm^3); (c) modulating voxel values by the Jacobian determinants derived from the spatial normalization to restore volumetric information; and (d) smoothing the images with a 12-mm full width at half-maximum isotropic Gaussian Kernel. After spatial normalization (step b above), images were checked again for potential misregistration artifacts. Given the age range of our subjects, we used a pediatric template and pediatric image priors derived from a sample of 148 healthy subjects from 5 to 18 years of age [Wilke et al., 2003].

Statistical Analyses

Global volume measurements

Global gray matter, white matter and CSF volumes, obtained from the original non-normalized images, were compared by univariate ANCOVA, with age and gender as covariates. Pearson's correlations were used to assess the relationship between age and tissue volumes in patients and healthy controls. SPSS (v.15) was used in these analyses.

Regional volume analysis

SPM2 tools were used for voxel-wise analyses. Between groups comparisons were conducted separately for gray and white matter, with age and gender as covariates. Each comparison generated two *t* statistic maps corresponding to volume decreases and increases. Regional differences were reported as significant at $P < 0.05$ after correction for multiple comparisons throughout the brain, although, for displaying purposes, results were presented at threshold $P < 0.001$, uncorrected. Significant results were overlaid onto a representative normalized brain image to assist in the anatomical localization of findings.

Relationships with age were assessed in SPSS by performing Pearson's correlations between subject's age and the values of the peak voxels from the former analyses. ANCOVA tests, with group and age as independent variables (and also controlling for gender), were performed to assess for the potential between-group differences (i.e., group × age interactions) in the relationship between regional tissue volumes and age.

SLI subgroup analysis and correlations with neuropsychological scores

Firstly, as the phonological-syntactic subgroup was the most prevalent in our sample, we performed an SPM conjunction analysis to assess for potential differences between this subgroup and both the rest of SLI subjects and the healthy control group. Secondly, the scores of the different neuropsychological scales were entered as regressors of interest in independent SPM analyses performed with the SLI subjects. Age and gender were entered as covariates in all these analyses. After an exploratory whole-brain assessment, small volume correction (SVC) procedures were used to restrict the analyses to the regions where anatomical alterations were detected in our sample of SLI.

To further explore the influence of age, groups were split according to the mean age of the sample, below and above 11 years. This specific cut-point differentiates two groups of subjects in both educational and developmental terms: primary (children) and secondary (adolescents) school students. All the above analyses were repeated separately for these subgroups of younger and older subjects. Independent-samples T tests (within SPSS) were used to compare the neuropsychological performance between these two age groups.

RESULTS

Neuropsychological Assessment

Scores more than 1 SD below the population mean in the language and intelligence assessment are indicated in Table I for the whole sample of children with SLI and for the two age groups. Although these abnormal scores were only present in one of the two age groups in six scales, between-group differences were not significant after applying the Bonferroni correction for multiple comparisons.

Global Volume Measurements

Children with SLI showed larger gray and white matter volumes than controls, but no differences were observed in CSF spaces (see Table I). Gender effects (boys showing larger volumes) were significant for both gray and white matter [$F_{(1,67)} = 25.01$; $P < 0.001$; and $F_{(1,67)} = 26.68$; $P < 0.001$, respectively], although no group × gender interaction was found. Significant linear correlations between age and gray matter were observed in healthy controls [$r = 0.42$; $n = 36$; $P = 0.01$], but not in children with SLI [$r = 0.09$; $n = 36$; $P > 0.05$], which resulted in a near significant group × age interaction [$F_{(1,67)} = 3.36$; $P = 0.07$]. Global white matter was significantly correlated with age in both control subjects [$r = 0.58$; $n = 36$; $P < 0.001$] and children with SLI [$r = 0.35$; $n = 36$; $P = 0.04$].

Age effects were further assessed by analyzing the younger and older children subgroups separately. Global gray matter was increased in younger children with SLI ($n = 19$) in comparison with younger control subjects ($n = 14$), but this difference was not observed in the older children subgroup (SLI, $n = 17$; Control subjects, $n = 22$). A similar scenario was observed for global white matter, with significant differences only observed between the younger children. These results are summarized in Table II.

Regional Volume Analysis

A whole-brain voxel-wise analysis including all subjects indicated that children with SLI had increased gray matter volume in two cortical regions (see Fig. 1): the right perisylvian region (Brodmann area (BA) 22) [$t = 4.89$; df = 68; corrected $P = 0.04$; cluster size = 45 voxels], and the occipital petalia, in the left middle occipital gyrus (BA 18) [$t = 4.83$; df = 68; corrected $P = 0.04$; cluster size = 30 voxels]. No significant correlation with age was observed for the volume of these regions in either the patient and control groups. Likewise, no significant voxel-wise volumetric changes were observed in white matter.

The influence of age on regional volumes was explored further with separate voxel-wise analyses for the younger and older children subgroups. In the younger children, we observed several regions of gray matter increase in SLI (see Fig. 2A and Table III), including the entorhinal area bilaterally, and the temporopolar cortex, the caudate nucleus, the motor-precentral cortex, and the precuneus of the left hemisphere. No significant changes were observed in the older subgroup. These results were confirmed by significant group × age interactions (see Tables III and IV). Interestingly, we also observed that the most medial aspect

TABLE II. Differences in global gray matter, white matter and CSF volumes between SLI and healthy children

	SLI, Mean (SD)	Healthy controls, Mean (SD)	*F*	*P*
Gray matter				
Whole sample	802.17 (63.86) ml	771.56 (80.33) ml	5.42	0.02
Younger children	809.46 (64.11) ml	734.00 (79.75) ml	10.09	0.004
Older children	794.03 (64.54) ml	795.46 (72.66) ml	0.047	ns
White matter				
Whole Sample	371.80 (40.19) ml	354.22 (49.09) ml	4.88	0.03
Younger children	363.75 (37.98) ml	318.65 (42.08) ml	12.95	0.001
Older children	380.80 (41.81) ml	376.85 (39.24) ml	0.05	ns
CSF				
Whole Sample	280.08 (41.09) ml	289.47 (34.04) ml	0.00	ns
Younger children	283.45 (47.24) ml	274.53 (30.86) ml	2.90	ns
Older children	276.30 (33.97) ml	298.98 (33.14) ml	2.05	ns

CSF, cerebrospinal fluid; ml, millilitres; ns, nonsignificant.

of the left middle occipital gyrus showed a specific volume increase in the subgroup of younger children with SLI [t = 5.46; df = 66; corrected P = 0.01; cluster size = 176 voxels; interaction with age: $F_{(1,67)}$ = 6.94, P = 0.01 (see Fig. 2A)]. Figure 3 depicts the relationship between gray matter volume and age for two representative areas: the right perisylvian region, that in comparison to controls, was increased during the whole age range (i.e., no interaction between gray matter volume and age), and the left temporopolar cortex, with a specific volume increase in younger children with SLI (i.e., interaction between gray matter volume and age).

Age specific analyses were also performed for white matter. Significant volume increases were observed in younger children with SLI in the juxtacortical white matter of the right medial frontal cortex [t = 5.05; df = 66; corrected P = 0.01; cluster size = 37 voxels], and bilaterally in the middle temporal gyrus [right: t = 4.79; df = 66; corrected P = 0.02; cluster size = 40 voxels; left: t = 4.54; df = 66; corrected P = 0.04; cluster size = 25 voxels (see Fig. 2B)]. No significant changes were observed in the older children subgroup. Age x group interaction was significant for all the above regions [$F_{(1,67)}$ = 5.27, P = 0.02 for the right medial frontal cortex; and $F_{(1,67)}$ = 10.36, P = 0.002 and $F_{(1,67)}$ = 5.82, P = 0.02 for the right and left middle temporal gyrus, respectively]. See Table IV for group specific correlations between white matter volumes and age.

SLI Subgroup Analysis and Correlations With Neuropsychological Scores

An exploratory SPM conjunction analysis did not find any volumetric changes specifically affecting the phonological-syntactic subgroup (the most prevalent in our sample) in comparison with both the rest of SLI subjects and the healthy control group. Neither were differences observed when the analysis was repeated and restricted (using SVC procedures) to the regions shown to be increased in our sample of SLI, even when such analyses were split by age group.

The scores of the different tests administered to the SLI subjects were entered as regressors of interest in different SPM analyses. We did not find any significant relationship with brain anatomy for the whole sample of subjects and for the two age groups. When the analyses were restricted to the regions increased in our sample of SLI, significant negative correlations were observed, in the older subjects subgroup, between verbal IQ and the right perisylvian region [t = 4.24; df = 30; SVC P = 0.01], and between PPTV score and the occipital petalia [t = 4.73; df = 30; SVC P = 0.001]. The relationship between these variables is depicted in Figure 4.

All the above analyses were repeated excluding the left-handed subjects with no relevant changes in the results.

DISCUSSION

In the present study, we observed global increases in gray and white matter volumes in the brains of children with SLI. These global changes were the consequence of a specific brain parenchyma increase in the younger SLI subgroup, whereas older subjects demonstrated no significant group differences. Regional specificity to our findings was provided by a voxel-wise analysis. For the whole sample, two clusters of cortical gray matter increase were detected; in the right perisylvian region and in the occipital petalia. In addition, when we investigated for regional changes in the younger and older children subgroups, we observed an extended pattern of regions showing gray and white matter volume increases in younger children with SLI, but not in the older subjects.

Global white matter and brain parenchyma increases have been previously reported in SLI [Herbert et al., 2003b, 2004]. Nevertheless, to our knowledge, this is the first study to report a global gray matter increase in this population of children. Although this discrepancy with previous studies may be partially explained by differences

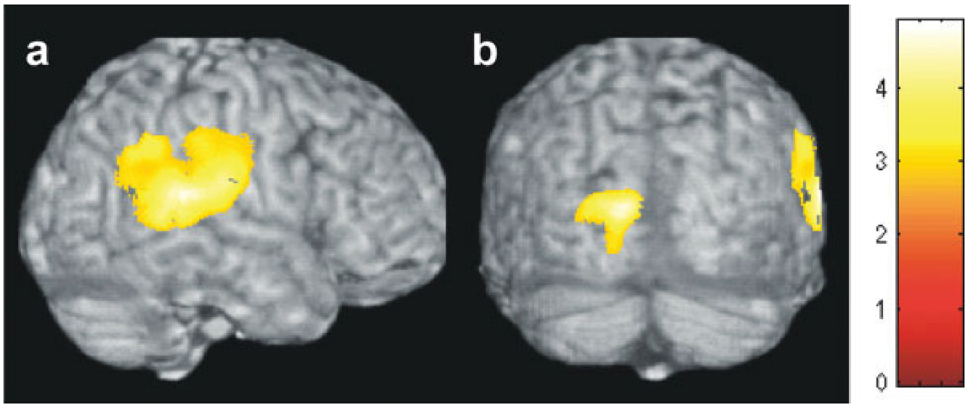

Figure 1.
Areas of gray matter volume increase in the whole sample of children with SLI superimposed on a rendered normalized brain. (a) Right perisylvian region. (b) Left middle occipital gyrus. Color bar represents the t value. Voxels with $P < 0.001$ (uncorrected) are displayed.

in the sample selection (e.g., we have not exclusively included patients from the phonological-syntactic subgroup), it is important to emphasize that such studies have typically assessed gray matter volume as different components (e.g., cortex, diencephalon or cerebellum), which may have resulted in less statistical power to detect overall volumetric changes. Volume increases in gray and white matter have also been described in other neurodevelopmental disorders, such as autism [Carper et al., 2002; Courchesne et al., 2001; Herbert et al., 2003a], suggesting that enlarged brain parenchyma may be an nonspecific feature of different, though probably related [Kjelgaard and

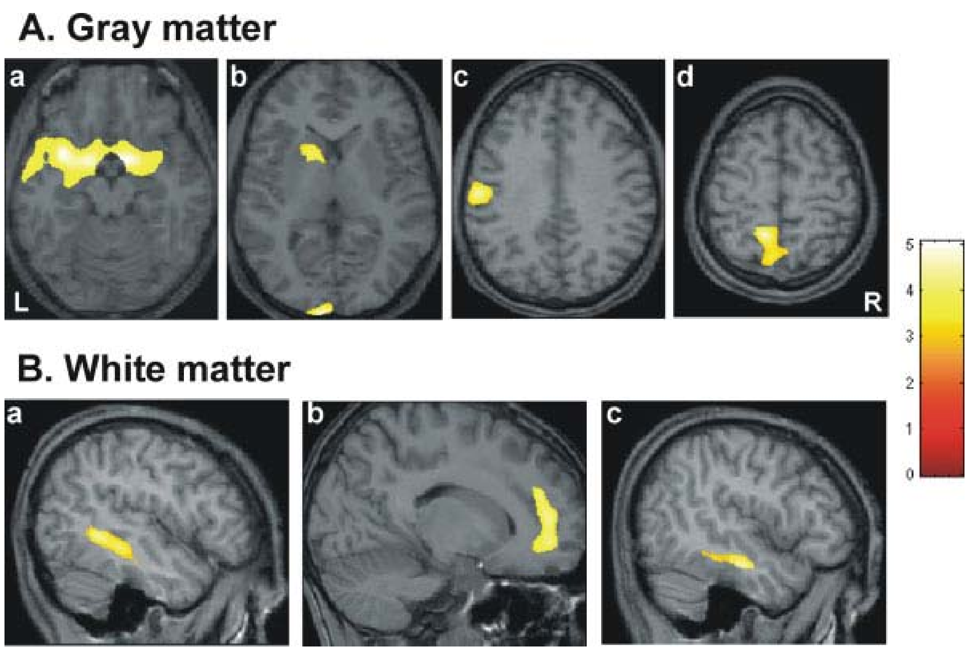

Figure 2.
Areas of gray (A) and white (B) matter volume increase in the subsample of younger children with SLI superimposed on selected slices of a normalized brain. **A:** (**a**) Bilateral entorhinal cortex and left temporopolar cortex; (**b**) left caudate nucleus and the most medial aspect of the left middle occipital gyrus; (**c**) left motor cortex; (**d**) left precuneus. **B:** (**a**) Right middle temporal gyrus; (**b**) right medial frontal cortex; (**c**) left middle temporal gyrus. Color bar represents the t value. Voxels with $P < 0.001$ (uncorrected) are displayed.

TABLE III. Areas of gray matter volume increase in younger children with SLI in comparison with younger control subjects

Location	Brodmann area	*t* value	Corrected *P* value	Cluster size (voxels)	*F* value (interaction with age)	*P* of the interaction
Right entorhinal area	28/34	5.46	0.01	819	5.38	0.02
Left entorhinal area	28/34	4.98	0.03	275	5.05	0.03
Left temporopolar cortex	38	5.07	0.02	257	8.41	0.005
Left caudate nucleus	—	4.94	0.03	40	8.01	0.01
Left motor cortex	4	4.84	0.04	19	13.58	< 0.0005
Left precuneus	7	5.10	0.02	116	6.93	0.01

Tager-Flusberg, 2001; Rapin and Dunn, 1997], neurodevelopmental disorders. Interestingly, in autism, overall volume enlargements also appear to be more prominent in younger subjects [Carper et al., 2002; Courchesne et al., 2001].

Voxel-wise analyses were used to map the regional distribution of these global volume enlargements, and to investigate whether specific changes may exist in language-related regions. Importantly, as voxel values were unadjusted for global volume, these results show the brain regions of the largest and most consistent between-group differences in the context of a global volume increase. One area identified was the perisylvian cortex, which has been consistently related to SLI in the form of an atypical asymmetry pattern [Gauger et al., 1997; Jernigan et al., 1991; Leonard et al., 2002, 2006; Plante et al., 1991]. Our finding of a volume increase in the right perisylvian region is in agreement with some of these studies [Plante et al., 1991], and suggests that unilateral volume increases, rather than decreases, may cause the abnormal asymmetries reported in SLI. Another region detected was the occipital petalia. In this case, however, the left side volume enlargement represented a larger expression of the typical leftward asymmetry of this region [Hervé et al., 2006]. Although the relationship of this last finding with language function is difficult to establish, such results suggest that in SLI normal asymmetry patterns may be reversed at the level of particular cortical regions (i.e., the perisylvian region), rather than in gross neuroanatomical patterns (i.e., the brain torque), as previously reported [Herbert et al., 2005].

Separate voxel-wise analyses for the younger and older SLI subjects allowed us to identify brain regions specifically enlarged in the younger subgroup. We observed volume increases in the left temporopolar cortex and, bilaterally, in the white matter of the middle temporal gyrus. Left temporopolar cortex has been related to language comprehension, possibly as part of a memory network for encoding and retrieval of linguistic material [Vigneau et al., 2006]. White matter tracks of the ventral part of the temporal lobe have also been proposed as part of this system by providing input from posterior occipitotemporal regions to the temporal pole [Duffau et al., 2005]. Interestingly, this ventral processing stream, which is essential for linking phonology with semantics, appears to be bilaterally organized [Hickok and Poeppel, 2007], which is in line with our finding of white matter increases in both temporal lobes. Beyond this region, other structures with volumetric changes in our younger subgroup have also been related to language function. The left precuneus, for example, has been shown to participate in auditory comprehension tasks [Schmithorst et al., 2006], and activity in the left caudate nucleus has been related to the level of accuracy in phonological processing [Tettamanti et al., 2005]. Caudate nucleus volume has also been shown to be bilaterally altered in the members of the KE family affected by a severe developmental disorder of speech and language

TABLE IV. Pearson's correlations (and *P* values) between age and regional volumes in areas increased in younger children with SLI

	Right EA	Left EA	Left TPC	Left CN	Left MC	Left PC	Right MFC	Right MTG	Left MTG
Children with SLI (n = 36)									
Age	0.09	0.03	−0.02	−0.24	−0.34	−0.35	0.07	0.10	0.11
	(ns)	(ns)	(ns)	(ns)	(0.04)	(0.04)	(ns)	(ns)	(ns)
Healthy controls (n = 36)									
Age	0.52	0.51	0.51	0.39	0.43	0.24	0.49	0.58	0.55
	(0.001)[a]	(0.002)[a]	(0.001)[a]	(0.017)	(0.009)	(ns)	(0.003)[a]	(<0.001)[a]	(0.001)[a]

CN, caudate nucleus; EA, entorhinal area; MC, motor cortex; MFC, medial frontal cortex (white matter region); MTG, middle temporal gyrus (white matter regions); ns, nonsignificant; PC, Precuneus; TPC, temporopolar cortex.
[a] Significant after Bonferroni correction for multiple comparisons.

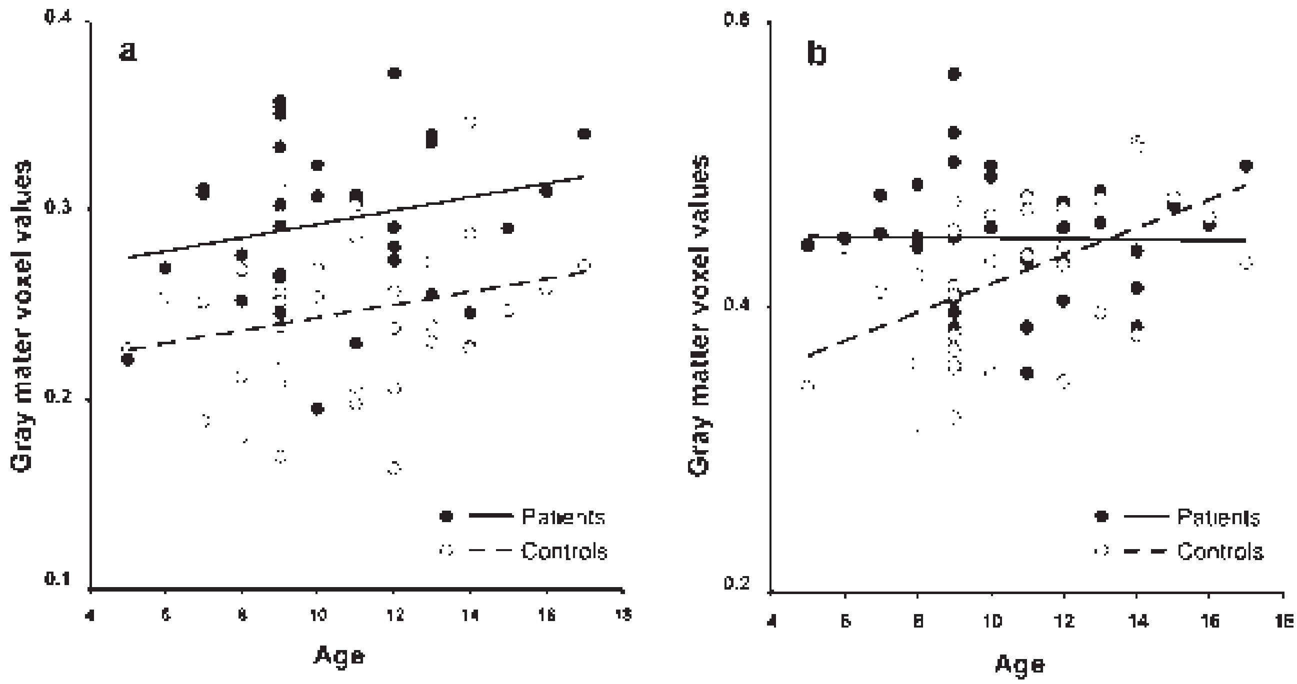

Figure 3.
Relationship between gray matter volume and age in two representative locations. (**a**) In the right perisylvian region, Pearson's correlation was positive, although not significant, in both groups. (**b**) In the left temporopolar cortex, correlation was significant only in the healthy controls group, resulting in a significant age × condition interaction (see Tables III and IV for details).

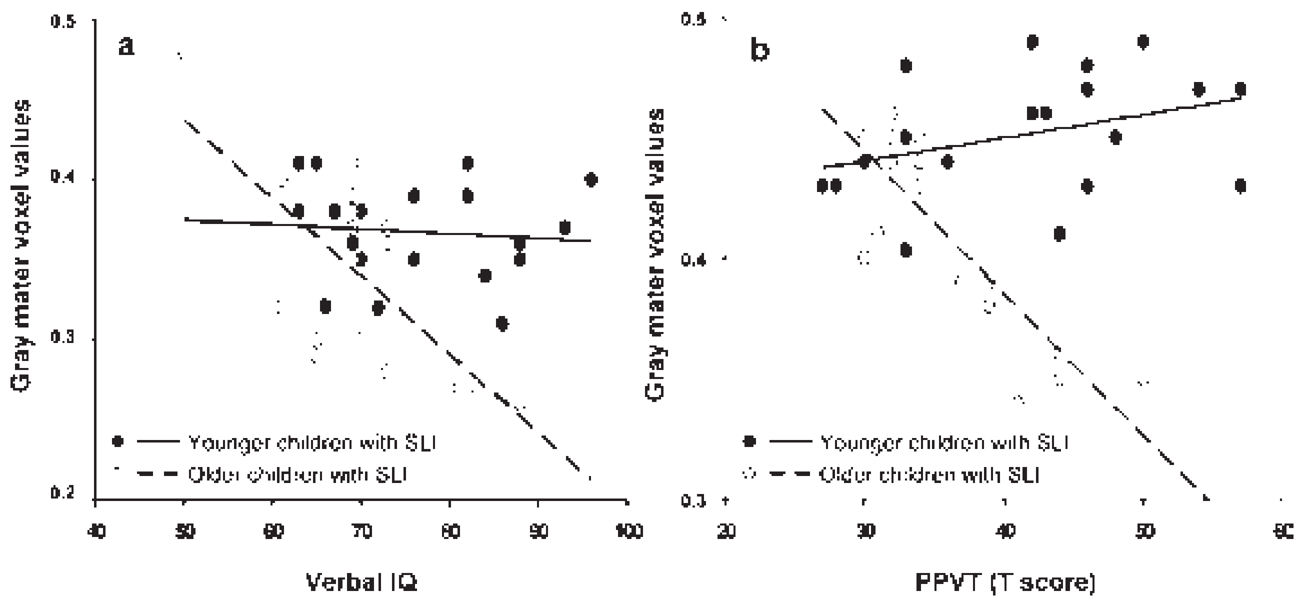

Figure 4.
Relationship between gray matter volume and neuropsychological scores in the younger and older children with SLI. (a) In the right perisylvian region, a negative relationship with verbal IQ was observed in the older children with SLI ($r = -0.72$). (b) In the occipital petalia, a negative relationship with the PPVT score was observed in the older children with SLI ($r = -0.81$).

[Vargha-Khadem et al., 1998], although, contrary to our results, in the sense of a volumetric reduction. The relationship of this volume decrease with language function; however, is not totally understood [Liégeois et al., 2003; Watkins et al., 2002]. Changes in other brain areas of our subjects might relate more indirectly to language abilities, perhaps as a consequence of large-scale system reorganization due to impaired language capacity. Nevertheless, they may also respond to the same underlying causes of the disorder, which is not fully specific of language function, as subtle alterations in motor ability and other cognitive domains have been described [Webster et al., 2006].

The findings of our study suggest that in SLI there are discrete and long-lasting volumetric changes (e.g., in the right perisylvian region) that may coexist with a more extended pattern of abnormalities that normalize throughout development. Although, in general terms, our data are consistent with clinical observations regarding the good outcome of a subgroup of children with SLI during adolescence, even in these cases isolated phonological and reading skill deficits typically exist [Stothard et al., 1998]. In addition, in our sample, older children with SLI showed no evidence of improvement in verbal function when compared to the younger subgroup (see Table I). This is not surprising considering that our older children with SLI still required medical and psychological assistance. Interestingly, the anatomical changes in this age-group, but not in the younger children, were correlated with language impairment (see Fig. 4), suggesting that in younger children with SLI anatomical changes, albeit more extended, do not directly express the degree of language disturbance. At the youngest ages, general educational and developmental factors may strongly influence the assessment of language function, which may even present periods of "illusory recovery," where performance of children with SLI in particular domains is similar to that of their age-peer controls [Bishop and Snowling, 2004; Scarborough and Dobrich, 1990]. In any case, significant individual differences exist in the outcome of SLI at adolescence, and, as such, further investigation is needed to elucidate which anatomical changes are present in good outcome children with SLI and the extent to which poor outcome may be predicted by the amount of anatomical alteration existing during early childhood. All in all, our data strongly suggest that the neuroanatomical basis of language function in SLI may be better characterized by considering the dynamic course of the disorder throughout children's development [Thomas and Karmiloff-Smith, 2002].

Brain volumetric anomalies in SLI are thought to begin postnatally during the first years of life [Herbert et al., 2004]. During these years, a number of progressive and regressive events take place, and the balance between them leads to the final volume of different brain structures. According to our data, in SLI an imbalance may occur between progressive (e. g., accelerated white-matter myelination) and regressive (e.g., delayed relative reduction of gray matter) events. Although in most brain regions these changes normalize over time, in others they seem to be long lasting. Even though some molecular mechanisms accounting for these volumetric changes may be suggested (e.g., increased neuronal size and arborization, synaptic density, or myelination), their precise characterization will require the use of other research methods in addition to MRI. Because of its limited spatial resolution, MRI volumetric measures may reflect neuronal, glial or vascular changes [Toga et al., 2006]. In this sense, the use of high resolution images may increase the ability to precisely characterize disease associated patterns of subtle structural alterations. Therefore, the relatively high slice thickness used here, despite providing accurate tissue segmentation [Pujol et al., 2002], may be considered as a study limitation. Nevertheless, anatomical MRI has been successfully applied to the study of brain maturation, especially within longitudinal designs [Giedd et al., 1999; Toga et al., 2006]. Unlike these studies, our cross-sectional assessment did not involve scanning subjects at multiple time-points. The longitudinal assessment of both patients and controls may probably lead to a more accurate characterization of the temporal dynamics of the volumetric changes in SLI.

CONCLUSION

In summary, we have described global and regional volumetric increases in gray and white matter of children with SLI. In younger children with SLI, such changes were more prominent, although they appear to normalize with age, suggesting an early neurodevelopmental alteration. In older children with SLI there were fewer volumetric alterations, albeit more directly related to the degree of language impairment. In general terms, our findings are consistent with clinical observations regarding the dynamic nature of the disorder, and emphasize the need to consider the influence of age when assessing the neuroanatomical basis of developmental language disorders.

ACKNOWLEDGMENTS

The authors thank Dr. Ben J. Harrison and Gerald Fannon PhD, for carefully revising the manuscript. Hector Ortiz thanks the Spanish Ministerio de Educación y Ciencia (AP2006-02869). Dr. Pujol thanks the contribution of the Networking Research Center on Bioengineering, Biomaterials, and Nanomedicine (CIBER-BBN), Barcelona, Spain.

REFERENCES

Ashburner J, Friston KJ (2000): Voxel-based morphometry—The methods. NeuroImage 11:805–821.

Bishop DV (2005): Handedness and specific language impairment: A study of 6-year-old twins. Dev Psychobiol 46:362–369.

Bishop DV, Snowling MJ (2004): Developmental dyslexia and specific language impairment: Same or different? Psychol Bull 130:858–886.

Botting N (2005): Non-verbal cognitive development and language impairment. J Child Psychol Psychiatry 46:317–326.

Carper RA, Moses P, Tigue ZD, Courchesne E (2002): Cerebral lobes in autism: Early hyperplasia and abnormal age effects. NeuroImage 16:1038–1051.

Conti-Ramsden G, Botting N (1999): Classification of children with specific language impairment: Longitudinal considerations. J Speech Lang Hear Res 42:1195–1204.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY (2001): Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 57:245–254.

De Fossé L, Hodge SM, Makris N, Kennedy DN, Caviness VS Jr, McGrath L, Steele S, Ziegler DA, Herbert MR, Frazier JA, Tager-Flusberg H, Harris GJ (2004): Language-association cortex asymmetry in autism and specific language impairment. Ann Neurol 56:757–766.

DiSimoni F (1978): Token Test for Children (TTFC). Austin: PRO-ED.

Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L (2005): New insights into the anatomo-functional connectivity of the semantic system: A study using cortico-subcortical electrostimulations. Brain 128:797–810.

Dunn LM, Dunn LM (1997): Peabody Picture Vocabulary Test, 3rd ed. Circle Pines: AGS Publishing.

Gathercole SE, Baddeley AD (1990): Phonological memory deficits in language disordered children: Is there a casual connection? J Mem Lang 129:336–360.

Gauger LM, Lombardino LJ, Leonard CM (1997): Brain morphology in children with specific language impairment. J Speech Lang Hear Res 40:1272–1284.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL (1999): Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 2:861–863.

Guerreiro MM, Hage SR, Guimarães CA, Abramides DV, Fernandes W, Pacheco PS, Piovesana AM, Montenegro MA, Cendes F (2002): Developmental language disorder associated with polymicrogyria. Neurology 59:245–250.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, Hodgson J, Adrien KT, Steele S, Makris N, Kennedy D, Harris GJ, Caviness VS Jr (2003a): Dissociations of cerebral cortex, subcortical, and cerebral white matter volumes in autistic boys. Brain 126:1182–1192.

Herbert MR, Ziegler DA, Makris N, Bakardjiev A, Hodgson J, Adrien KT, Kennedy DN, Filipek PA, Caviness VS Jr (2003b): Larger brain and white matter volumes in children with developmental language disorder. Dev Sci 6:F11–F22.

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr (2004): Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol 55:530–540.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Kennedy DN, Filipek PA, Bakardjiev AI, Hodgson J, Takeoka M, Makris N, Caviness VS Jr (2005): Brain asymmetries in autism and developmental language disorder: A nested whole-brain analysis. Brain 128:213–226.

Hervé PY, Crivello F, Perchey G, Mazoyer B, Tzourio-Mazoyer N (2006): Handedness and cerebral anatomical asymmetries in young adult males. NeuroImage 29:1066–1079.

Hickok G, Poeppel D (2007): The cortical organization of speech processing. Nat Rev Neurosci 8:393–402.

Jancke L, Siegenthaler T, Preis S, Steinmetz H (2007): Decreased white-matter density in a left-sided fronto-temporal network in children with developmental language disorder: Evidence for anatomical anomalies in a motor-language network. Brain Lang 102:91–98.

Jernigan TL, Hesselink JR, Sowell E, Tallal PA (1991): Cerebral structure on magnetic resonance imaging in language- and learning-impaired children. Arch Neurol 48:539–545.

Kirk S, MCCarthy J, Kirk W (1968): Illinois Test of Psycholinguistic Abilities. Urbana: Illinois University Press.

Kjelgaard MM, Tager-Flusberg H (2001): An investigation of language impairment in autism: Implications for genetic subgroups. Lang Cogn Process 16:287–308.

Lenroot RK, Giedd JN (2006): Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev 30:718–729.

Leonard C, Eckert M, Given B, Virginia B, Eden G (2006): Individual differences in anatomy predict reading and oral language impairments in children. Brain 129:3329–3342.

Leonard CM, Lombardino LJ, Walsh K, Eckert MA, Mockler JL, Rowe LA, Williams S, DeBose CB (2002): Anatomical risk factors that distinguish dyslexia from SLI predict reading skill in normal children. J Commun Disord 35:501–531.

Liégeois F, Baldeweg T, Connelly A, Gadian DG, Mishkin M, Vargha-Khadem F (2003): Language fMRI abnormalities associated with FOXP2 gene mutation. Nat Neurosci 6:1230–1237.

McArthur GM, Hogben JH, Edwards VT, Heath SM, Mengler ED (2000): On the "specifics" of specific reading disability and specific language impairment. J Child Psychol Psychiatry 41:869–874.

Plante E, Swisher L, Vance R, Rapcsak S (1991): MRI findings in boys with specific language impairment. Brain Lang 41:52–66.

Preis S, Jäncke L, Schittler P, Huang Y, Steinmetz H (1998): Normal intrasylvian anatomical asymmetry in children with developmental language disorder. Neuropsychologia 36:849–855.

Preis S, Steinmetz H, Knorr U, Jäncke L (2000): Corpus callosum size in children with developmental language disorder. Brain Res Cogn Brain Res 10:37–44.

Pujol J, López-Sala A, Deus J, Cardoner N, Sebastián-Gallés N, Conesa G, Capdevila A (2002): The lateral asymmetry of the human brain studied by volumetric magnetic resonance imaging. NeuroImage 17:670–679.

Rapin I (1996): Practitioner review: Developmental language disorders: A clinical update. J Child Psychol Psychiatry 37:643–655.

Rapin I, Dunn M (1997): Language disorders in children with autism. Semin Pediatr Neurol 4:86–92.

Scarborough HS, Dobrich W (1990): Development of children with early language delay. J Speech Hear Res 33:70–83.

Schmithorst VJ, Holland SK, Plante E (2006): Cognitive modules utilized for narrative comprehension in children: A functional magnetic resonance imaging study. NeuroImage 29:254–266.

Snowling M, Bishop DV, Stothard SE (2000): Is preschool language impairment a risk factor for dyslexia in adolescence? J Child Psychol Psychiatry 41:587–600.

Stothard SE, Snowling MJ, Bishop DV, Chipchase BB, Kaplan CA (1998): Language-impaired preschoolers: A follow-up into adolescence. J Speech Lang Hear Res 41:407–418.

Tettamanti M, Moro A, Messa C, Moresco RM, Rizzo G, Carpinelli A, Matarrese M, Fazio F, Perani D (2005): Basal ganglia and language: phonology modulates dopaminergic release. NeuroReport 16:397–401.

Thomas M, Karmiloff-Smith A (2002): Are developmental disorders like cases of adult brain damage? Implications from connectionist modelling. Behav Brain Sci 25:727–750.

Toga AW, Thompson PM, Sowell ER (2006): Mapping brain maturation. Trends Neurosci 29:148–159.

Trauner D, Wulfeck B, Tallal P, Hesselink J (2000): Neurological and MRI profiles of children with developmental language impairment. Dev Med Child Neurol 42:470–475.

Vargha-Khadem F, Watkins KE, Price CJ, Ashburner J, Alcock KJ, Connelly A, Frackowiak RS, Friston KJ, Pembrey ME, Mishkin M, Gadian DG, Passingham RE (1998): Neural basis of an inherited speech and language disorder. Proc Natl Acad Sci USA 95:12695–12700.

Vigneau M, Beaucousin V, Hervé PY, Duffau H, Crivello F, Houdé O, Mazoyer B, Tzourio-Mazoyer N (2006): Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. NeuroImage 30:1414–1432.

Watkins KE, Vargha-Khadem F, Ashburner J, Passingham RE, Connelly A, Friston KJ, Frackowiak RS, Mishkin M, Gadian DG (2002): MRI analysis of an inherited speech and language disorder: Structural brain abnormalities. Brain 125:465–478.

Webster RI, Erdos C, Evans K, Majnemer A, Kehayia E, Thordardottir E, Evans A, Shevell MI (2006): The clinical spectrum of developmental language impairment in school-aged children: Language, cognitive, and motor findings. Pediatrics 118:e1541–e1549.

Webster RI, Shevell MI (2004): Neurobiology of specific language impairment. J Child Neurol 19:471–481.

Wechsler D (1991): Wechsler Intelligence Scale for Children, 3rd ed. San Antonio: Psychological Corporation.

Wilke M, Schmithorst VJ, Holland SK (2003): Normative pediatric brain data for spatial normalization and segmentation differs from standard adult data. Magn Reson Med 50:749–757.

World Health Organization(1992): International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Geneva: World Health Organization.

4.2. Neuroanatomía de la circunvolución cingulada anterior y personalidad.

4.2.1. *Artículo 3: Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality*

NeuroImage 15, 847–855 (2002)
doi:10.1006/nimg.2001.1004, available online at http://www.idealibrary.com on IDEAL®

Anatomical Variability of the Anterior Cingulate Gyrus and Basic Dimensions of Human Personality

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Received June 5, 2001

This study focused on investigating a possible relationship between interindividual variability in the morphology of the cingulate gyrus and behavioral styles. Using magnetic resonance images obtained from 100 healthy young volunteers (50 women and 50 men), we measured the surface area of the anterior cingulate gyrus and related it to the scores on the Temperament and Character Inventory. Anatomical data revealed that hemispheric asymmetry in the anterior cingulate gyrus surface area was very common (83% of cases) and that a prominent right anterior cingulate was more frequent in women than in men. In the correlational analysis, surface measurements of the right anterior cingulate gyrus accounted for a 24% score variance in Harm Avoidance. Both women and men with larger right anterior cingulate described themselves as experiencing greater worry about possible problems, fearfulness in the face of uncertainty, shyness with strangers, and fatigability. Furthermore, women reported overall higher scores in Harm Avoidance than men; these gender differences were largely explained by gender differences in the right anterior cingulate area in a covariate analysis. Our observations suggest that a large right anterior cingulate is related to a temperamental disposition to fear and anticipatory worry in both genders and that a higher prevalence of these traits in women may be coupled with a greater expansion of this brain region.

INTRODUCTION

The cingulate sulcus is a major anatomical landmark in the medial wall of the primate brain. It separates medial motor, premotor, and prefrontal areas from the limbic convolution adjacent to the corpus callosum, namely the cingulate gyrus (Fig. 1). Transitional (paralimbic) cortices are buried in the cingulate sulcus and extend, in some individuals, onto the paracingulate gyrus (Vogt *et al.*, 1992, 1995). The limbic cingulate gyrus and related paralimbic areas involve two functionally differentiated anterior (executive) and posterior (evaluative) parts (Vogt *et al.*, 1992, 1995; Paus *et al.*, 1993, 1998; Pujol *et al.*, 2001).

The gyral and sulcal pattern in this region is highly variable from person to person and between the left and the right hemispheres, as is evident in magnetic resonance imaging (MRI) studies of brain morphology carried out in large numbers of healthy individuals (Paus *et al.*, 1996a,b; Yücel *et al.*, 2001). Anatomical variability may also reflect cytoarchitectural variability. Indeed, in the majority of cases, the medial surface of the anterior cingulate gyrus contains Brodmann areas 24a, 24b, and 25 (Vogt *et al.*, 1995). Therefore, in general, a larger anterior cingulate gyrus denotes a greater limbic cortex presence.

The anterior cingulate is a major contributor to behavior through its modulation of the entire span of brain responses (reviewed in Devinsky *et al.*, 1995, and Paus, 2001). This part of the brain influences movement by means of direct corticospinal projections and reciprocal connections to motor and premotor areas. The cingulate cortex mediates responses to pain involving both the motor and the affective components that follow noxious stimulation. It is involved in attention and response selection in cognitively demanding situations. The ventral (subcallosal) part of the cingulate gyrus contains visceromotor areas that modulate autonomic activity associated with emotions and participates in regulating many aspects of affectivity and even complex social behavior (Devinsky *et al.*, 1995).

Overall, the anterior cingulate gyrus is a highly variable brain region involved in adjusting people's responses to the environment. The goal of the present study was to investigate whether interindividual variability in the extent of the anterior cingulate gyrus and, by inference, the "limbic" cingulate cortex is associated with a specific behavioral style characteristic for

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FIG. 1. Right medial surface of the brain in healthy volunteers. Note large difference in the extent of the anterior cingulate gyrus (shaded in red) in these two subjects.

a given individual. Different individuals respond to an environmental challenge in different but consistent ways, and the usual way in which an individual responds defines his or her personality.

We used the Temperament and Character Inventory (TCI) of Cloninger (Cloninger *et al.*, 1993) as a reliable tool for measuring personality traits and administered it to 100 healthy volunteers. Structural MRI exams were acquired in these subjects and the surface area of the cingulate gyrus was measured in both hemispheres. Interindividual variability in the cingulate measurements, their hemispheric asymmetries, and possible gender differences were analyzed in order to establish the correlation between anatomical data and personality scores.

MATERIALS AND METHODS

Subjects

Volunteers were recruited to make up a series of 100 healthy subjects including 50 women and 50 men aged between 20 and 40 years. Recruitment was individually performed by university teachers in the university environment of Barcelona with no payment offered. The subjects were screened for a positive history of neurological, psychiatric, and serious medical disorders, as well as for alcohol and drug abuse. Right-hand preference according to the Edinburgh Inventory (Oldfield, 1971) was required. Subjects were also excluded if their MRI scans were abnormal; 4 subjects were excluded (and replaced) for this reason (2 subjects showed scattered punctate foci of white-matter hyperintensities, 1 subject showed a circumscribed cortical dysplasia, and another subject a cavernous angioma).

Mean age ± SD for the final sample was 25.5 ± 3.9 years (25.5 ± 3.7 years for women and 25.5 ± 4.2 years for men). All selected participants were Caucasian residents from Barcelona and all were in the final year of university or graduates. IQ estimated using the verbal part of the Kaufman Brief Intelligence Test (Kaufman and Kaufman, 1994) was 108.6 ± 6.1 in women and 108.1 ± 6.2 in men. After a complete description of the study to the subjects, written informed consent was obtained.

Personality Assessment

A validated Spanish translation (Gutiérrez *et al.*, 2000) of Cloninger's TCI version 9 (Cloninger *et al.*, 1994) was used in this study. After individual instructions were given, the test was carried out in a quiet room with each subject reading the TCI and self rating the 240 items as true or false. This questionnaire produces separate scores for four temperament dimensions (Harm Avoidance, Novelty Seeking, Reward

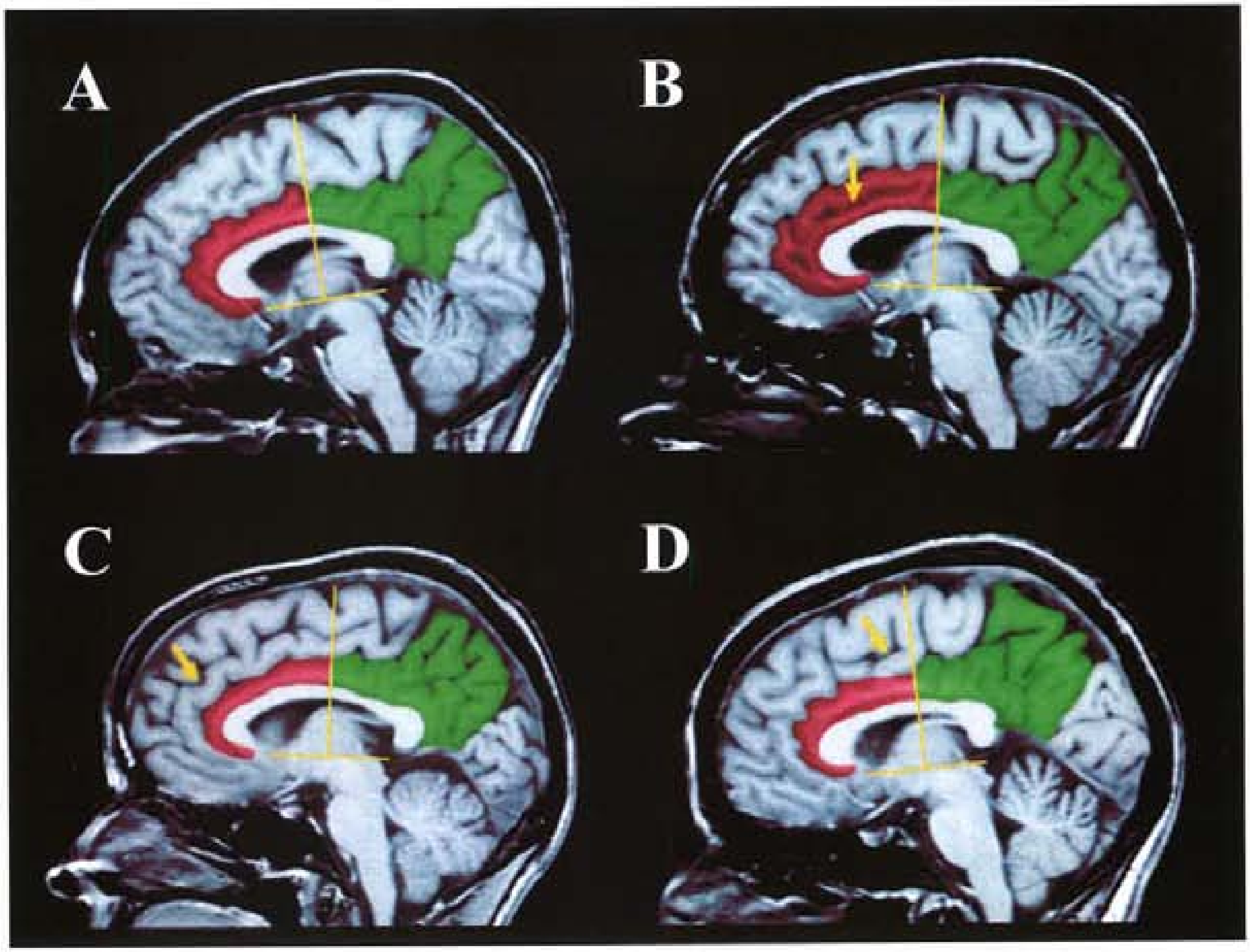

FIG. 2. Region delimitation adopted in different anatomical patterns: continuous and well-defined cingulate gyrus (A), presence of intralimbic sulcus (arrow in B), presence of second cingulate (paracingulate) sulcus (arrow in C), and presence of cingulate sulcus interruptions (arrow in D).

Dependence, and Persistence) and three character dimensions (Self Directedness, Cooperativeness, and Self Transcendence). All dimensions, except Persistence, have three to five lower order subscales.

Harm Avoidance reflects a tendency to respond intensely to aversive stimuli and involves *anticipatory worry* about possible problems, *fear of uncertainty, shyness with strangers*, and consequent easy *fatigability*. Novelty Seeking reflects a tendency toward *exploratory excitability* in response to novelty, *impulsiveness* in decision making, *extravagance* in approach to cues of reward, and *disorderliness* with quick loss of temper. Reward Dependence reveals a tendency to respond intensely to reward and includes *sentimentality*, social *attachment*, and *dependence* upon others' approval. Persistence reflects a tendency to industriousness, ambitious overachieving, and perseveration despite frustration.

Although our study was primarily focused on investigating possible anatomical correlates for temperament traits, character dimension results were also analyzed. Self Directedness refers to the ability to control, regulate, and adapt one's behavior in accord with chosen goals and values. Cooperativeness reveals an inclination toward social tolerance, empathy, helpfulness, and compassion. Self-Transcendence reflects a tendency toward spirituality and identification with the wider world, as well as the ability to accept ambiguity and uncertainty.

A computer program was used that provided raw scores and calculated *T* scores according to norms (Cloninger *et al.*, 1994) for the seven scales and the corresponding subscales. Raw scores were calculated by adding 1 point for each item answered in the direction predicted by the scale. Standardization to *T* scores adjusts mean scores of each scale to the reference value of 50 points.

MRI Examination

The imaging studies were acquired within the same day of the behavioral assessment using a 1.5 T magnet (Signa; GE Medical Systems, Milwaukee, WI). A 60-slice 3-D spoiled gradient recalled acquisition in the steady state sequence was obtained in the sagittal plane. Acquisition parameters were TR 40 ms, TE 4 ms, pulse angle 30°, field of view 26 cm, and matrix size 256 × 192 pixels. Section thickness varied according to the brain size, ranging from 2.4 to 2.6 mm.

The first phase of image analysis was performed on an auxiliary workstation (SPARCstation 20; Sun Microsystems, Mountain View, CA), using commercially available software (Advantage Windows, version 2.0; GE Medical Systems) and adapting procedures used previously (Pujol *et al.*, 1998). A 3-D MRI model of each subject's head was constructed and reformatted to high-resolution 1 mm slices. Axial views of the reformatted MRI were used to identify the plane of the interhemispheric fissure and to select two oblique sagittal images that optimally exposed left and right medial brain surfaces. Finally, each oblique-sagittal image was coded and stored with no reference to the subject's name, age, gender, or hemisphere.

To obtain cerebral volume measurements, a 3-D surface rendering of each subject's brain was built by isolating neural tissue from the surrounding CSF using volume segmentation tools (Pujol *et al.*, 1998). The analysis system directly provided the volume (ml) of the entire brain after its isolation in each subject.

In the second phase, reformatted sagittal views were interpolated to a high-resolution matrix (512 × 512 pixels) in order to carry out the surface measurements. A general software for image analysis was used (Image-Pro Plus; Media Cybernetics, Silver Spring, MD). Two cingulate regions were manually traced on each hemisphere according to the individual sulcal patterns (Fig. 2) and measured in square millimeters. The anterior region corresponded to the anterior cingulate gyrus. The posterior cingulate region included the posterior cingulate gyrus and the medial parietal cortex (precuneus). The border between anterior and posterior cingulate regions was established at the midpoint between anterior and posterior commissures, which approximates the boundary between Brodmann areas 24 and 23 (Vogt *et al.*, 1995; Paus *et al.*, 1996a,b).

An asymmetry index (Pujol *et al.*, 1999) was computed for both cingulate regions according to the expression $100 \times (L - R)/(L + R)$, where L and R were measurements for the left and right hemispheres. This index is identical to that used by Paus *et al.* (1996a). In accordance with these authors, an absolute value of 5% was considered the minimum level of asymmetry. This corresponds to the 0.1 asymmetry index values of Galaburda *et al.* (1987) and is conventionally used (Shapleske *et al.*, 1999) to compare anatomical asymmetries from different studies. Asymmetrical cases, therefore, were those showing values below −5 (right-sided pattern) or above 5 (left sided pattern).

The measurements were performed by a researcher blind to the subject's age and gender and to any reference identifying brain hemisphere [images from both hemispheres were presented with identical left–right orientation (Fig. 2)]. The reproducibility of measurements proved to be good. An intraclass correlation coefficient of 0.92 was obtained for 100 surface measurements of the right anterior cingulate gyrus repeated after 2 weeks. To assess interrater reliability, a second researcher measured this region in a subsample of 40 randomly chosen cases, also under blind conditions. The intraclass correlation coefficient between the two raters was 0.91.

Statistical differences of parametric data were analyzed on the basis of 95% confidence intervals. Analysis of variance (ANOVA) with covariates was used to remove the effect of brain volume and to evaluate main effects of gender (women, men) and hemisphere (left, right) and their interaction. Asymmetry index rates between genders were compared with a χ^2 test. Pearson's correlations, adjusted to brain volume using partial correlations, served to examine the association between the MRI measurements and the seven high-order personality dimensions. Correlations for the subscales were established post hoc whenever significant association with the main scale was observed.

RESULTS

Anatomical Analysis

Table 1 summarizes the anatomical data. One can appreciate large measurement dispersion (SD relative to mean) mainly for anterior cingulate surface areas (left, 32%; right, 25%), indicating a relevant amount of interindividual variability in the extent of this brain region.

For the anterior cingulate gyrus, ANOVA including brain volume as a covariate showed significant main effect of hemisphere ($F = 12.1$, $df = 1, 98$, $P = 0.001$) and gender ($F = 4.0$, $df = 1, 97$, $P = 0.048$). Post hoc comparisons revealed that the right anterior cingulate gyrus was significantly larger than the left only in women ($F = 12.6$, $df = 1, 49$, $P = 0.001$; see also 95% confidence intervals in Table 1) and that women showed larger right anterior cingulate than men after controlling for gender differences in brain volume ($F = 9.2$, $df = 1, 97$, $P = 0.003$). Hemisphere-by-gender interaction, however, was not significant ($F = 2.1$, $df = 1, 98$, $P = 0.15$). For the posterior cingulate region, no effects or interactions were significant.

Hemispheric asymmetry for the anterior cingulate gyrus was very common (Table 1). In 83% of subjects, the asymmetry index for this brain region was below

TABLE 1

Summary of Anatomical Results

Surface area (mm²)	Left Mean	Left SD	Left CV	Right Mean	Right SD	Right CV	Mean difference	95% CI of the difference
Anterior cingulate gyrus								
Total (N = 100)	819	262	32	932	231	25	112	−177 to −48
Women	787	237	30	946	204	22	−159	−249 to −69
Men	852	284	33	918	256	28	66	159 to 28
Posterior cingulate region								
Total (N = 100)	2157	259	12	2158	248	11	1	42 to 40
Women	2079	245	12	2088	247	12	10	71 to 52
Men	2235	250	11	2229	232	10	7	49 to 63

Brain volume (ml)	Mean	SD	CV
Women (N = 50)	1248	78	6
Men (N = 50)	1383	93	7

Asymmetry (No. of subjects)	Left > right	Left = right	Left < right
Anterior cingulate gyrus			
Total (N = 100)	31	17	52
Women	11	8	31
Men	20	9	21
Posterior cingulate region			
Total (N = 100)	14	71	15
Women	6	37	7
Men	8	34	8

Note. CI, confidence interval; SD, standard deviation; CV, coefficient of variation, 100 × ratio between SD and mean.

−5 or above 5. In contrast, the posterior cingulate region was asymmetrical in only 29% of subjects. This regional difference in the frequency of hemispheric asymmetry was significant at $\chi^2 = 59.2$ and $P < 0.001$. The distribution of asymmetry patterns for the anterior cingulate gyrus was not the same in both genders ($\chi^2 = 4.5$, $P = 0.03$). In men, right-sided and left-sided asymmetries were equally likely (42% vs 40%), whereas the right-sided pattern predominated in women (62% vs 22%).

Temperament and Character Profiles

Table 2 describes results obtained in Cloninger's TCI. Women and men showed personality profiles similar to those reported for a normal population (i.e., *T* score values around 50), except in Self-Transcendence. Our subjects scored notably low in this culture-loaded personality dimension.

The comparisons between genders produced some relevant findings. Women scored significantly higher than men in Harm Avoidance and Reward Dependence. Men had a tendency to score higher in Novelty Seeking, although mean group differences were not significant in this case (see 95% confidence intervals in Table 2).

Correlations between Anatomical Data and Personality Traits

Table 3 provides the results from the correlations (controlled for brain volume) between the four cingulate measurements and the seven TCI scores. In this analysis, surface measurements of the right anterior cingulate gyrus accounted for a significant 24% of score variance in Harm Avoidance ($r = 0.49$, $N = 100$, $P < 0.001$, adjusted $r^2 = 0.24$). The correlation was significant in both gender groups (women $r = 0.48$, $N = 50$, $P < 0.001$; men $r = 0.43$; $N = 50$, $P = 0.002$).

We examined the effect of controlling the correlations for brain volume and found that its influence was not substantial. If no adjustment was applied, the correlation between raw area measurements of the right anterior cingulate and Harm Avoidance scores was $r = 0.41$ ($N = 100$, $P < 0.001$) in the total series, $r = 0.48$ ($N = 50$, $P < 0.001$) in women, and $r = 0.38$ ($N = 50$, $P = 0.007$) in men.

We investigated which of the different subscales included in Harm Avoidance were responsible for the association observed and found significant correlations for all four components: *anticipatory worry* ($r = 0.35$, $N = 100$, $P < 0.001$), *fear of uncertainty* ($r = .29$, $N = 100$, $P = 0.004$), *shyness with strangers* ($r = 0.26$, $N =$

TABLE 2

Personality Traits in the Total Series ($N = 100$) and Gender Groups ($N = 50$ each)

TCI dimension	Total series (mean (SD))	Women (mean (SD))	Men (mean (SD))	Mean difference	95% CI of difference
Harm Avoidance	52.1 (8.0)	54.8 (8.0)	49.3 (6.9)	5.5	2.6 to 8.5
Novelty Seeking	53.2 (9.6)	51.5 (9.8)	54.9 (9.2)	3.4	7.1 to 0.4
Reward Dependence	54.2 (8.3)	56.7 (7.5)	51.7 (8.3)	4.9	1.8 to 8.1
Persistence	45.6 (10.7)	44.5 (11.6)	46.7 (9.8)	2.3	6.5 to 2.0
Self-Directedness	52.1 (9.0)	52.5 (9.0)	51.6 (9.2)	0.9	2.7 to 4.5
Cooperativeness	51.2 (7.4)	52.3 (6.6)	50.1 (7.8)	2.2	0.7 to 5.1
Self-Transcendence	38.3 (10.3)	38.2 (9.1)	38.4 (11.3)	0.1	4.2 to 4.0

Note. CI, confidence interval. Temperament and Character Inventory (TCI) scores are standardized *T* scores.

100, $P = 0.011$), and *fatigability* ($r = 0.40$, $N = 100$, $P < 0.001$).

As can also be seen in Table 3, there was a significant positive correlation ($r = 0.37$, $N = 100$, $P < 0.001$) between surface measurements of the left posterior cingulate region and Novelty Seeking scores. This correlation was significant in women ($r = 0.48$, $N = 50$, $P < 0.001$), but not in men ($r = 0.24$, $N = 50$, $P = 0.102$). Three of the four Novelty Seeking subscales contributed to this correlation in women: *exploratory excitability* ($r = 0.48$, $N = 50$, $P = 0.001$), *impulsiveness* ($r = 0.31$, $N = 50$, $P = 0.03$), and *extravagance* ($r = 0.39$, $N = 50$, $P = 0.005$).

As mentioned above, women showed higher scores than men did for Harm Avoidance and also exhibited larger relative right anterior cingulate areas. We further analyzed gender differences in Harm Avoidance by using the anatomical variables as covariates. As expected, gender differences in the total brain volume were unable to explain gender differences in Harm Avoidance substantially. Univariate ANOVA comparing Harm Avoidance between women and men was highly significant before ($F = 13.7$, $df = 1, 98$, $P < 0.001$) and after ($F = 9.8$, $df = 1, 97$, $P = 0.002$) adding brain volume as the first covariate. In contrast, gender differences in Harm Avoidance were substantially reduced when the right anterior cingulate area was added to the analysis as a second covariate ($F = 3.7$, $df = 1, 96$, $P = 0.058$).

DISCUSSION

Our results confirm that surface area of the anterior cingulate gyrus varies largely from person to person and between the left and the right hemispheres. We found that asymmetry is the norm in this brain region and that a prominent right anterior cingulate is more frequent in women than in men. Surface measurements of the right anterior cingulate gyrus significantly correlated with Harm Avoidance, a personality dimension for which women reported higher scores. Interestingly, differences between women and men in Harm Avoidance paralleled gender differences in the extent of the right anterior cingulate gyrus.

Several authors noted anatomical variability in the pattern and location of the cingulate sulcus and related sulci and described hemisphere asymmetries (Vogt *et al.*, 1995; Paus *et al.*, 1996a,b; Yucel *et al.*, 2001; Ono *et*

TABLE 3

Correlation between Cingulate Region Areas and TCI Scores ($N = 100$)

	Anterior Cingulate Gyrus				Posterior Cingulate Region			
	Left		Right		Left		Right	
TCI dimension	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Harm Avoidance	0.02	0.854	**0.49**	**<0.001**	0.18	0.069	0.07	0.509
Novelty Seeking	0.21	0.035	0.12	0.226	**0.37**	**<0.001**	0.09	0.393
Reward Dependence	0.09	0.395	0.12	0.234	0.04	0.708	0.05	0.611
Persistence	0.06	0.589	0.12	0.254	0.04	0.704	0.01	0.925
Self-Directedness	0.10	0.306	0.22	0.026	0.12	0.228	0.10	0.351
Cooperativeness	0.08	0.455	0.19	0.059	−0.04	0.727	0.02	0.878
Self-Transcendence	0.11	0.291	0.03	0.779	0.14	0.164	0.05	0.657

Note. Adjusted to brain volume using partial correlations. *P* values are two-tailed. Significant correlations after Bonferroni correction are indicated in bold.

al., 1990; Ide *et al.*, 1999). Paus *et al.* (1996a) measured the intrasulcal gray matter volume of the cingulate sulcus in healthy volunteers and found larger relative volumes in women and a right-sided asymmetry for the anterior segment. Our study provides morphometric data expanding on previous anatomical studies and reports specific behavioral correlates for structural variations in this region.

We found that the right anterior cingulate gyrus was significantly larger than the left only in women. This finding contrasts with the results of Yücel *et al.* (2001) showing less asymmetry in women for the fissurization pattern of the paracingulate sulcus. The paracingulate sulcus delineates a cortical area mostly devoted to cognitive operations (Devinsky *et al.*, 1995; Paus *et al.*, 1993). Women indeed tend to show reduced asymmetry in some cognitive functions such as language (Springer and Deutsch, 1998). As our study assessed the "limbic" part of the cingulate cortex, the question is open as to whether women, compared to men, show different asymmetry levels in the affective and cognitive brain domains.

We found that healthy university subjects with a prominent right anterior cingulate gyrus described themselves as being more careful, cautious, worried about possible problems, tense and fearful in situations of uncertainty, shy with strangers, and easily fatigable than average. Cloninger's Harm Avoidance dimension correlates with introversion in some studies and with increased emotional responsivity in others (Cloninger *et al.*, 1994; Cloninger, 1987). Therefore, the extent of the right anterior cingulate gyrus and, by inference, of limbic Brodmann areas 24a, 24b, and 25 seems to be associated with a tendency to withdrawal-related behavior as opposed to approach related behavior.

The anterior cingulate cortex may indeed account for several physiological and behavioral phenomena assembled with these temperamental traits. Anterior cingulate activity fluctuates with the level of both cortical arousal (Paus, 2000) and peripheral autonomic arousal (Critchley *et al.*, 2000), which are arguably higher in worried and fearful people (Davis, 1997). Intense alertness may lead to early fatigue. The anterior cingulate cortex also modulates physiological events accompanying behavioral inhibition. Specifically, stimulation of the perigenual cingulate cortex produces strong inhibitory effects on respiration, decreases arterial blood pressure, and inhibits neural reflexes and movements induced by cortical stimulation (Kaada, 1960). Lesions on the anterior cingulate impair the acquisition of avoidance learning and increase risk-taking behavior in animals (Vogt *et al.*, 1992). In humans, anterior cingulotomy reduces responsivity to and worry caused by noxious stimuli and relieves anxiety in patients with psychiatric disorders (Vogt *et al.*, 1992).

In a broad sense, our findings are consistent with the assumed specialization of each hemisphere in the control of behavior. The right hemisphere is more efficient than the left in monitoring sensory inputs for alerting signals and mediating stimulus triggered reactions (Heilman, 1997; Pujol *et al.*, 2000). Specifically, an asymmetrical (greater right than left) frontal activation is associated with emotional responses related to suppression of ongoing activity such as fear and disgust (Davidson, 1995). The association of large right, but not left, anterior cingulate with Harm Avoidance further supports the right-hemisphere role in such processes.

The left hemisphere appears to be involved more than the right in the control of motivation and approach-related behavior (Pujol *et al.*, 1997, 2000; Davidson, 1995; Tucker and Liotti, 1989; Gainotti, 1997). For example, people who exhibit greater relative left frontal activity tend to be socially outgoing and extraverted (Schmidt and Fox, 1994). The association of Novelty Seeking with surface area of the left posterior cingulate region thus conforms to the expected direction.

Our study supports investigations suggesting that Cloninger's TCI separates basic dimensions of personality closely related to biological aspects of brain functioning. Cloninger proposes, for example, that variations in Harm Avoidance are correlated with high serotonergic activity, Novelty Seeking with low basal dopaminergic activity, and Reward Dependence with low noradrenergic activity (Cloninger, 1987). This framework of central monoaminergic pathways proposed for interpreting TCI results is supported by specific biochemical, genetic, and neuroimaging research (Cloninger, 1994; Suhara *et al.*, 2001; Peirson *et al.*, 1999; Okuyama *et al.*, 2000).

The anterior cingulate gyrus is only one of many components of the complex serotonin-modulated behavior inhibitory system—a neural system that is not restricted to a single hemisphere (Cloninger, 1987). The studies of brain metabolism actually show a variety of brain regions correlating with personality scores (Sugiura *et al.*, 2000; Johnson *et al.*, 1999; Menza *et al.*, 1995). Likewise, structural changes that may account for specific personality profiles wholly involve both frontal lobes (Matsui *et al.*, 2000, Raine *et al.*, 2000). It is obvious that our lateralized finding in humans may only explain a part of the biological substrate of Harm Avoidance. It is remarkable, however, that significant asymmetry exists even in the distribution of brain monoamines. The available data conform to our results as they point to a right hemisphere lateralization of serotonin and noradrenaline activity and a higher left hemisphere concentration of dopamine (Wittling, 1995).

In keeping with the normative study of Cloninger *et al.* (1991), we found that women scored higher than men in Harm Avoidance. Gender differences for Harm Avoidance covaried with the gender dimorphism observed for the right anterior cingulate gyrus. This finding may be relevant in the extent to which a greater development of this brain region in women could, in turn, codetermine increased caution, anticipatory worry, or a major tendency to avoid possible danger.

Our correlational study, however, does not inform as to the direction of this structure–function relationship. It is equally likely, for example, that these personality characteristics and the associated pattern of behavior may lead to a cascade of physiological events, such as the release of monoamines in the anterior cingulate region, which affect the volume of the target region (Paus, 2001). We would also emphasize that the studied sample was made up of university students and graduates, who do not represent the general population, but rather a homogeneous sector of young adults from Barcelona with a high educational level.

We conclude that anatomical variations in the medial brain surface may account for a significant part of individual differences in Cloninger's Harm Avoidance. The behavioral expression of this basic personality dimension is consistent with the role of the cingulate cortex in the control behavior. Our observations suggest that a large right anterior cingulate gyrus is related to a temperamental disposition to fear and anticipatory worry in both genders and that a higher prevalence of these traits in women may be coupled with a greater expansion of this brain region.

ACKNOWLEDGMENTS

This study was supported in part by the Fondo de Investigación Sanitaria (Grant 00/0226) and the Direcció General de Recerca de la Generalitat de Catalunya (Grants 1999SGR-328 and 2000XT-43). We thank Gerald Fannon, Ph.D., for revising the manuscript and Fernando Gutiérrez, Ph.D., for his contribution.

REFERENCES

Cloninger, C. R. 1987. A systematic method for clinical description and classification of personality variants. *Arch. Gen. Psychiatry* **44:** 573–588.

Cloninger, C. R., Przybeck, T. R., and Svrakic, D. M. 1991. The tridimensional personality questionnaire: U.S. normative data. *Psychol. Rep.* **69:** 1047–1057.

Cloninger, C. R., Svrakic, D. M., and Przybeck, T. R. 1993. A psychobiological model of temperament and character. *Arch. Gen. Psychiatry* **50:** 975–990.

Cloninger, C. R., Przybeck, T. R., Svrakic, D. M., and Wetzel, R. D. 1994. *The Temperament and Character Inventory (TCI): A Guide to Its Development and Use.* Center for Psychobiology of Personality, St. Louis.

Critchley, H. D., Corfield, D. R., Chandler, M. P., Mathias, C. J., and Dolan, R. J. 2000. Cerebral correlates of autonomic cardiovascular arousal: A functional neuroimaging investigation in humans. *J. Physiol. London* **523:** 259–270.

Davidson, R. J. 1995. Cerebral asymmetry, emotion, and affective style. In *Brain Asymmetry* (R. J. Davidson and K. Hugdahl, Eds.), pp. 361–387. MIT Press, Cambridge, MA.

Davis, M. 1997. Neurobiology of fear responses: The role of the amygdala. In *The Neuropsychiatry of Limbic and Subcortical Disorders* (S. Salloway, P. Malloy, and J. L. Cummings, Eds.), pp. 71–91. Am. Psychiatric Press, Washington, DC.

Devinsky, O., Morrell, M. J., and Vogt, B. A. 1995. Contributions of anterior cingulate cortex to behaviour. *Brain* **118:** 279–306.

Gainotti, G. 1997. Emotional disorders in relation to unilateral brain damage. In *Behavioral Neurology and Neuropsychology* (T. E. Feinberg and M. J. Farah, Eds.), pp. 691–698. McGraw–Hill, New York.

Galaburda, A. M., Corsiglia, J., Rosen, G. D., and Sherman, G. F. 1987. Planum temporale asymmetry, reappraisal since Geschwind and Levitsky. *Neuropsychologia* **25:** 853–868.

Gutierrez, F., Torrens, N., Bogel, T., Martin-Santos, R., Sangorrin, J., Perez, G., and Salamero, M. 2000. Psychometric properties of the Temperament and Character Inventory (TCI) questionnaire in a Spanish psychiatric population. *Acta Psychiatr. Scand.* **102:** 1–5.

Heilman, K. M. 1997. The neurobiology of emotional experience. In *The Neuropsychiatry of Limbic and Subcortical Disorders* (S. Salloway, P. Malloy, and J. L. Cummings, Eds.), pp. 133–142. Am. Psychiatric Press, Washington, DC.

Ide, A., Dolezal, C., Fernández, M., Labbe, E., Mandujano, R., Montes, S., Segura, P., Verschae, G., Yarmuch, P., and Aboitiz, F. 1999. Hemispheric differences in variability of fissural patterns in parasylvian and cingulate regions of human brains. *J. Comp. Neurol.* **410:** 235–242.

Johnson, D. L., Wiebe, J. S., Gold, S. M., Andreasen, N. C., Hichwa, R. D., Watkins, G. L., and Boles Ponto, L. L. 1999. Cerebral blood flow and personality: A positron emission tomography study. *Am. J. Psychiatry* **156:** 252–257.

Kaada, B. 1960. Cingulate, posterior orbital, anterior insular and temporal pole cortex. In *Neurophysiology* (J. Field, H. Magoun, and V. Hall, Eds.), Vol. 2, pp. 1345–1372. Am. Physiol. Soc., Washington, DC.

Kaufman, A. S., and Kaufman, N. L. 1994. *Kaufman Brief Intelligence Test (K-BIT).* American Guidance Service, Circle Pines, MN.

Matsui, M., Gur, R. C., Turetsky, B. I., Yan, M. X. H., and Gur, R. E. 2000. The relation between tendency for psychopathology and reduced frontal brain volume in healthy people. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **13:** 155–162.

Menza, M. A., Mark, M. H., Burn, D. J., and Brooks, D. J. 1995. Personality correlates of [^{18}F]dopa striatal uptake: Results of positron-emission tomography in Parkinson's disease. *J. Neuropsychiatry Clin. Neurosci.* **7:** 176–179.

Okuyama, Y., Ishiguro, H., Nankai, M., Shibuya, H., Watanabe, A., and Arinami, T. 2000. Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. *Mol. Psychiatry* **5:** 64–69.

Oldfield, R. C. 1971. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* **9:** 97–113.

Ono, M., Kubik, S., and Abernathey, C. D. 1990. *Atlas of the Cerebral Sulci.* Thieme, Stuttgart.

Paus, T. 2000. Functional anatomy of arousal and attention systems in the human brain. *Prog. Brain Res.* **126:** 65–77.

Paus, T. 2001. Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nat. Rev. Neurosci.* **2:** 417–424.

Paus, T., Petrides, M., Evans, A. C., and Meyer, E. 1993. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: A positron emission tomography study. *J. Neurophysiol.* **70:** 453–469.

Paus, T., Otaky, N., Caramanos, Z., MacDonald, D., Zijdenbos, A., D'Avirro, D., Gutmans, D., Holmes, C., Tomaiuolo, F., and Evans, A. C. 1996a. In vivo morphometry of the intrasulcal gray matter in the human cingulate, paracingulate, and superior-rostral sulci

Hemispheric asymmetries, gender differences and probability maps. *J. Comp. Neurol.* **376:** 664–673.

Paus, T., Tomaiuolo, F., Otaky, N., MacDonald, D., Petrides, M., Atlas, J., Morris, R., and Evans, A. C. 1996b. Human cingulate and paracingulate sulci: Pattern, variability, asymmetry, and probabilistic map. *Cereb. Cortex* **6:** 207–214.

Paus, T., Koski, L., Caramanos, Z., and Westbury, C. 1998. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: A review of 107 PET activation studies. *NeuroReport* **9:** R37–R47.

Peirson, A. R., Heuchert, J. W., Thomala, L., Berk, M., Plein, H., and Cloninger, C. R. 1999. Relationship between serotonin and the temperament and character inventory. *Psychiatry Res.* **89:** 29–37.

Pujol, J., Bello, J., Deus, J., Martí-Vilalta, J. L., and Capdevila, A. 1997. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* **49:** 1105–1110.

Pujol, J., Conesa, G., Deus, J., López-Obarrio, L., Isamat, F., and Capdevila, A. 1998. Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. *J. Neurosurg.* **88:** 863–869.

Pujol, J., Deus, J., Losilla, J. M., and Capdevila, A. 1999. Cerebral lateralization of language in normal left-handed people studied by functional MRI. *Neurology* **52:** 1038–1043.

Pujol, J., Bello, J., Deus, J., Cardoner, N., Martí-Vilalta, J. L., and Capdevila, A. 2000. Beck Depression Inventory factors related to demyelinating lesions of the left arcuate fasciculus region. *Psychiatr. Res. Neuroimaging* **99:** 151–159.

Pujol, J., Vendrell, P., Deus, J., Junqué, C., Bello, J., Martí-Vilalta, J. L., and Capdevila, A. 2001. The effect of medial frontal and posterior parietal demyelinating lesions on Stroop interference. *NeuroImage* **13:** 68–75. doi:10.1006/nimg.2000.0662.

Raine, A., Lencz, T., Bihrle, S., LaCasse, L., and Colletti, P. 2000. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch. Gen. Psychiatry* **57:** 119–127.

Schmidt, L. A., and Fox, N. A. 1994. Patterns of cortical electrophysiology and autonomic activity in adults' shyness and sociability. *Biol. Psychol.* **38:** 183–198.

Shapleske, J., Rossell, S. L., Woodruff, P. W. R., and David, A. S. 1999. The planum temporale: A systematic, quantitative review of its structural, functional and clinical significance. *Brain Res. Rev.* **29:** 26–49.

Springer, S. P., and Deutsch, G. 1998. Sex differences in cognition and asymmetry. In *Left Brain, Right Brain: Perspectives from Cognitive Neuroscience* (R. C. Atkinson, G. Lindzey, and R. F. Thompson, Eds.), 5th ed., pp. 139–156. Freeman, New York.

Sugiura, M., Kawashima, R., Nakagawa, M., Okada, K., Sato, T., Goto, R., Sato, K., Ono, S., Schormann, T., Zilles, K., and Fukuda, H. 2000. Correlation between human personality and neural activity in cerebral cortex. *NeuroImage* **11:** 541–546. doi:10.1006/nimg.2000.0564.

Suhara, T., Yasuno, F., Sudo, Y., Yamamoto, M., Inoue, M., Okubo, Y., and Suzuki, K. 2001. Dopamine D2 receptors in the insular cortex and the personality trait of novelty seeking. *NeuroImage* **13:** 891–895. doi:10.1006/nimg.2001.0761.

Tucker, D. M., and Liotti, M. 1989. Neuropsychological mechanisms of anxiety and depression. In *Handbook of Neuropsychology* (F. Boller and J. Grafman, Eds.), Vol. 3, pp. 443–475. Elsevier, Amsterdam.

Vogt, B. A., Finch, D. M., and Olson, C. R. 1992. Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. *Cereb. Cortex* **2:** 435–443.

Vogt, B. A., Nimchinsky, E. A., Vogt, L. J., and Hof, P. R. 1995. Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *J. Comp. Neurol.* **359:** 490–506.

Wittling, W. 1995. Brain asymmetry in the control of autonomic-physiologic activity. In *Brain Asymmetry* (R. J. Davidson and K. Hugdahl, Eds.), pp. 305–357. MIT Press, Cambridge, MA.

Yucel, M., Stuart, G. W., Maruff, P., Velakoulis, D., Crowe, S. F., Savage, G., and Pantelis, C. 2001. Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: An MRI morphometric study. *Cereb. Cortex* **11:** 17–25.

4.2.2. *Artículo 4: Alexithymia correlates with the size of the right anterior cingulate*

Alexithymia Correlates With the Size of the Right Anterior Cingulate

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Objective: The authors investigated a possible relationship between interindividual variability in anterior cingulate gyrus (ACG) morphology and alexithymia. **Materials and Methods:** Magnetic resonance images were obtained in 100 healthy university graduates (51 female, 49 male; mean age 25.6 y). Surface area measurements of the ACG were performed on reformatted sagittal views in both hemispheres. The Toronto Alexithymia Scale (TAS-20) and the Temperament and Character Inventory (TCI) were administered. **Results:** Right ACG surface area significantly correlated with TAS-20 total score in men ($r = 0.37$; $p = 0.009$) and in women ($r = 0.30$; $p = 0.034$). After controlling for three TCI subscales (harm avoidance, self-directedness, and self-transcendency), the correlation between TAS-20 total and right ACG became nonsignificant in women, but was only slightly reduced ($r = 0.32$; $p = 0.032$) in men. A linear regression model with right ACG as a dependent variable revealed brain volume, TCI-harm avoidance and TAS 20 total score as significant predictors in the total sample (explained proportion of total variation (EPTV) 37%). In men, beside brain volume, only TAS-20 total score showed a highly significant contribution (EPTV 41%), whereas in women only TCI-harm avoidance was a significant predictor (EPTV 36%). **Conclusions:** The authors' findings indicate that there is a significant positive relation between the size of the right ACG and alexithymia as measured with the TAS in healthy subjects. This applies especially for men whereas in women ACG size is more associated with the subscale harm avoidance of the TCI. Our findings also suggest a partial lateralization of human emotion processing, especially negative emotion. **Key words:** alexithymia, anterior cingulate, emotion processing, lateralization, personality.

ACG = anterior cingulate gyrus; **ACC** = anterior cingulate cortex; **TAS-20** = Toronto Alexithymia Scale, 20-item version; **TCI** = Temperament and Character Inventory; **HA** = TCI subscale harm avoidance; **SD** = TCI subscale self-directedness; **ST** = TCI subscale self-transcendence; **BA** = Brodmann's area; **MRI** = magnetic resonance imaging; **PET** = positron emission tomography; **CSF** = cerebrospinal fluid; **CBF** = cerebral blood flow; **CNS** = central nervous system; **PTSD** = posttraumatic stress disorder; **THC** = tetra-hydro-cannabinol. **EPTV** = explained proportion of total variation.

INTRODUCTION

Alexithymia (from the Greek "a" for lack, "lexis" for word, and "thymos" for emotion) refers to a specific disturbance in emotional processing that is manifested clinically by difficulties in identifying and verbalizing feelings, in elaborating fantasies, and by a tendency to focus on and amplify the somatic sensations accompanying emotional arousal. Nowadays, alexithymia is conceptualized as multifaceted and dimensional, rather than a categorical construct. Salient features are the inability to distinguish one's feelings from the accompanying bodily sensations, the inability to communicate feelings to others, and an externally orientated cognitive style reflecting an absence of inner thoughts and fantasies. These three lower-order concepts reflect separate, yet empirically related, facets of the alexithymia construct (1).

Referring to the neurobiological basis of alexithymia, a structural/cerebral deficit was hypothesized as early as in the end of the 1970s. MacLean (2) inferred that the limbic system ("visceral brain") functions as a crude analyzing mechanism that derives information and interprets experience in terms of emotional states instead of symbolic thoughts (3). He further speculated that, instead of being related to the neocortex (which he referred to as the "word brain"), distressing emotions find immediate expression through autonomic pathways (4). Nemiah suggested a neurophysiological dysfunction, caused by a "lack of adequate neuronal connections" between limbic system and neocortex (5). Theories further evolved from Nemiah's "vertical" model to a "horizontal" model. Hoppe and Bogen (6) observed a paucity of fantasies, difficulty in describing feelings, and an operative style of thinking in 12 "split-brain" individuals (ie, patients who had undergone cerebral commissurotomies for treatment of intractable epilepsy). Thus Hoppe assumed a "functional commissurotomy" in alexithymia (6). Numerous studies were then conducted, hypothesizing a hemispheric specialization (7–10) and/or an interhemispheric transfer deficit in alexithymia (6,8,11–19).

This deficit could apply particularly to men, as was suggested by a study showing that among men, alexithymic deficits in the ability to identify or describe feelings were related to both a relative impairment in the functioning of the right hemisphere and an impairment in the ability to transfer information between cerebral hemispheres. In contrast, women exhibited less hemisphericity and appeared to be more bilaterally organized (20), suggesting that the neurobiological substrate of alexithymia may be different in men and women.

In addition, some studies have explored the relationship between alexithymia and personality traits. Two studies found

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Received for publication November 10, 2002; revision received May 27, 2003.

Within the n = 9 left-handed subjects, right AC surface area (730.1 mm^2) is smaller than left AC surface area (765.9 mm^2), whereas we find the opposite asymmetry pattern in the n = 91 right-handed subjects (right AC: 931.0 mm^2; left AC: 811.2 mm^2). There is no significant difference in TAS-20 (39.7 vs. 36.3) or TCI-HA (52.5 vs. 49.2), TCI-SD (52.2 vs. 51.7), and TCI-ST (38.2 vs. 41.3) values between right- and left-handed people. In addition there is a positive correlation between right AC extent and TAS-20 score within the n = 9 left-handed subjects ($r = 0.45$, $p = 0.261$), the n = 91 right-handed subjects ($r = 0.23$, $p = 0.027$) and the whole sample (n = 100; $r = 0.27$, $p = 0.006$). Because it is unclear if the different asymmetry of the right versus left AC surface area in right- and left-handed people is caused by systematic or coincidental differences, and the correlations between AC extent and TAS-20 score are significant in the right-handed subjects as well as the whole sample, we have reported the results of the whole (n = 100) sample.

DOI: 10.1097/01.PSY.0000097348.45087.96

0033-3174/04/6601-0132

a positive correlation between alexithymia and neuroticism and a negative correlation with openness and extraversion (21,22). The correlations with the temperament and character dimensions and subscales described within Cloninger's empirically confirmed psychobiological model of personality (23) have also been studied. Thus, in a recent study including 254 psychiatric inpatients and outpatients, the temperament and character inventory (TCI) dimensions harm avoidance, low self-directedness, and low reward dependence were found to be independent predictors for alexithymia (24). These personality traits may contribute to the characterization of high alexithymic patients as experiencing predominantly poorly differentiated emotional distress because they lack the necessary psychological capacities for modulating emotions (25). In recent years, several personality theorists have emphasized the need for linking personality constructs with neurobiological processes that might underlie individual differences in personality (3).

The anterior cingulate cortex (ACC) has classically been related to affect (26) and is part of a circuit involved in a form of attention that serves to regulate emotional processing (2–30). However, in addition to emotion, the ACC is now recognized to play important roles in attention processing, pain, response selection, maternal behavior, skeletomotor function, and autonomic control (31). Convergent data suggest that the ACC is functionally divided into two major subdivisions that subserve distinct functions, ie, a dorsal cognitive part (BA areas 24b'-c' and 32') and a rostral–ventral affective part (BA areas 24a-c and 32, ventral areas 25 and 33) (32). There is some evidence suggesting that the rostral ACC serves a more exclusively emotional function, whereas the dorsal ACC appears to serve a superordinate function that may be greatly influenced by, but is not exclusively dedicated to, emotional processing. Lane (33) considered the possibility that both of these areas of the ACC are participating in different aspects of conscious emotional experience. He hypothesized that the dorsal ACC may reflect phenomenal awareness (direct experience) of emotion. In keeping with this, a PET study showed that individual differences in the ability to accurately detect emotional signals interoceptively or exteroceptively was a function of the right dorsal ACC (BA 24) (34, 35). In contrast, the rostral ACC (together with the medial prefrontal cortex) may participate in cognitive operations performed on the contents of phenomenal experience of emotion, ie, in reflective awareness of emotion or "knowing how one is feeling" (33). Thus, the tight anatomical linkage (33) between the rostral and dorsal anterior cingulate cortices may be the anatomical basis for generating the interaction between the phenomenal experience of emotion and establishing and elaborating on the representations of that emotional experience (33).

On the basis of the findings that: (1) emotional awareness is negatively correlated with alexithymia; (2) emotional awareness is correlated with blood flow in the ACC during emotion; and (3) the ACC is one of those structures involved in emotional experience. Lane et al. hypothesized alexithymia as a deficit in the conscious awareness of emotion that would be associated with a circumscribed, strategically located deficit in the anterior cingular cortex activation during emotional arousal, and proposed to conceptualize alexithymia as the emotional equivalent of blindsight (34). This "blindfeel" hypothesis therefore introduces the possibility that the sensory component of attention, ie, the spotlight of consciousness, is another essential function of the ACC, and that the ACC could thus mediate conscious attention to both "cognitive" and "emotional" stimuli.

There is growing evidence that variations in the morphology of the ACC reflect underlying functional anatomy (36–38). Interestingly, Good et al. (39) used voxel-based morphometry to examine the MRI exams of 465 normal subjects and found left-predominant asymmetry for the anterior cingulate sulcus and right-predominant asymmetry for the anterior cingulate gyrus. Moreover, females had significantly more gray matter volume within the right cingulate gyrus than males. Summarizing these data and our own results (40) suggests that the right cingulate gyrus is larger than the left, particularly in women.

In addition, in a previous article linking cingulate measurements to personality constructs (four temperament and three character dimensions of the TCI), our group found a significant positive correlation between surface measurements of the right anterior cingulate gyrus and the character dimension "harm avoidance" in both sex groups (40).

In the present study we tested the hypothesis that alexithymia may also have a structural substrate in that interindividual variability in ACG morphology correlates with the Toronto-Alexithymia-Scale (TAS-20). Specifically, the primary hypothesis of the study was that the surface area of the right ACG is negatively correlated with the TAS-20 score.

As secondary hypothesis, we expected that right ACG and TAS-20 are more correlated in men than in women.

MATERIALS AND METHODS

Subjects

Recruited volunteers included 100 healthy subjects, with 51 women and 49 men between ages 20 and 43 years. This sample overlaps partly with a sample described elsewhere (40). Recruitment was individually performed by university teachers in the university environment of Barcelona with no payment offered. The subjects were screened for a positive history of neurological, psychiatric, and serious medical disorders, as well as for alcohol and drug abuse.

Mean age for the total sample was 25.6 (SD 4.2) years and was 25.5 (SD 3.6) years for women and 25.8 (SD 4.8) years for men. All selected participants were white residents from Barcelona and all were in final year of university or graduates. According to the Edinburgh Handedness Inventory (41) 91) subjects had a right-hand preference and 9 subjects had a left-hand preference. After a complete description of the study to the subjects, written informed consent was obtained.

Alexithymia and Personality Assessment

A validated Spanish translation using back-translation methodology (42) of the 20-item TAS-20 was applied in this study as a screening device for measuring alexithymia. The TAS-20 is the most widely used and validated alexithymia measure. In this study, the total score was analyzed, as well as the score of the three facets: factor 1 (f1; difficulty identifying feelings); factor 2 (f2; difficulty describing feelings); factor 3 (f3; externally orientated thinking). We analyzed these scores as continuous dimensions rather than by comparing extreme groups.

Additionally, a validated Spanish translation (43) of the 240-item Temperament and Character Inventory (TCI) version 9 (44) was used in this study. This questionnaire produces separate scores for four temperament and three character dimensions. The four temperament dimensions novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS) are thought to determine predominantly inherited automatic emotional responses that can already be observed early in life. These dimensions involve preconceptual biases in perceptual memory and habit formation toward external and internal stimuli (45,46). Contrary to the temperament dimensions, the character dimensions self-directedness (SD), cooperativeness (CO), and self-transcendence (ST) are thought to develop with the maturing self-concept in adulthood, influencing personal and social style by insight learning (24). All dimensions, except persistence, have three to five lower-order subscales. Within this context, harm avoidance reflects a tendency to respond intensely to aversive stimuli and involves anticipatory worry about possible problems, fear of uncertainty, shyness with strangers, and consequent easy fatigability. People with a high score in harm avoidance are described as pessimistic, worrisome, fearful, fatiguing, and shy.

MRI Examination

The imaging data were acquired using a 1.5 T magnet (Signa, GE Medical Systems, Milwaukee, WI). A 60-slice three-dimensional (3D) spoiled gradient recalled acquisition in the steady-state sequence was obtained in the sagittal plane. Acquisition parameters were TR 40 ms, TE 4 ms, pulse angle 30°, field of view 26 cm, and matrix size 256 × 192 pixels. Section thickness varied according to the brain size, ranging from 2.4 to 2.6 mm.

The first phase of image analysis was performed on an auxiliary workstation (SPARCstation 20; Sun Microsystems, Mountain View, CA) using commercially available software (Advantage Windows, version 2.0; GE Medical Systems) and adapting procedures used previously (47). A 3D MRI model of each subject's head was constructed and reformatted to high-resolution 1-mm slices. Axial views of the reformatted MRI were used to identify the plane of the interhemispheric fissure and to select two oblique sagittal images that optimally exposed left and right medial brain surfaces. Finally, each oblique sagittal image was coded and stored with no reference to the subject's name, age, sex and hemisphere.

To obtain cerebral volume measurements, a 3D surface rendering of each subject's brain was built by isolating neural tissue from the surrounding CSF using volume segmentation tools (47). The analysis system directly provided the volume (ml) of the entire brain after its isolation in each subject.

In a second phase, reformatted sagittal views were interpolated to a high-resolution matrix (512 × 512 pixels) to perform the surface measurements. A general software for image analysis was used (Image-Pro plus; Media Cybernetics, Silver Spring, MD). Two cingulate regions were manually traced on each hemisphere according to the individual sulcal patterns (Figure 1) and measured in mm^2. The anterior region corresponded to the anterior cingulate gyrus. The posterior cingulate region included the posterior cingulate gyrus and the medial parietal cortex (precuneus). The border between anterior and posterior cingulate regions was established at the midpoint between anterior and posterior commissures, which approximates the boundary between BA areas 24 and 23 (36, 48, 49).

An asymmetry index (50) was computed for both cingulate regions according to the expression 100 * (L − R)/(L + R), in which L and R were measurements for the left and right hemispheres. This index is identical to that used by Paus et al. (48). In accordance with these authors, an absolute value of 5% was considered as the minimum level of asymmetry. This corresponds to the 0.1 asymmetry index values of Galaburda et al. (51) and is conventionally used to compare anatomical asymmetries from different studies (52). Asymmetrical cases, therefore, were those showing values less than −5 (right-side pattern) or more than $^+5$ (left-side pattern).

The measurements were performed by a researcher blind to the subject's age and sex and to any reference identifying brain hemisphere (images from both hemispheres were presented with identical left–right orientation). The reproducibility of measurements proved to be good. Intraclass correlation coefficient of 0.92 was obtained for 100 surface measurements of the right anterior cingulate gyrus repeated after 2 weeks. To assess interrater reliability, a second researcher measured this region in a subsample of 40 randomly chosen cases also in blind conditions. The intraclass correlation coefficient between the two raters was 0.91.

Figure 1. Region delimitation adopted in this study. The anterior cingulate gyrus appears shaded darker than the posterior cingulate region. The arrow of the left picture indicates the presence of a second cingulate sulcus delimiting a paracingulate gyrus that was not included in our region of interest. The arrow in the right picture points to an intralimbic sulcus within the cingulate gyrus. Note the large difference in the extent of the anterior cingulate gyrus in these two subjects.

Statistical Analysis

SPSS for Windows, version 10.0, was used for statistical analysis. Sex differences in anatomical data (Table 1) were tested with *t* tests for independent samples or with ANCOVAs. Asymmetry index rates between anterior and posterior cingulate regions and between sexes were compared with χ^2 tests. To assess the effects of sex and hemisphere and their interaction on cingulate region surface areas, a repeated measures ANCOVA was performed with hemisphere as a within subjects factor, sex as a between subjects factor and brain volume as a covariate. Sex differences in psychometric data were assessed with a *t* test for TAS-20 total score, and with a repeated measures ANOVA for the single facets, with sex as a between subjects, and the three facets as within subjects factors. Correlations between TAS-20 and cingulate region surface areas and between TAS-20 and TCI-scores were presented as bivariate or partial Pearson's product–moment correlation coefficients. Finally, multiple linear regression analysis with right ACG as dependent variable was used to assess the predictive power of TAS-20 total score controlling for several possible confounders. For variable selection we used forward method with the entry criterion $p < 0.05$.

RESULTS

Anatomical Analysis

Table 1 summarizes the anatomical data for the study population. Referring to the raw mean, men showed a slightly larger right ACG than women, although differences were not statistically significant. In contrast, after controlling for brain volume, women showed a larger right ACG than men ($F = 5.64$; $df = 1, 97$; $p < 0.05$) (Table 1). For the left ACG and for the posterior cingulate region, no sex differences were significant after adjusting for brain volume.

It has been observed that hemispheric asymmetry for ACG is very frequent. In 83% of subjects the asymmetry index for this brain region was less than −5 or more than 5. In contrast, the posterior cingulate region was asymmetrical in only 29%

TABLE 1. Summary of Anatomical Results

Surface Area (mm^2)	Left		Right	
	Raw Mean (SD)	Adjusted Mean* (SE)	Raw Mean (SD)	Adjusted Mean* (SE)
Anterior Cingulate Gyrus				
Total	807 (255)	807 (25)	913 (236)	912 (22)
Women	770 (225)	807 (40)	903 (223)	977 (35)
Men	845 (281)	807 (41)	923 (251)	846 (36)
Posterior cingulate region				
Total	2148 (259)	2148 (23)	2153 (244)	2152 (22)
Women	2082 (245)	2155 (37)	2121 (243)	2184 (35)
Men	2217 (258)	2141 (38)	2199 (239)	2121 (36)

Brain Volume (ml)	Mean	SD
Women	1246	78
Men	1377	90

Asymmetry (% of Subjects)	Left > Right	Left = Right	Left < Right
Anterior cingulate gyrus			
Total	32	17	51
Women	25	18	57
Men	39	16	45
Posterior cingulate region			
Total	14	71	15
Women	10	76	14
Men	18	65	16

SD, standard deviation; SE, standard error.
* Adjusted for brain volume.

of subjects. This regional difference in the frequency of hemispheric asymmetry was significant at $\chi^2 = 59.2$ and $p < 0$ 0.001. Inspection of Table 1 shows that the distribution of asymmetry patterns for the anterior cingulate gyrus was not quite the same in both sexes. However, this difference was not statistically significant.

This asymmetrical pattern of the ACG surface area was further confirmed by means of a repeated measures model with hemisphere as a within–subject factor, sex as a between-subject factor, and total brain volume as covariate, which revealed a significant effect of hemisphere (right > left) (F = 10.3; $df = 1, 98$; $p < 0.01$). Although hemisphere multiplied by sex interaction was not significant (F = 0.7; $df = 1, 98$; $p = 0.404$), post hoc comparisons showed that the right anterior cingulate gyrus was significantly larger than the left only in women (F = 8.9; $df = 1, 49$, $p < 0.01$). Men, however, showed no significant difference in hemispheres (F = 2.6; $df = 1, 48$, $p = 0.113$).

Psychometric Analysis

Table 2 provides alexithymia scores measured with the TAS-20 scale and the scores for each of the subscales for the total sample and for men and women separately. Mean TAS-20 total score was 39.38 (SD: 9.3; range: 24–60). According to the categorical approach of TAS-20 guidelines, 84% ($N = 84$) of the sample could be classified as within the nonalexithymic range (TAS-20 less than or equal to 51), and 16% ($N = 16$) scored greater than 51 but less than 61 (neither alexithymic nor nonalexithymic). Thus, none of the subjects was alexithymic by TAS-20 definition. The quartiles of the

TABLE 2. Summary of Psychometric Data

	Total Series Mean (SD)	Women Mean (SD)	Men Mean (SD)
TAS-20 total score	39.38 (9.27)	37.35 (8.83)	41.49 (9.34)*
TAS-20 factor 1	11.80 (4.89)	11.22 (4.07)	12.41 (5.59)
TAS-20 factor 2	10.93 (4.22)	10.72 (4.28)	11.14 (4.20)
TAS-20 factor 3	16.65 (3.66)	15.41 (3.42)	17.94 (3.47)*

SD: standard deviation.
* Significant sex differences, $p < 0.05$.

distribution of the TAS-20 score were 33 (25%), 37 (50%), and 44 (75%). The comparisons between sexes revealed that men scored higher than women in the total score of the TAS-20 (t = 2.28; *df* = 98; $p < 0.05$) and in factor 3 (externally orientated thinking) (t = 3.66; *df* = 98; $p < 0.001$).

Correlations Between Anatomical and Psychometric Data

Table 3 displays the correlations (controlled for total brain volume) between the extension of the four cingulate regions and the alexithymia scores for the total sample and for men and women separately. Only right ACG significantly correlated with TAS-20 total score in men ($r = 0.37$; $N = 49$; $p < 0.01$) and in women ($r = 0.30$; $N = 51$; $p < 0.05$).

With regard to the single facets of the TAS-20 scale, we found that correlations with right ACG differed between sexes (Table 4). While significant correlations were observed in men between right ACG and factor 1 (difficulty identifying feelings) ($r = 0.40$; $N = 49$; $p < 0.01$) and factor 2 (difficulty describing feelings) ($r = 0.35$; $N = 49$; $p < 0.05$); in women, only a nearly significant correlation was observed with factor 3 (externally orientated thinking) ($r = 0.28$; $N = 51$; $p = 0.052$).

In a previous report (15), we have shown that right ACG surface area was related to harm avoidance, as measured by Cloninger's TCI (19). In our sample TCI harm avoidance, TCI self-directedness and TCI self-transcendence scores were correlated to TAS-20 total score (TCI-HA: $r = 0.21$, $p < 0.05$; TCI-SD: $r = -0.36$, $p < 0.01$; TCI-ST: $r = 0.22$, $p < 0.05$). Thus we studied in how far these three TCI subscales may account for the observed correlation between TAS-20 total score and right ACG surface area.

Controlling for TCI-HA, TCI-SD, and TCI-ST has a differentiating effect depending on sex. In women, the correlation between TAS-20 total score and right ACG became nonsignificant (before controlling for TCI-HA, TCI-SD, TCI-ST: $r = 0.30$; $N = 51$; $p < 0.05$; controlling for TCI-HA, TCI-SD, TCI-ST: $r = 0.09$; $N = 51$;$p = 0.566$). On the contrary, in men, this same correlation was only slightly reduced after controlling for TCI-HA, TCI-SD, and TCI-ST (before controlling for TCI-HA, TCI-SD, TCI-ST: $r = 0.37$; $N = 49$; $p < 0.01$; controlling for TCI-HA, TCI-SD, TCI-ST: $r = 0.32$; $N = 49$; $p < 0.05$).

TABLE 3. Correlations Between AC/PC Surface Area and TAS-20 Total Score

	Total Series (r)	Women (r)	Men (r)
AC			
Right	0.27*	0.30*	0.37*
Left	–0.02	0.06	–0.13
PC			
Right	–0.08	–0.19	0.08
Left	–0.04	–0.04	–0.05

Correlations (r) adjusted to brain volume using partial correlations.
Significance: * $p < 0.01$; ** $p < 0.05$ for two-sided tests.

TABLE 4. Correlations Between TAS-20 Subscales and Right ACG

	Total Series (r)	Women (r)	Men (r)
TAS-F1	0.27*	0.22	0.40*
TAS-F2	0.24*	0.19	0.35*
TAS-F3	0.05	0.28	–0.07

Correlations (r) adjusted for brain volume using partial correlations.
Significance: * $p < 0.01$; ** $p < 0.05$ for two-sided tests.

To further investigate the relationship between right ACG and TAS-20 total score and the possible confounding effects of the TCI dimensions, a linear regression model was applied to the total sample ($N = 100$) with right ACG as dependent variable. As predictor variables we included TAS-20 total score and the psychological subscales, which showed a significant correlation to TAS-20 total score in univariate analysis: TCI-HA, TCI-SD, TCI-ST. Controlling for brain volume and sex in a first block, we used forward selection of psychological variables from a second block. Only TCI-harm avoidance and TAS 20 total score met the entry criterion. From the first block brain volume showed a highly significant correlation to right ACG in this model (Table 5, model 1). We next examined the regression models in the two sexes separately. In men, beside brain volume, only TAS-20 total score showed a highly significant contribution, whereas in women only TCI-harm avoidance was a significant predictor. To see what happens to the TAS-20 and TCI-HA variables, we report the full model including TAS-20, TCI-HA and brain volume for both sexes (Table 5, models 2 and 3).[1]

DISCUSSION

In contrast to our primary hypothesis, our findings indicate that there is a significant positive correlation between the size of the right anterior cingulate gyrus and alexithymia as measured with the 20-item TAS in healthy subjects. As hypothesized, this applies especially for men, whereas in a previous publication we already suggested that a prominent right anterior cingulate was associated with a tendency to withdrawal-related behavior (harm avoidance), especially in women (40). The relationship between the size of the right anterior cingulate gyrus and alexithymia in women observed in the present investigation seems to rely on what alexithymia and harm avoidance have in common.

Our results add further evidence to the findings from earlier studies which described different neurobiological patterns of high alexithymia in men vs. women. Lumley and Sielky (20) looked at the relationship of alexithymia and an impairment of the right hemisphere or a deficiency in interhemispheric transfer in a nonclinical sample of 47 college men and 58 college women. Using a tactile finger localization task, they calculated a hemisphere index to test the right hemisphere dysfunction hypothesis and a crossing index to test the interhemispheric transfer deficit hypothesis of alexithymia. Interestingly, among men, alexithymic deficits in the ability to identify or describe feelings are related to both a relative impairment in the function-

TABLE 5. Linear Regression Models with AC Right as Dependent Variable

Model 1: Dependent Right ACG; Total Sample (n = 100)				EPTV 37.3%	
Independent Variables	Unstand. Coeff. B	SE (B)	Stand. Coeff. β	T	*p*
Constant	–1288.1	343.0		–3.756	.000
Brain volume	1.060	0.237	0.476	4.466	.000
Gender	103.3	53.8	0.220	1.920	.058
TCI Harm avoidance	10.213	2.617	0.348	3.902	.000
TAS20 total score	5.759	2.245	0.226	2.565	.012
Model 2: Dependent Right ACG; Men (n = 49)				**EPTV 43.2%**	
Independent Variables	Unstand. Coeff. B	SE (B)	Stand. Coeff. β	T	*p*
Constant	–1640.2	453.0		–3.621	.001
Brain volume	1.435	0.323	0.516	4.447	.000
TAS20 total score	7.128	3.126	0.265	2.280	.027
TCI harm avoidance	5.820	4.004	0.174	1.453	.153
Model 3: Dependent Right ACG; Women (n = 51)				**EPTV 36.7%**	
Independent Variables	Unstand. Coeff. B	SE (B)	Stand. Coeff. β	T	*p*
Constant	–663.1	475.6		–1.394	.170
Brain volume	.558	.354	0.194	1.574	.122
TAS20 total score	3.064	3.234	0.121	0.947	.348
TCI harm avoidance	14.007	3.393	0.514	4.128	.000

EPTV, explained proportion of total variation; Unstand. Coeff., unstandard coefficient; Stand., standard; SE, standard error.

ing of the right hemisphere and an impairment in the ability to transfer information between cerebral hemispheres. In contrast, within the female sample, alexithymia and its facets are unrelated to the measures of hemispheric dysfunction (20). Additionally, Spalletta et al. (53) reported that men with a right-hemisphere stroke had a high level of alexithymia and were more alexithymic than those with a left-hemisphere stroke. In women, there was no difference between patients with a left-hemisphere and a right-hemisphere stroke, and both female subsamples had a high level of alexithymic features. We found a significant positive correlation between the size of the right anterior cingulate and alexithymia in male and in female university students. But only in men was this relationship maintained after controlling for HA, whereas this was not true in women.

Lane et al. (54) found some support for the hypothesis that the degree to which the right hemisphere participates in the processing of emotion-laden stimuli influences the degree to which emotional information is processed in a differentiated and complex manner. According to our findings, the ability to accurately detect emotional signals interoceptively or exteroceptively may indeed be a function of the right ACC (BA 24). This was suggested in a PET activation study by Lane et al. during film- and recall-induced emotion. These authors correlated regional cerebral blood flow (CBF) changes attributable to emotion with subjects' scores on the Levels of Emotional Awareness Scale (LEAS), a measure of individual differences in the capacity to experience emotion in a differentiated and complex way (35). Correlations between LEAS scores (which is inversely correlated with alexithymia) and rCBF overlapped significantly in BA area 24 of the right anterior cingulate cortex.

A recent functional magnetic resonance imaging (fMRI) study investigated the neural response to emotional stimuli in a group of eight men with and eight men without alexithymia and hypothesized that, according to the blindfeel hypothesis (34), alexithymia would be associated with a deficit in the participation of the anterior cingulate cortex during emotional arousal (55). Indeed, negative high-arousal emotional stimuli induced less activation in the left mediofrontal-paracingulate gyrus in men with alexithymia than in those without alexithymia. Nothing can be said about the excitatory or inhibitory quality of anterior cingulate activation during this emotion-arousing paradigm. However, the decrease of activity in the rostral anterior cingulate cortex/mediofrontal cortex when viewing negative pictures might suggest that alexithymia is associated with a deficit in reflective awareness (ie, the mental representation of the current emotional state) of negative affect (55). Although this preliminary data are difficult to interpret in terms of laterality, the partially convergent findings of this study (fMRI study of alexithymic vs. nonalexithymic males) and our results provide further evidence that functional differences in ACC activation during emotional processing may be related to structural differences in this specific region.

How could we—in contrast to our primary hypothesis of a negative correlation between ACG surface area and TAS-20 total score—explain an increased size of particularly the right anterior cingulate surface area in high alexithymia? The right hemisphere is more efficient than the left in monitoring sensory inputs for alerting signals and mediating stimulus-triggered reactions (56, 57). In addition, Damasio suggests that the right somatosensory cortices are "dominant" with regard to integrated body mapping and therefore most important for generating emotions and feelings (58). Also, an asymmetrical (greater right than left) frontal activation is associated with emotional responses related to suppression of ongoing activity such as fear and disgust (59).

Characteristic alexithymic features, especially the suppression of traumatic memories and the conscious awareness of related feelings, have early been described in a subgroup of severe PTSD patients (60). Recently, dissociative PTSD patients, defined as showing no concomitant increase in heart rate while recalling a traumatic memory (ie, suppressing emotional arousal), showed greater activation than the control group specifically in the right anterior cingulate gyrus (BA 24 and 32) (61). This finding is somewhat consistent with the finding of increased global cerebral blood flow in the anterior cingulate gyrus following THC-induced depersonalization, another mode of dissociative processes (62). Dissociation is considered to serve as a defense mechanism against intolerable, trauma-associated memories and feelings, and results from a disintegration of consciousness, memory, identity and perception (63). In dissociation as well as in alexithymia, patients may have difficulties in integrating aspects of certain neuropsychological functions, namely memories and feelings, into current awareness. Indeed, several authors (63, 64) found a strong positive correlation between the TAS-20 total score, the subscores "difficulty identifying feelings" and "difficulty expressing feelings" and dissociative symptomatology. In accord with these findings, a recent study suggested the existence of an active inhibitory control mechanism which is likely to include the anterior cingulate and prevents the retention of unwanted memories when encountering a certain stimulus. This finding supports the notion of a suppression mechanism that pushes unwanted associations out of awareness (65), and may point to the possible existence of other active inhibitory mechanisms within cognitive and emotional processing as well. Thus our finding of a positive correlation between alexithymia and right ACG surface area could therefore neurobiologically represent a dysfunctional organization of an environmentally induced neuronal inhibitory system in the allocation of attentional resources especially toward (internal and external) emotional cues, particularly in men. This hypothesis is supported by our finding of a significant correlation between right ACG surface area and TAS-20 factor 1 (difficulty identifying feelings) Therefore, we speculate that the larger extent of right ACG surface area in higher alexithymia may represent the structural, neuroanatomical correlate of an active inhibitory system causing a down regulation of emotional processing during the exposition to experimental or expressive aspects of emotion.

There are some restrictions to our study. First, regarding the sex differences in our findings, alexithymia (66) is less pronounced in women and also in our cohort. It is therefore statistically more difficult to demonstrate a relationship between large anterior cingulate and alexithymia specifically for women. Secondly, we did not study psychiatric patients with alexithymia in a clinical sense but healthy young university graduates. Therefore our finding may relate to differences on the continuous scale of emotional intelligence rather than to clinically meaningful alexithymia. There clearly is an additional need for a similar study in clinical subjects. Thirdly, although alexithymia and depression are clearly distinct constructs (67), it is now well established that alexithymia is often associated with depression and trait anxiety (66,68). Honkalampi (66) found in a large epidemiological study that the prevalence of alexithymia was only 4.3% among nondepressed subjects, whereas, among the depressed subjects, the prevalence of alexithymia was higher by eight-fold (32%). Thus depression and trait anxiety are critical dimensions, particularly when studying the links between affective style and brain structure. Therefore another potential confounding factor of our study is that the correlations between alexithymia and right ACG surface area have not controlled for these dimensions. As we studied healthy young subjects, we assume a relatively low level of depression and anxiety within our sample. However, future studies should include the measurement of depression and trait anxiety by using appropriate anxiety and depression self-report questionnaires in conjunction with the TAS-20.

In conclusion, our data further contribute to the hypotheses that right anterior cingulate gyrus morphology significantly correlates with alexithymia as measured with the 20-item TAS and that there are sex-specific differences in emotional processing.

The authors thank Montse Vall-llovera for her assistance in results assessment, and Mary-Frances O'Connor for her assistance in the preparation of the manuscript.

REFERENCES

1. Taylor G, Bagby M. Affect dysregulation and alexithymia. In: Taylor G, Bagby RM, Parker JDA, eds. Disorders of affect regulation. Cambridge University Press; 1997:26.
2. MacLean PD. Psychosomatic disease and the "visceral brain": recent developments bearing on the Papez theory of emotion. Psychosom Med 1949;11:338–353.
3. Parker J, Taylor G. The neurobiology of emotion, affect regulation, and alexithymia. In: Taylor G, Bagby RM, Parker JDA, eds. Disorders of affect regulation. Cambridge University Press; 1997:95.
4. MacLean PD. The triune brain in conflict. Psychother Psychosom 1977; 28:207–220.
5. Nemiah JC, Sifneos PE, Apfel-Savitz R. A comparison of the oxygen consumption of normal and alexithymic subjects in response to affect-provoking thoughts. Psychother Psychosom 1977;28:167–171.
6. Hoppe KD, Bogen JE. Alexithymia in twelve commissurotomized patients. Psychother Psychosom 1977;28:148–155.
7. Cole G, Bakan P. Alexithymia, hemisphericity, and conjugate lateral eye movements. Psychother Psychosom 1985;44:139–143.

8. Montreuil M, Jouvent R, Carton S, et al. Parallel Visual Information Processing Test. An experimental assessment of alexithymia. Psychother Psychosom 1991;56:212–219.
9. Parker JDA, Taylor GJ, Bagby RM. Alexithymia and the recognition of facial expressions of emotions. Psychother Psychosom 1993;59:197–202.
10. Berenbaum H, Prince JD. Alexithymia and the Interpretation of Emotion-Relevant Information. Cognition and Emotion 1994;8:231–244.
11. TenHouten WD, Hoppe KD, Bogen JE, et al. Alexithymia: An experimental study of cerebral commissurotomy patients and normal control subjects. Am J Psychiatry 1986;143:312–316.
12. Zeitlin SB, McNally RJ. Alexithymia and anxiety sensitivity in panic disorder and obsessive-compulsive disorder. Am J Psychiatry 1993;150: 658–660.
13. TenHouten WD, Hoppe KD, Bogen JE, et al. Alexithymia and the split brain. I. Lexical-level content analysis. Psychother Psychosom. 1985;43: 202–208.
14. TenHouten WD, Hoppe KD, Bogen JE, et al. Alexithymia and the split brain. II. Sentential-level content analysis. Psychother Psychosom. 1985; 44:1–5.
15. TenHouten WD, Hoppe KD, Bogen JE, et al. Alexithymia and the split brain. III. Global-level content analysis of fantasy and symbolization. Psychother Psychosom 1985;44:89–94.
16. TenHouten WD, Hoppe KD, Bogen JE, et al. Alexithymia and the split brain. IV. Gottschalk-Gleser content analysis, an overview. Psychother Psychosom 1985;44:113–121.
17. TenHouten WD, Hoppe KD, Bogen JE, et al. Alexithymia: An experimental study of cerebral commissurotomy patients and normal control subjects. Am J Psychiatry 1986;143:312–316.
18. Dewaraja R, Sasaki Y. A left to right hemisphere callosal transfer deficit of nonlinguistic information in alexithymia. Psychother Psychosom. 1990;54:201–207.
19. Parker JD, Keightley ML, Smith CT, et al. Interhemispheric transfer deficit in alexithymia: an experimental study. Psychosom Med 1999;61: 464–468.
20. Lumley MA, Sielky K. Alexithymia, gender, and hemispheric functioning. Compr Psychiatry 2000;41:352–359.
21. Bagby RM, Taylor GY, Parker JDA. The twenty-item Toronto Alexithymia Scale. II. Convergant, discriminant and concurrent validity. J Psychosom Res 1994;38:33–40.
22. Luminet O, Bagby RM, Wagner H, et al. Relation between alexithymia and the five-factor model of personality: a facet-level analysis. J Pers Assess 1999;73:345–358.
23. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;50:975–990.
24. Grabe HJ, Spitzer C, Freyberger HJ. Alexithymia and the Temperament and Character Model of Personality. Psychother Psychosom 2001;70: 261–267.
25. Krystal H. Integration and Self Healing. Affect, Trauma, Alexithymia. Hillsdale Analytic Press; 1988.
26. Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry 1937;38:725–733.
27. George MS, Ketter TA, Parekh PI, et al. Brain Activity During transient Sadness and Happiness in Healthy Women. Am J Psychiatry 1995;1995: 152:341–351.
28. Teasdale JD, Howard RJ, Cox SG, et al. Functional MRI Study of the Cognitive Generation of Affect. Am J Psychiatry 1999;156:209–215.
29. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215–222.
30. Damasio AR, Grabowski TJ, Bechara A, et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neurosci 2000;3(10):1049–1056.
31. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118:279–306.
32. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215–222.
33. Lane RD. Neural Correlates of Conscious Emotional Experience. In: Cognitive Neuroscience of Emotion (eds: RD Lane & L Nadel). New York, Oxford: Oxford University Press; 2000:359–360.
34. Lane RD, Ahern GL, Schwartz GE, et al. Is alexithymia the emotional equivalent of blindsight? Biol Psychiatry 1997;42:834–844.
35. Lane RD, Reimann EM, Axelrod B, et al. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. J Cogn Neurosci 1998;10: 525–535.
36. Vogt BA, Nimchinsky EA, Vogt LJ, et al. Human cingulate cortex: surface features, flat maps, and cytoarchitecture. J Comp Neurol 1995; 359:490–506.
37. Yücel M, Stuart GW, Maruff P, et al. Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/ paracingulate cortex in normal volunteers: an MRI morphometric study. Cereb Cortex 2001;11:17–25.
38. Yücel M, Pantelis C, Stuart GW, et al. Anterior cingulate activation during Stroop task performance: a PET to MRI coregistration study of individual patients with schizophrenia. Am J Psychiatry 2002;159: 251–254.
39. Good CD, Johnsrude IS, Ashburner J, et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001; 14:21–36.
40. Pujol J, López A, Deus J, et al. Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. Neuroimage 2002;15:847–855.
41. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 1971;9:97–113.
42. Martínez Sánchez F. Adaptación espanola de la escala de Alexitimia de Toronto (TAS-20). Clinica y Salud 1996;7:19–32.
43. Gutiérrez F, Torrens N, Boget T, et al. Psychometric properties of the Temperament and Character Inventory (TCI) questionnaire in a Spanish psychiatric population. Acta Psychiatr Scand 2000;102:1–5.
44. Cloninger CR, Przybeck TR, Svrakic DM, et al. The Temperament and Character Inventory (TCI): a Guide to its Development and Use. St. Louis, MO: Center for Psychobiology of Personality; 1994.
45. Heath AC, Cloninger CR, Martin NG. Testing a model for the genetic structure of personality: A comparison of the personality systems of Cloninger and Eysenck. J Pers Soc Psychol 1994;66:762–775.
46. Stallings MC, Hewitt JK, Cloninger CR, et al. Genetic and environmental structure of the Tridimensional Personality Questionnaire. Three or four temperament dimensions? J Pers Soc Psychol 1996:70:127–140.
47. Pujol J, Conesa G, Deus J, et al. Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. J Neurosurg 1998;88:863–869.
48. Paus T, Otaky N, Caramanos Z, et al. In vivo morphometry of the intrasulcal gray matter in the human cingulate, paracingulate, and superior-rostral sulci: hemispheric asymmetries, gender differences and probability maps. J Comp Neurol 1996;376:664–673.
49. Paus T, Tomaiuolo F, Otaky N, et al. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cereb Cortex 1996;6:207–214.
50. Pujol J, Deus J, Losilla JM, et al. Cerebral lateralization of language in normal left-handed people studied by functional MRI. Neurology 1999; 52:1038–1043.
51. Galaburda AM, Corsiglia J, Rosen GD, et al. Planum temporale asymmetry, reappraisal since Geschwind and Levitsky. Neuropsychologia 1987;25:853–868.
52. Shapleske J, Rossell SL, Woodruff PWR, et al. The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. Brain Res Rev 1999;29:26–49.
53. Spalletta G, Pasini A, Costa A, et al. Alexithymic features in stroke: effects of laterality and gender. Psychosom Med 2001;63:944–950.
54. Lane RD, Kevley LS, DuBois MA, et al. Levels of emotional awareness and the degree of right hemispheric dominance in the perception of facial emotion. Neuropsychologia 1995;33:525–528.
55. Berthoz S, Artiges E, van de Moortele PF, et al. Effect of impaired recognotion and expression of emotions on frontocingulate cortices: An fMRI study of men with alexithymia. Am J Psychiatry 2002;159:961–967.
56. Heilman KM. The neurobiology of emotional experience. In The Neuropsychiatry of Limbic and Subcortical Disorders (S Salloway, P Malloy, and JL Cummings, Eds). Washington, DC: American Psychiatric Press; 1997:133–142.
57. Pujol J, Bello J, Deus J, et al. Beck Depression Inventory factors related to demyelinating lesions of the left arcuate fasciculus region. Psychiat Res-Neuroim 2000;99:151–159.
58. Damasio AR. Looking for Spinoza: Joy, sorrow, and the feeling brain. Orlando, FL: Harcourt; 2003:117.
59. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. Trends in Cognitive Neuroscience 1999;1:11–21.
60. Krystal H. Psychic traumatization. Aftereffects in individuals and communities. Review of the findings and implications of this symposium. Int Psychiatry Clin 1971;8:217–229.

61. Lanius RA, Williamson PC, Boksman K, et al. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. Biol Psychiatry 2002; 52:305–311.
62. Mathew RJ, Wilson WH, Chiu NY, et al. Regional cerebral blood flow and depersonalization after tetrahydrocannabinol administration. Acta Psychiatr Scand 1999;100:67–75.
63. Grabe HJ, Rainermann S, Spitzer C, et al. The relationship between dimensions of alexithymia and dissociation. Psychother Psychosom 2000;69:128–131.
64. Zlotnick C, Zakriski AL, Shea MT, et al. The long-term sequelae of sexual abuse: Support for a complex posttraumatic stress disorder. J Trauma Stress 1996;9:195–205.
65. Andersen MC, Green C. Suppressing unwanted memories by executive control. Nature 2001;410:366–369.
66. Honkalampi K, Hintikka J, Tanskanen A, et al. Depression is strongly associated with alexithymia in the general population. J Psychosom Res 2000;48:99–104.
67. Parker JD, Bagby RM, Taylor GJ. Alexithymia and depression: distinct or overlapping constructs? Compr Psychiatry 1991;32:387–394.
68. Hendryx MS, Haviland MG, Shaw DG. Dimensions of alexithymia and their relationships to anxiety and depression. J Pers Assess 1991;56:227–237

5. *Discusión*

Este trabajo ha aportado nuevos datos sobre el significado funcional de la variabilidad anatómica de las regiones cerebrales clásicamente asimétricas en relación a dimensiones conductuales básicas de la esfera cognitiva y emocional.

A lo largo de la evolución del ser humano se han ido produciendo cambios que han modulado el cerebro. Hay estudios filogenéticos que apoyan esta modulación y la aparición progresiva de unas asimetrías cerebrales. Probablemente el desarrollo de estrategias complejas de coordinación y estrategias de conducta competitiva entre los diferentes miembros de un grupo social pusieron una fuerte presión selectiva para aumentar la plasticidad cerebral y la capacidad de aprendizaje que implicó el desarrollo asimétrico de las conexiones córtico-corticales (Aboitiz, García, 1997). Las constantes luchas del ser humano para conseguir la máxima adaptación y el control del medio, gracias al desarrollo del lenguaje, la coordinación en motricidad fina y el control conductual, pueden explicar parcialmente la presencia y relevancia de estas asimetrías cerebrales.

En la esfera de la cognición, la adquisición del lenguaje en el proceso de hominización y socialización ha permitido expresar ideas y experiencias a otros y es un elemento fundamental para la construcción del pensamiento. Implica crear categorías y dar nombre a los objetos y sensaciones del mundo externo e interno, así como realizar asociaciones con los símbolos mentales. La máxima expresión de la cultura es la comunicación. La capacidad de transmitir información de una generación a otra ha convertido al ser humano (*Homo sapiens*) en un ser con grandes ventajas de adaptación. "Un ser equipado por capacidades simbólicas es un rival extraordinario" (Tattersal, 2000). El desarrollo del lenguaje ha permitido acumular y almacenar información para ser traspasada a otras generaciones.

Los inicios de la adquisición del lenguaje oral se remontan a unos dos millones de años. Es lógico pensar que una función tan específica y largamente desarrollada pueda tener una representación especializada a nivel cerebral. La repercusión de esta capacidad se traduce en la presencia de una progresiva asimetría cerebral en la región perisilviana, siendo la región izquierda la que sustenta, generalmente y no de forma absolutista, las funciones lingüísticas. Estudios filogenéticos así lo sugieren. Estudios ontogenéticos constatan estas asimetrías ya en el tercer trimestre de gestación intrauterina.

Se sabe, mediante estudios funcionales, que el lenguaje está lateralizado en la región perisilviana izquierda en un 96% de los sujetos diestros (Rasmussen, Milner, 1977; Pujol, Deus, Losilla et al, 1999) y la lateralización funcional acontece a nivel receptivo (temporal) y expresivo (frontal). Hasta el momento, una de las estructuras que se ha correlacionado con esta lateralización de las funciones lingüísticas es el '*planum temporale*'. En el presente estudio, y de acuerdo con lo publicado previamente en la literatura, un 70% de la muestra presentó un '*planum temporale*' izquierdo mayor que el derecho. Pero este porcentaje queda lejos del 96%. Si se considera el volumen global de las regiones perisilvianas analizadas, un 66% presentó una región temporal izquierda mayor y no se observó una clara asimetría en la región frontal. Pero referente a la sustancia blanca relativa se ha encontrado que más del 90% presenta una asimetría a favor del hemisferio izquierdo en la región temporal y frontal. Por lo tanto, hasta el momento, el parámetro físico/estructural que concuerda mejor con la lateralización funcional del lenguaje es la asimetría de predominio izquierdo del volumen relativo de la sustancia blanca en la región frontal y temporal perisilvianas.

Este hallazgo está en consonancia con lo descrito en el trabajo de Good y colaboradores (2001a y b). Estos autores usaron un potente estudio morfométrico basado en el estudio del voxel (VBM) para examinar 465 sujetos sanos y detectaron un aumento de la sustancia blanca en el hemisferio izquierdo, y disminución de sustancia gris, relativo al hemisferio derecho en la porción lateral periférica de los lóbulos temporal y frontal. El estudio de Good y colaboradores (2001) y la de la presente tesis representan dos aproximaciones muy diferentes anatómica y técnicamente para demostrar un aumento relativo de la sustancia blanca en las regiones que sustentan el lenguaje y funciones afines. Este aumento relativo de la sustancia blanca probablemente facilita las operaciones rápidas de asociación cortical auditiva y, consecuentemente, podría otorgar al hemisferio izquierdo el papel dominante para las funciones lingüísticas (Tallal, Millar, Fitch, 1993; Penhune, Zatorre, MacDonald et al, 1996; Anderson, Southern, Powers, 1999).

Siguiendo la misma línea, sería esperable encontrar, ante un Trastorno Específico del Desarrollo del Lenguaje (TEDL), un menor volumen relativo de sustancia blanca en la región perisilviana izquierda. Pero paradójicamente, no ha sido así. Los datos de la presente tesis apuntan a un patrón distinto de distribución de volúmenes. Coincidiendo con estudios del equipo de Herbert y colaboradores (2003, 2004), donde encontraban un aumento del parénquima y de la sustancia blanca en niños con un diagnóstico clínico de disfasia del desarrollo, los datos aportados en la presente tesis no sólo muestran un mayor volumen global de sustancia blanca sino también de sustancia gris y, de forma específica, un mayor volumen de sustancia gris en el lóbulo temporal derecho y occipital izquierdo. Este aumento se encuentra sólo en el grupo de los más jóvenes, no en el grupo de mayores a 11 años. Se puede inferir que un TEDL podría relacionarse con una distribución anómala de sustancia gris en etapas tempranas. Esta distribución anómala, mayor presencia de sustancia gris en las regiones perisilvianas derechas, se traduce en una asimetría invertida a nivel de estas regiones. Estos hallazgos plantean dos posibilidades que no tienen porque ser excluyentes: i) la posibilidad de que se activen mecanismos de compensación ante un malfuncionamiento cerebral; ii) en consonancia con las hipótesis que planteaba Galaburda, que se produzca una limitada involución del hemisferio derecho y ésta puede ser debida a un desequilibrio entre eventos progresivos (i.e. mielinización acelerada de la sustancia blanca) y regresivos (i.e. una retrasada/retardada reducción relativa de sustancia gris). Esta diferente distribución de volúmenes tanto por un aumento unilateral de la región temporal derecha como por una más marcada asimetría de la '*petalia*' occipital izquierda se detecta con mayor claridad en edades tempranas ya que en el grupo de mayores, como se ha dicho anteriormente, estas diferencias respecto al grupo control se disipan. Estos datos apoyan que el cerebro es un órgano dinámico, que a lo largo de su desarrollo se produce una permanente evolución que lo va remodelando y los patrones de normalidad dependen del momento en que se analicen.

En este sentido, otra patología de marcado interés, en los trastornos del desarrollo, presenta un patrón similar. Así, en el autismo se ha observado un aumento del parénquima cerebral que se ha interpretado como una característica no específica pero probablemente relacionada con un trastorno del neurodesarrollo (Kjelgaard, Tager-Flusberg, 2001; Rapin, Dunn, 1997). Curiosamente, este aumento global también parece ser más prominente en los sujetos jóvenes (Carper, Moses, Tigue, 2002; Courchesne, Karns, Davis et al, 2001).

Los hallazgos del segundo trabajo, presentado en la presente tesis, muestran al cerebro como un órgano dinámico. En músicos se ha detectado el doble de asimetría en el '*planum* *temporale'* que en los no músicos y los músicos que presentan un "oído absoluto" son los que tienen mayores asimetrías. Por lo tanto, asimetrías exageradas podrían indicar un aumento de capacidades para el procesamiento de determinados rasgos auditivos (Steinmetz, 1996; Schlaug, Jäncke, Huang, 1995). Un estudio de seguimiento reveló que estas marcadas asimetrías se atribuían a un '*planum temporale'* derecho más pequeño, y no a un gran *planum temporal* izquierdo, comparado con los controles no músicos. Estos datos sugieren una posible poda más marcada en el neurodesarrollo del '*planum temporale'* derecho en los músicos con "oído absoluto" (Keenan, Thangaraj, Halpern et al, 2001). Posiblemente las diferencias en la maduración de sustancia blanca (Sowell, Thompson, Rex et al, 2002; Thompson, Giedd, Woods et al, 2000; Taylor, 1969) podrán dar más información sobre la etiología de estas habilidades o disfunciones.

Referente a las posibles diferencias entre géneros, en el primer estudio del tema, se observa que ambos presentaban asimetrías claras del volumen relativo de sustancia blanca frontal y temporal, pero las asimetrías fueron más pronunciadas en los hombres. Este dato concuerda con lo publicado en la literatura sobre la menor lateralización del lenguaje en mujeres (Hécaen, Ruel, 1981; Shaywitz, Shaywitz, Pugh et al, 1995; Springer, Deutsch, 1998; Josse, Tzourio-Mazoyer, 2004).

En cuanto a otras regiones de la zona perisilviana, el mayor volumen regional y el mayor volumen relativo de sustancia blanca a nivel de la región témporo-párieto-occipital derecha, coincide con la lateralización de las funciones visoespaciales en este hemisferio. En este sentido, Aboitiz y colaboradores (1997) ya apuntaba que la lateralidad funcional de los dos hemisferios estaba explicada por las proyecciones témporo-parieto-frontales que presentaba cada hemisferio en vez del desarrollo de áreas corticales específicas. En el hemisferio izquierdo están potenciadas las conexiones temporales, inferoparietales y frontales, en cambio en el hemisferio derecho las proyecciones de las áreas parietales posteriores hacia el frontal. Sus impresiones concuerdan con los datos expuestos en el segundo trabajo de la presente tesis.

En los dos primeros estudios, se relacionan las asimetrías regionales observadas con funciones cognitivas. En el primero, la asimetría del volumen relativo de sustancia blanca en las regiones temporales y frontales de la región persilviana concuerda con el porcentaje de dominancia lateral esperada para las funciones lingüísticas. En el segundo, los volúmenes de sustancia gris medidos con VBM diferenciaban el grupo de disfásicos del desarrollo del grupo control sano. En este segundo trabajo no se encuentran las esperadas asimetrías perisilvianas clásicas, sino que se encuentran mayores volúmenes de sustancia gris en la región temporal derecha y occipital izquierda. Estos datos apoyan una evolución anómala de la sustancia gris en los sujetos disfásicos.

En conjunto, los resultados de ambos estudios destacan el importante papel de las asimetrías como expresión de la maduración o evolución funcional de regiones específicas. Además, del primer estudio se resalta la sustancia blanca como parámetro morfológico decisivo para la lateralización de las funciones lingüísticas. En este sentido, en la literatura se encuentra referido que este mismo parámetro es el que diferencia los lóbulos frontales de los seres humanos del de los grandes simios (Schoenemann, Sheehan, Glotzer, 2005) y paralelamente hay trabajos que ponen de manifiesto la relación de sustancia blanca asimétrica con la aparición o existencia de una habilidad (Bengtsson, Nagy, Skare et al 2005; Carreiras, Seghier, Baquero et al, 2009; Lebel, Beaulieu, 2009; Tamnes, Ostby, Walhovd et al, 2010).

En referencia a la esfera conductual, con esta tesis se ha podido constatar la relación entre una dimensión de la personalidad y el grado de desarrollo anatómico de una región claramente asimétrica, la circunvolución cingulada anterior. Recientemente, ha habido otros trabajos que han aportado datos sobre la base biológica de la personalidad (Wright, Williams, Feczko et al 2006; De Young, Hirsh, Shane et al, 2010), pero el estudio presentado en la presente tesis fue pionero en demostrar una relación directa entre una dimensión de la personalidad y una estructura cerebral específica.

Como ya se ha descrito previamente, la superficie medial de la región anterior de la corteza cingulada varía enormemente de persona a persona y entre el hemisferio derecho e izquierdo (Paus, Otaky, Caramano, 1996; Yücel, Stuart, Maruff et al, 2001; Vogt, Nimchinsky, Vogt, et al, 1995; Ono, Kubik, Abernathey, 1990; Ide, Dolezal, Fernández et al, 1999). Un 83% de los sujetos de la muestra estudiada en la presente tesis, presentó una clara asimetría entre la superficie medial de la CCA izquierda y derecha. Un 40% de los hombres presentó una región izquierda mayor *versus* un 42% derecha. En cambio, en las mujeres se encontró que un 22% presentó una corteza cingulada izquierda mayor *versus* un 62% que presentó un mayor tamaño derecho. Este predominio que sólo presentan las mujeres de la CCA derecha mayor que la izquierda contrasta con la menor asimetría que en general presentan las mujeres a nivel cerebral, como se ha descrito para las funciones lingüísticas (Springer, Deutsch, 1998).

De acuerdo con nuestra predicción, se obtuvo una correlación entre la dimensión de Evitación del Daño y la superficie medial de la CCA. Los sujetos del estudio expuesto en la presente tesis que se definían como cautos, cuidadosos, preocupados por los posibles problemas, tensos y temerosos en situaciones de incertidumbre, tímidos con los extraños y fácilmente fatigables presentaban una prominente CCA derecha. Independientemente del género, las personas que puntuaron alto en Evitación del Daño presentaban una región cingulada prominente. Esta dimensión define un patrón de comportamiento caracterizado por personas que están muy influidas por estímulos aversivos o por señales que indican que serán castigados y por tanto actúan para evitar el daño. Se puede inferir que un mayor tamaño de las áreas de Brodmann 24a, 24b y 25 tienden a asociarse a un comportamiento de retirada en oposición a un comportamiento de aproximación. Este patrón, a lo largo de la evolución del hombre, ha podido suponer un mecanismo de adaptación o de supervivencia, sobre todo en las mujeres, ya que su función era cuidar de los hijos y del entorno inmediato; a diferencia del hombre que era el responsable de la caza.

Se sabe que el hemisferio derecho es más eficiente que el izquierdo para monitorizar los estímulos sensoriales de señales de alerta y para mediar reacciones desencadenadas por un estímulo (Heilman, 1997; Pujol, Bello, Deus et al, 2000). La asociación de la CCA con la Evitación del Daño apoya el rol del hemisferio derecho en estos procesos.

A pesar de no encontrar asimetrías en la región posterior de la corteza cingulada, la dimensión Búsqueda de Novedad se correlacionó con la región posterior sólo en mujeres. El hemisferio izquierdo parece estar más involucrado en el control de la motivación y la conducta de aproximación (Pujol, Bello, Deus et al, 1997 y 2000; Davidson, 1995; Tucker, Liotti, 1989; Gainotti, 1997). La asociación de la Búsqueda de Novedad con la superficie posterior de la corteza cingulada izquierda apunta en esta dirección.

Del estudio expuesto en la presente tesis, se desprende que un tamaño grande de la CCA se relaciona con una disposición temperamental hacia el miedo y sufrimiento anticipatorio en ambos sexos y que una mayor prevalencia de estos rasgos en mujeres se puede relacionar con un mayor tamaño de esta región cerebral paralímbica.

Los datos expuestos en la presente tesis, apoyan que las dimensiones de personalidad propuestas por Cloninger tienen una base neurobiológica. A parte del sustrato anatómico aportado por el trabajo expuesto en la tesis presente, existen otros que aportan datos bioquímicos y genéticos (Cloninger, 1994; Okuyama, Ishiguro, Nankai et al, 2000; Peirson, Heuchert, Thomala et al, 1999; Suhara, Yasuno, Sudo et al, 2001).

Para complementar esta línea de estudio, se propuso valorar las puntuaciones de alexitimia del grupo de estudio del presente trabajo ya que el lenguaje, la expresión verbal, ha sido y es una vía utilizada para expresar y compartir sentimientos. Las personas con niveles bajos de alexitimia son capaces de identificar y verbalizar sentimientos con facilidad, diferenciar sensaciones corporales de afectos, y tienden a no actuar impulsivamente ante situaciones conflictivas sino a analizarlas y racionalizarlas. Se esperaba encontrar una correlación negativa entre la superficie de la CCA y la alexitimia, ya que se otorgaba a esta región cerebral la función de integrar la información sensorial y visceral con la cognitiva.

Pero paradójicamente los resultados no salieron en la dirección que se hipotetizaba. ¿Cómo puede correlacionarse un aumento de la CCA derecha con una tendencia a presentar niveles altos de alexitimia?

Una posible explicación es ahondar en los posibles efectos adaptativos de la alexitimia. Freyberger (1977) introdujo el término de alexitimia secundaria. La alexitimia secundaria sería una reacción transitoria específica que acompaña o permanece tras una situación de enfermedad orgánica, un traumatismo importante o determinadas situaciones de conflicto en cualquier sujeto, que puede desaparecer cuando la situación remite (alexitimia secundaria aguda) o puede ser un estado permanente en pacientes cuya enfermedad o cuyo traumatismo tiende hacia un desarrollo crónico (alexitimia secundaria crónica) (Otero, 1999).

Una de las características de las personas alexitímicas es la capacidad de suprimir los recuerdos traumáticos y el conocimiento consciente de los sentimientos que se relacionan con los recuerdos traumáticos. Esta disociación puede considerarse como un mecanismo de defensa. Supone una desintegración de la consciencia, memoria, identidad y percepción (Grabe, Rainermann, Spitzer et al, 2000). Teniendo en cuenta una visión histórica de la evolución del ser humano, puede ser que la alexitimia fuera un factor favorable para su adaptación.

En conjunto, los cuatro trabajos contribuyen a elucidar el significado funcional de la variabilidad anatómica de las regiones cerebrales clásicamente asimétricas en relación a dimensiones conductuales básicas de la esfera cognitiva y emocional. El estudio de las asimetrías cerebrales regionales aporta datos sobre los estilos cognitivos y las dimensiones de la personalidad.

El cerebro sigue siendo un órgano apasionante, mágico y desconocido. Queda un largo camino para entender su evolución. Los múltiples factores, las relaciones entre ellos y su altísima complejidad invitan a su eterno estudio.

5. Conclusiones

1. El parámetro anatómico que mejor pudo explicar la lateralización del lenguaje fue la asimetría del volumen relativo de sustancia blanca localizado en la región perisilviana temporal y frontal.

2. Niños con un diagnóstico de TEDL presentan un aumento de volumen global de sustancia blanca y sustancia gris y una distribución de volúmenes relativos diferentes. Los mecanismos de compensación y la modulación dinámica temporal a que está expuesto el cerebro pueden explicar estas anormalidades a nivel estructural.

3. Un tamaño grande de la corteza cingulada anterior derecha se relaciona con una disposición temperamental hacia el miedo y sufrimiento anticipatorio en ambos sexos, y una mayor prevalencia de estos rasgos en mujeres se puede relacionar con un mayor tamaño de esta región.

4. Niveles altos de alexitimia correlacionan con mayor superficie de la corteza cingulada anterior derecha y se interpreta como una buena estrategia de adaptación del ser humano ante situaciones problemáticas.

6. Referencias Bibliográficas

Aboitiz F, García R, Bosman D, Brunetti E. Cortical memory mechanism and language origins. Brain Lang 2006; 98: 40-56.

Aboitiz F, García RV. The evolutionary origin of the language areas in the human brain. A neuroanatomical perspective. Brain Research Reviews 1997; 25: 381-396.

Al-Halabí S, Herrero R, Sáiz PA, García-Portilla MP, Errasti JM, Corcoran P et al. A cross-cultural comparison between Spain and the USA: Temperament and character distribution by sex and age. Psychiatry Res 2010 Aug, 26: [Epub ahead of print]

Achenbach TM, Edelbrock CS. Manual for the Child Behavior Checklist and Revised Child Behavior Profile. Burlington, VT: University of Vermont (1983).

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV. Washington: APA, 1994. Edición española: Manual diagnóstico y estadístico de los trastornos mentales DSM-IV, Masson, Barcelona: Masson, 1995.

Amunts K, Schleicher A, Ditterich A, Zilles K. Broca's region: cytoarchitectonic asymmetry and developmental changes. J Comp Neurol. 2003 Oct 6;465(1):72-89.

Anderson B, Southern BD, Powers RE. Anatomic asymmetries of the posterior superior temporal lobes: a postmortem study. Neuropsychiatry Neuropsychol Behav Neurol. 1999 Oct;12(4):247-54.

Annett M. The growth of manual preference and speed. Br J Psychol. 1970 Nov;61(4):545-58.

Ankney CD. Differences in brain size. Nature. 1992 Aug 13;358(6387):532.

Ashburner J, Friston KJ. Voxel-Based Morphometry-The Methods. Neuroimage 2000 June, 11(6): 805-821.

Bagby RM, Taylor GY, Parker JDA. The twenty-item Toronto Alexythimia Scale. II. Convergant, discriminant and concurrent validity. J Psychosom Res 1994; 38:33-40.

Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch Gen Psychiatry. 2001 May;58(5):461-5.

Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullén F Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci. 2005 Sep;8(9):1148-50.

Bigler ED, Abildskov TJ, Petrie JA, Johnson M, Lange N, Chipman J et al. Volumetric and voxel-based morphometry findings in autism subjects with and without macrocephaly. Dev Neuropsychol 2010 May; 35(3):278-95.

Binder J. The new neuroanatomy of speech perception. Brain 2000 123(12), 2371-2.

Boes AD, Tranel D, Anderson SW, Nopoulos P. Right anterior cingulated: a neuroanatomical correlate of aggression and defiance in boys. Behav Neurosci 2008 June; 122 (3): 677-84.

Branch C B, Rasmussen T. Intracarotid sodium amytal for the lateralization of cerebral speech dominance; observations in 123 patients. J neurosurg. 1964 may; 21:399-405.

Broca P. Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). Bull Soc Anthropol 1861 ; 6: 330-357.

Bourgeois JP, Rakic P. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci. 1993 Jul;13(7):2801-20.

Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000; 4 (6): 215-222.

Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. NeuroImage 2002; 16: 1038-1051.

Carreiras M, Seghier ML, Baquero S, Estévez A, Lozano A, Devlin JT et al. An anatomical signature for literacy. Nature. 2009 Oct 15;461(7266):983-6.

Cattell RB, Eber HW, Tatsuoka MM. Handbook for the Sixteen Personality Factor Inventory. Champaign, IL, Institute for Personality and Ability Testing, 1970.

Chi JG, Dooling EC, Gilles FH. Left-Right Asymmetries of the Temporal Speech Areas of the Human Fetus. Arch Neurol 1977; 34(6):346-348

Cloninger CR. A systematic method for clinical description and classification of personality variants. Arch Gen Psychiatry 1987; 44: 573-588.

Cloninger CR, Przybeck TR, Svrakic DM. The Tridimensional Personality Questionnaire: U.S. normative data. Psychol Rep 1991; 69: 1047-1057.

Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50: 975-990.

Cloninger CR. Temperament and personality. Curr Opin Neurobiol 1994; 4: 266-273.

Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. The Temperament and Character Inventory (TCI): A guide to its development and use. Center for Psychobiology of Personality, St Louis 1994.

Costa PT, McCrae RR. NEO PI-r professional manual. Odessa, FL: Psychological Assessment Resources, 1992.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD et al. Unusual brain growth patterns in eraly life in patients with autistic disorder : an MRI study. Neurology 2001; 57: 245-254.

Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: A functional neuroimaging investigation in humans. J Physiol. London 2000; 523: 259-279.

Crystal D, Enciclopedia del lenguaje de la Universidad de Cambridge. Madrid, Taurus, 1994

Cuningham, D.J. Contribution to the surface anatomy of the cerebral hemispheres. Roy. Irish Acad., 1892.Cunningham Memoirs, No. 7.

Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci. 2000 Oct;3(10):1049-56.

Dapretto M, Bookheimer SY. Form and content: dissociating syntax and semantics in sentence comprehension. Neuron 1999; 24(2): 427-32.

Davidson RJ. Cerebral asymmetry, emotion, and affective style. In brain Asymmetry (R.J. Davidson and K. Hugdahl, Eds.), 361-387. MIT Press, Cambridge, MA.

Davis M. Neurobiology of fear responses. The role of the amygdale. In The Neuropsychiatry of Límbi and Subcortical Disorders (S. Salloway, P. Malloy and JL Cummings Eds.), pp. 71-91. Am Psychiatric Press, Washington, DC.

De Fossé L, Hodge SM, Makris N, Kennedy DN, CAviness VS Jr, McGrath K et al. Language-association cortex asymmetry in autism and specific language impairment. Ann Neurol 2004; 56: 757-766.

Deus J, Junqué C, Pujol J, Vendrell P, Vila M, Capdevila A. Neuropsychological and neuroimaging findings of developmental dysphasia: a longitudinal case study. Clin Linguist & Phon 1997; 11 (2): 139-152.

Devinsky O, Morrell M J and Vogt B A. Contributions of anterior cingulated cortex to behaviour. Brain 1995; 118: 279-306.

Dewel RA. Colonial origin for Emetazoa: major morphological transitions and the origin of bilaterian complexity. J Morphol. 2000 Jan;243(1):35-74.

DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing predictions from personality neuroscience: brain structure and the big five. Psychol Sci. 2010 Jun;21(6):820-8.

Dorsaint-Pierre R, Penhune VB, Watkins KE, Neelin P, Lerch JP, Bouffard M et al. Asymmetries of the *planum temporale* and Heschl's gyrus: relationship to language lateralization. Brain. 2006 May;129(Pt 5):1164-76.

Dos Santos Sequeira S, Woerner W, Walter C, Kreuder F, Lueken U, Westerhausen R et al. Handedness, dichotic-listening ear advantage, and gender effects on *planum* *temporale* asymmetry--a volumetric investigation using structural magnetic resonance imaging. Neuropsychologia. 2006;44(4):622-36

Dubois J, Benders M, Lazeyras F, Borradori-Tolsa C, Leuchter RH, Mangin JF et al. Structural asymmetries of perisylvian regions in the preterm newborn. NeuroImage 2010 Aug ;52(1):32-42. Epub 2010 Mar 31.

Eysenck SJ y Eysenck SBG. Manual of de Eysenck Personality Questionnaire, Londres, Hodder & Stoughton. (1975)

Falzi G, Perrone P, Vignolo LA. Right-left asymmetry in anterior speech region. Arch Neurol. 1982 Apr;39(4):239-40.

Filley CM. White matter: organization and functional relevance. Neuropsychol Rev. 2010 Jun;20(2):158-73.

Fornito A, Yücel M, Wood S, Stuart GW, Buchanan J, Proffitt T et al. Individual Differences in Anterior Cingulate/Paracingulate Morphology Are Related to Executive Functions in Healthy Males. Cereb Cortex 2004 April;14:424–431.

Foundas AL, Leonard CM, Gilmore RL, Fennell EB, Heilman KM. Pars triangularis asymmetry and language dominance. Proc Natl Acad Sci U S A. 1996 Jan 23;93(2):719-22.

Foundas AL, Eure KF, Luevano LF, Weinberger DR. MRI asymmetries of Broca's area: the pars triangularis and pars opercularis. Brain Lang. 1998 Oct 1;64(3):282-96.

Foundas AL, Faulhaber JR, Kulynych JJ, Browning CA, Weinberger DR. Hemispheric and sex-linked differences in Sylvian fissure morphology: A quantitative approach using volumetric magnetic resonance imaging. Neuropsychiatry Neuropsychol Behav Neurol. 1999; 12: 1-10.

Freyberger H. Supportive psychotherapeutic techniques in primary and secondary alexithymia. Psychother Psychosom. 1977;28(1-4):337-42.

Gainotti G. Emotional disorders in relation to unilateral brain damage. In Behavioural Neurology and Neuropsychology (TE Feinberg and MJ Farah,Eds) 1997; 691-698. McGraw-Hill, New York.

- Galaburda AM. Anatomic basis of cerebral dominance. In: Davidson RJ, Hugdahl K, editors. Brain asymmetry. MIT Press; Cambridge, MA: 1995.

Galaburda AM, Corsiglia J, Rosen GD, Sherman GF. Planum temporale asymmetry, reappraisal since Geschwind and Levitsky. Neuropsychologia. 1987; 25: 853-868.

Gannon PJ, Holloway RL, Broadfield DC, Braun AR. Asymmetry of chimpanze *planum temporale*; humanlike pattern of Wernicke's brain language area homolog. Science 1998; 279, 220-2.

Gauger LM, Lombardino LJ, Leonard CM. Brain morphology in children with specific language impairment. J Speech Lang Hear Res 1997; 40:1272-1284.

Geschwind N, W Levitsky. Human brain: left-right asymmetries in temporal speech region. Science 1968; 161: 186-187.

Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch Neurol. 1985a May;42(5):428-59

Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. Arch Neurol. 1985b Jun;42(6):521-52

Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. Arch Neurol. 1985c Jul;42(7):634-54.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999 Oct;2(10):861-3.

Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci. 2004 Jun;1021:77-85.

Gillespie NA, Cloninger CR, Heath AC, Martin NG. The genetic and environmental relationship between Cloninger's dimensions of temperament and character. Personality & Individual Differences 2003; 35:1931-1946.

Gilmore JH, Lin W, Prastawa MW, Looney CB, Vetsa YS, Knickmeyer RC et al. Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain. J Neurosci. 2007 Feb 7;27(6):1255-60.

Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS Jr et al Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb Cortex. 2001 Jun;11(6):490-7.

Good CD, Johnsrude I, Ashburner J, Henson RNA, Friston KJ,Frackowiak RSJ. A voxel Based Morphometric Study of Ageing in 465 Normal Adults Human Brains. Neuroimage 2001a; 14: 21-36.

Good CD, Johnsrude I, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ. Cerebral Asymmetry and the Effects of Sex and Handedness on Brain Structure: A Voxel-Based Morphometric Analysis of 465 Normal Adult Human Brains. NeuroImage 2001b Sep; 14 (3): 685–700.

Gould SJ. No hay sentido de la evolución (entrevista). Mundo Científico 1997, 184, 976-979.

Grabe HJ, Rainermann S, Spitzer C, Gänsicke M, Freyberger HJ. The relationship between dimensions of alexithymia and dissociation. *Psychother Psychosom. 2000 May-Jun;69(3):128-31.*

Guerreiro MM, Hage SR, Guimarães CA, Abramides DV, Fernandes W, Pacheco PS. Developmental language disorder associated with polymicrogyria 2002; 59: 245-250.

- Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci. 1999;19(10):4065-72.

Gur RC, Gunning-Dixon F, Bilker WB, Gur RE. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. Cereb Cortex. 2002 Sep;12(9):998-1003.

Habib M, Robichon F, Lévrier O, Khalil R, Salamon G. Diverging asymmetries of temporo-parietal cortical areas: A reappraisal of Geschwind/Galaburda theory. Brain Lang 1995; 48: 238-258.

Hécaen H, Ruel J. [Verbal fluency test and sites of frontal lesions (author's transl)] Rev Neurol (Paris). 1981;137(4):277-84.

Heilman KM. The neurobiology of emotional experience. J Neuropsychiatry Clin Neurosci. 1997 Summer;9(3):439-48.

Henshilwood CS, d'Errico F, Marean CW, Milo RG, Yates R. An early bone tool industry from the Middle Stone Age at Blombos Cave, South Africa: implications for the origins of modern human behaviour, symbolism and language. J Hum Evol 2001 Dec ;41(6):631-78.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 2003; 126:1182-1192.

Herbert MR, Ziegler DA, Makris N, Bakardjiev A, Hodgson J, Adrien KT et al. Larger brain and white matter volumes in children with developmental language disorder. Dev Sci 2003; 6:F11-F22.

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ et al. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol. 2004 Apr;55(4):530-40.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Kennedy DN, Filipek PA et al. Brain asymmetries in autism and developmental language disorder: A nested whole brain analysis. Brain 2005; 128: 213-226.

Hines M. Sex-related variation in human behavior and the brain. Trends Cogn Sci. 2010 Aug; 17. [Epub ahead of print]

Holloway RL, De La Costelareymondie MC. Brain endocast asymmetry in pongids and hominids: some preliminary findings on the paleontology of cerebral dominance. Am J Phys Anthropol. 1982 May;58(1):101-10.

Hopkins WD, Marino L. Asymmetries in cerebral width in nonhuman primate brains as revealed by magnetic resonance imaging (MRI). Neuropsychologia. 2000;38(4):493-9.

Hopkins WD, Taglialatela JP, Meguerditchian A, Nir T, Schenker NM, Sherwood CC. Gray matter asymmetries in chimpanzees as revealed by voxel-based morphometry. Neuroimage. 2008 Aug 15;42(2):491-7.

Hugdahl K, Gundersen H, Brekke C, Thomsen T, Rimol LM, Ersland L et al. FMRI brain activation in a Finnish family with specific language impairment compared with a normal control group. J Speech Lang Hear Res 2004 Feb; 47(1):162-72.

Huster RJ, Westerhausen R, Kreuder F, Schweiger E, Wittling W. Morphologic asymmetry of the human anterior cingulate cortex. Neuroimage. 2007 Feb 1;34(3):888-95

Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997 Oct 20;387(2):167-78.

Ide A, Dolezal C, Fernández M, Labbé M, Mandujano R, Montes S et al. Hemispheric differences in variability of fissural patterns in perisylvian and cingulate regions of human brains. J Comp Neurol 1999; 410: 235-242.

Jäncke L, Siegenthaler T, Preis S, Steinmetz H. Decreased white-matter density in a left-sided fronto-temporal network in children with developmental language disorder: Evidence for anatomical anomalies in a motor-language network. Brain Lang 2007; 102: 91-98.

Jerison HJ. Evolution of the brain and intelligence. Academic Press, New York. 1973

Jernigan TL, Hesselink JR, Sowell E, Tallal PA. Cerebral structure on magnetic resonance imaging in language- and learning-impaired children. Arch Neurol 1991; 48: 539-545.

Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. Brain. 1991 Oct;114 (Pt 5):2037-49.

Joos M. Acoustic phonetics. Language 1948; 24-2. 1-136

Josse G, Tzourio-Mazoyer N. Hemispheric specialization for language. Brain Res Brain Res Rev. 2004 Jan;44(1):1-12.

Kandel ER, Schwartz JH, Jessell TM 2000. Principles of Neural Science, 4th ed. McGraw-Hill, New York.

Keenan JP, Thangaraj V, Halpern AR, Schlayg G. Absolute pitch and planum temporale. Neuroimage 2001; 14: 1402-1408.

Kjelgaard MM, Tager-Flusberg H. An Investigation of Language Impairment in Autism: Implications for Genetic Subgroups. Lang Cogn Process. 2001 Apr 1;16(2-3):287-308.

Kovalev VA, Kruggel F, Gertz HJ, von Cramon DY. Three-dimensional texture analysis of MRI brain datasets. IEEE Trans Med Imaging. 2001 May;20(5):424-33.

Krause J, Lalueza-Fox C, Orlando L, Enard W, Green RE, Burbano HA et al. The derived FOXP2 variant of modern humans was shared with Neandertals. Curr Biol 2007 Nov; 6,17(21):1908-12.

Lancaster JL, Kochunov PV, Thompson PM, Toga AW, Fox PT. Asymmetry of the brain surface from deformation field analysis. Hum Brain Mapp 2003; 19:79–89.

Lane RD, Ahern GL, Schwartz GE, Kaszniak AW. Is alexithymia the emotional equivalent of blindsight? Biol Psychiatry 1997; 42: 834-844.

Larsen JP, Hoien T, Lundberg I, Odegaard H. MRI evaluation of the size and symmetry of the *planum temporale* in adolescents with developmental dyslexia. Brain Lang 1990; 39, 289-301.

Leask SJ, Crow TJ. Word acquisition reflects lateralization of hand skill. Trends Cogn Sci 2001; 5: 513-6.

Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C. Microstructural maturation of the human brain from childhood to adulthood. Neuroimage. 2008 Apr 15;40(3):1044-55.

Lebel C, Beaulieu C. Lateralization of the arcuate fasciculus from childhood to adulthood and its relation to cognitive abilities in children. Hum Brain Mapp. 2009 Nov;30(11):3563-73.

Le Journal De Net (2010). Volume cérébral des Hominidés. Retrieved on January 31, 2010, from http://www.journaldunet.com/science/biologie/dossiers/06/0608-memoire/8.shtml. Lee S, Wolpoff MH. The pattern of evolution in Pleistocene human brain size. Paleobiology. 2003; 29(2), 186–196.

Le Bihan D, Mangin J, Poupon C, Clark CA, Pappata S, Molko N et al. Diffusion tensor imaging: concepts and applications. Journal of Magnetic Resonance Imaging 2001; 13:534–546.

LeMay M. Asymmetries of the brains and skulls of nonhuman primates. In: Glick SD, editor. Cerebral lateralization in nonhuman species. Academic Press; New York: 1985. p. 223–245.

LeMay M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. Ann N Y Acad Sci. 1976;280:349-66.

Lenneberg EH. Fundamentos biológicos del lenguaje. AU. 114. Alianza. Madrid 1976.

Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, Blumenthal JD, Lerch J, Zijdenbos AP, Evans AC, Thompson PM, Giedd JN. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage. 2007 Jul 15;36(4):1065-73.

Leonard CM, Lombardino LJ, Walsh K, Eckert MA, Mockler JL, Rowe LA et al. Anatomical risk factors that distinguish dyslexia from SLI predict reading skill in normal children. J Commun Disord 2002; 35:501-531.

Leonard C, Eckert M, Given B, Virginia B, Eden G. Individual differences in anatomy predict reading and oral language impairments in children. Brain. 2006 Dec;129(Pt 12):3329-42

Leonard CM, Eckert MA. Asymmetry and dyslexia. Dev Neuropsychol. 2008;33(6):663-81

Lindgren SD, Koeppl GK. Assessing child behavior problems in a medical setting: Development of the Pediatric Behavior Scale. In: Prinz RJ, editor. Advances in behavioral assessment of children and families. Greenwich, CT: JAI; 1987. pp. 57–90.

Luminet O, Bagby RM, Wagner H, Taylor GJ, Parker JD. Relation between alexithymia and the five-factor model of personality: a facet-level analysis. J Pers Assess. 1999 Dec;73(3):345-58.

Martin, RD. Body size, brain size and feeding strategies, in Food acquisition and processing in primates. Chivers, D; Wood, B; Bilsborough, A, eds. Plenum Press, New York. 1984

Martínez-Sánchez F. Adaptación española de la Escala de Alexitimia de Toronto (TAS-20). Clínica y Salud. 1996; 7(1): 19-32.

Matsui M, Gur RC, Turetsky BI, Yan MX, Gur RE. The relation between tendency for psychopathology and reduced frontal brain volume in healthy people. Neuropsychiatry Neuropsychol Behav Neurol. 2000 Jul;13(3):155-62.

McCrae RR. The five-factor model and its assessment in clinical settings. J Pers Assess. 1991 Dec;57(3):399-14.

MacLean PD. Psychosomatic disease and the «visceral brain»: recent developments bearing on the Papez theory of emotion. Psychosom Med 1949; 11(6): 338-353.

Mendlowicz MV, Girardin JL, Likkin C, Akiskal HS, Furlanetto LM, Rapaport MH. Sociodemographic predictors of temperament and character. Journal of Psychiatric Research 2000; 34:221-226.

Miettunen J, Veijola J, Lauronen E, Kantojärvi I, Joukama M. Sex differences in Cloninger's temperament dimensions-a meta-analysis. Comprehensive Psychitatry 2007; 48:161-169.

Millon T. Manual for the Millon Clinical Multiaxial Inventory. Mineapolis, National Computer Systems, 1980.

Mithen, SJ. The Singing Neanderthals: the Origins of Music, Language, Mind and Body Cambridge, Mass. : Harvard University Press, 2006. Weidenfeld & Nicolson, London (2005).

Morgan LH., La sociedad primitiva, 2ª Edición, Editorial Ayuso, Madrid,1971 *Traducción de Morgan LH. Ancient Society of Research in the Lines of Human Progress from Savagery through Barbarium to Civilization (1881).*

Morgane PJ, Galler JR, Mokler DJ. A review of systems and networks of the limbic forebrain/limbic midbrain. Prog Neurobiol 2005 Feb;75(2):143-60.

Nemiah JC, Sifneos PE, Apfel-Savitz R. A comparison of the oxygen consumption of normal and alexithymic subjects in response to affect-provoking thoughts. Psychoter Psychosom 1977; 28: 167-171.

Nopoulos P, Flaum M, O'Leary D, Andreasen NC. Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. Psychiatry Res. 2000 Feb 28;98(1):1-13.

Okuyama Y, Ishiguro H, Nankai M, Shibuya H, Watanabe A, Arinami T. Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. Molt Psychiatry 2000; 5: 64-69.

Ono M, Kubik S, Abernathey CD. Atlas of the Cerebral Sulci. Thieme, Stuttgart 1990.

Ormorod JE. Aprendizaje humano. Barcelona: Prentice Hall, 2005.

Oros N, Steuber V, Davey N, Canamero L, Adams R. Evolution of Bilateral Symmetry in Agents Controlled by Spiking Neural Networks. In: Proceedings of the 2009 IEEE Symposium on Artificial Life.

Ostby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. J Neurosci. 2009 Sep 23;29(38):11772-82.

Otero J. Alexitimia: una revisión. Revista de la Asociación Española de Neuropsiquiatría. 1999, 27: 587-596.

Oxnard CE. Brain evolution: mammals, primates, chimpanzees, and humans. Int J Primatol 2004; 25: 1127-58.

Pakkenberg B, Gundersen HJ. Neocortical neuron number in humans: effect of sex and age. J Comp Neurol. 1997 Jul 28;384(2):312-20.

Palmer AR. Symmetry Breaking and the Evolution of Development. Science 2004; 306: 828-833.

Parazzini C, Baldoli C, Scotti G, Triulzi F. Terminal Zones of Myelination: MR Evaluation of Children Aged 20–40 Months. AJNR Am J Neuroradiol 2002; 23:1669–1673.

Parker G, Cheah YC, Paker K. Properties of temperament and character inventory in a Chinese sample. Acta Psychiatrica Scandinavica 2003; 108:367-373.

Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulated cortex in the control of oculomotor, manual, and speech responses: A positron emission tomography study. N Neurophysiol 1993; 70: 453-469.

Paus T, Otaky N, Caramanos Z, MacDonald D, Zijdenbos A, D'Avirro D et al. In vivo morphometry of the intrasulcal grey matter in the human cingulate, paracingulate, and superior-rostral sulci: Hemispheric asymmetries, gender differences and probability maps. J Com Neurol 1996; 376: 664-673.

Paus T, Tomaiuolo F, Otaky N, MacDonald D, Petrides M, Atlas J et al. Human cingulate and paracigulate sulci: pattern, variability, asymmetry and probabilistic map. Cereb Cortex 1996; 6: 207-214.

Paus T. Functional anatomy of arousal and attention systems in the human brain. Prog Brain Res 2000; 126: 65-77.

Paus T. Primate anterior cingulated cortex: Where motor control, drive and cognition interface. Nat Rev Neurosci 2001; 2: 417-424.

Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull. 2001 Feb;54(3):255-66.

Paus T, Nawaz-Khan I, Leonard G, Perron M, Pike GB, Pitiot A et al. Sexual dimorphism in the adolescent brain: Role of testosterone and androgen receptor in global and local volumes of grey and white matter. Horm Behav. 2010 Jan;57(1):63-75.

Peirson AR, Heuchert JW, Thomala L, Berk M, Plein H, Cloninger CR. Relationship between serotonin and the temperament and character inventory. Psychiatry Res 1999; 89: 29-37.

Penhune VB, Zatorre RJ, MacDonald JD, Evans AC. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cereb Cortex. 1996 Sep-Oct;6(5):661-72.

Perrin JS, Leonard G, Perron M, Pike GB, Pitiot A, Richer L et al. Sex differences in the growth of white matter during adolescence. Neuroimage. 2009 May 1;45(4):1055-66.

Perrin JS, Hervé PY, Leonard G, Perron M, Pike GB, Pitiot A et al. Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. Neurosci. 2008 Sep 17;28(38):9519-24.

Peters M. Sex differences in human brain size and the general meaning of differences in brain size. Can J Psychol. 1991 Dec;45(4):507-22.

Peters M, Jäncke L, Staiger JF, Schlaug G, Huang Y, Steinmetz H. Unsolved problems in comparing brain sizes in Homo sapiens. Brain Cogn. 1998 Jul;37(2):254-85.

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. Radiology 1996 Dec;201(3):637-48.

Pilcher DL, Hammock EA, Hopkins WD. Cerebral volumetric asymmetries in non-human primates: a magnetic resonance imaging study. Laterality 2001 Apr;6(2):165-79.

Plante E, Swisher L, Vance R, Rapcsak S. MRI findings in boys with specific language impairment. Brain Lang 1991; 41: 52-66.

Preuss TM. The discovery of cerebral diversity: an unwelcome scientific revolution. In Falk D, Gibson KR, eds. Evolutionary anatomy of the primate cerebral cortex. Cambridge; Cambridge University Press; 2001. p .138-64.

Price C J. The anatomy of language: contributions from functional neuroimaging. J Anat 2000; 197(3): 335-59.

Pujol J, Bello J, Deus J, Martí-Vilalta JL, Capdevila A. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. Neurology. 1997 Oct;49(4):1105-10

Pujol J, Deus J, Losilla JM, Capdevila A. Cerebral lateralization of language in normal left-handed people studied by functional MRI. Neurology. 1999 Mar 23;52(5):1038-43.

Pujol J, Bello J, Deus J, Cardoner N, Martí-Vilalta JL, Capdevila A. Beck Depression Inventory factors related to demyelinating lesions of the left arcuate fasciculus region. Psychiatry Res. 2000 Oct 30;99(3):151-9.

Pujol J, Vendrell P, Deus J, Junqué C, Bello J, Martí-Vilalta JL et al. The effect of medial frontal and posterior parietal demyelinating lesions on Stroop interference. NeuroImage 2001; 13: 68-75.

Rademacher J, Caviness VS Jr, Steinmetz H, Galaburda AM. Topographical variation of the human primary cortices: implications for neuroimaging, brain mapping, and neurobiology. Cereb Cortex. 1993 Jul-Aug;3(4):313-29.

Rapin I. Developmental language disorders. En Rapin I (ed.): Children with brain dysfunction, pags 139-151. Raven Press, Nueva York, 1982.

Rapin I, Allen DA, Dunn Ma. Developmental language disorders. En Segalowitz SJ, Rapin I (eds.): Child neuropsychology, Handbook of neuropsychology. Vol. 7, cap. 2. Elsevier Science Publishers, Amsterdam, 1992.

Rapin I. Practionar review. Developmental language disorders: A clinical update. J child Psychol Psychiatry. 1996; 37: 643-655.

Rapin I, Dunn M. Language disorders in children with autism. Semin Pediatr Neurol. 1997 Jun;4(2):86-92.

Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann N Y Acad Sci. 1977 Sep 30;299:355-69.

Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB. Brain development, gender and IQ in children. A volumetric imaging study. Brain. 1996 Oct;119 (Pt 5):1763-74.

Reiss AL, Kesler SR, Vohr B, Duncan CC, Katz KH, Pajot S et al. Sex differences in cerebral volumes of 8-year-olds born preterm. J Pediatr. 2004 Aug;145(2):242-9.

Rivkin MJ. Developmental neuroimaging of children using magnetic resonance techniques. Ment Retard Dev Disabil Res Rev. 2000;6(1):68-80.

Rosenzweig MR, Leiman AL, Breedlove SM. Biological Psychology: an introduction to behavioural, cognitive and clinical neuroscience. Sunderland MA: Sinauer Associates, 1999.

Rudebeck PH, Bannerman DM, Rushworth MF. The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. Cogn Affect Behav Neurosci. 2008 Dec;8(4):485-97.

Schlaug G, Jäncke L, Huang Y, Steinmetz H. In vivo evidence of structural brain asymmetry in musicians. Science. 1995; 267 (5198): 699-701.

Schoenemann PT, Sheehan MJ, Glotzer LD. Prefrontal white matter volume is disproportionately larger in humans than in other primates. Nat Neurosci. 2005 Feb;8(2):242-52.

Semendeferi K, Lu A, Schenker N, Damasio H.Humans and great apes share a large frontal cortex. Nat Neurosci. 2002 Mar;5(3):272-276.

Shapleske J, Rossell SL, Woodruff PWR, David AS. The *planum temporale*: a systematic, quantitative review of its structural, functional and clinical significance. Brain Res Rev 1999; 29: 26-49.

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N et al. Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci. 2008 Apr 2;28(14):3586-94.

Shaywitz BA, Shaywitz SE, Pugh KR, Constable RT, Skudlarski P, Fulbright RK et al. Sex differences in the functional organization of the brain for language. Nature. 1995 Feb 16;373(6515):607-9.

Skinner BF. Sobre el conductismo. Barcelona: Editorial Fontanella, 1977.

Skullerud K. Variations in the size of the human brain. Influence of age, sex, body length, body mass index, alcoholism, Alzheimer changes, and cerebral atherosclerosis. Acta Neurol Scand Suppl. 1985;102:1-94.

Snelson CD, Gamse JT. Building an asymmetric brain: development of the zebrafish epithalamus. Semin Cell Dev Biol 2009 Jun;20(4):491-7.

Sneou EA, en Le Cuorriere de L`UNESCO, Enero, 1976

Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. Neuroimage. 1999 Jun;9(6 Pt 1):587-97.

Sowell ER, Thompson PM, Rex D, Kornsand D, Tessner KD, Jernigan TL et al. Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: maturation in perisylvian cortices. Cereb Cortex. 2002 Jan;12(1):17-26.

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci. 2003 Mar;6(3):309-15.

Springer S, Deutsch G. Left brain, right brain, 5 edn (San Francisco: Freeman).(1997)

Springer SP, Deutsch G. Sex differences in cognition and asymmetry. In Left Brain, Right Brain: Perspectives from Cognitive neuroscience (RC Atkinson, G Lindzey, RF Thompson, Eds.), 5ª ed, pp. 139-156. Freeman, New York 1998.

Steinmetz H. Structure, function and cerebral asymmetry: in vivo morphometry of the *planum temporale*. Neurosci Biobehav Rev 1996;20(4):587-91

Steinmetz H, Volkmann J, Jäncke K, Freund HJ. Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right handers. Ann Neurol 1991; 29: 315-319.

Suhara T, Yasuno F, Sudo Y, Yamamoto M, Inoue M, Okubo Y et al. Dopamine D2 receptors in the insular cortex and the personality trait of novelty seeking. NeuroImage 2001; 13: 891-895.

Tallal P, Miller S, Fitch RH. Neurobiological basis of speech: a case for the preeminence of temporal processing. Ann N Y Acad Sci. 1993 Jun 14;682:27-47.

Tamnes CK, Østby Y, Walhovd KB, Westlye LT, Due-Tønnessen P, Fjell AM. Intellectual abilities and white matter microstructure in development: a diffusion tensor imaging study. Hum Brain Mapp. 2010 Oct;31(10):1609-25.

Tattersall, I. Homínidos contemporáneos. Investigación y Ciencia 2000; 282: 14-20.

Taylor DC. Different rates of cerebral maturation between sexes and between hemispheres. Lancet 1969; 2: 140-142.

Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. Nature. 2000 Mar 9;404(6774):190-3.

Trauner D, Wulfeck B, Tallal P, Hesselink J. Neurological and MRI profiles of children with developmental language impairment. Dev Med Child Neurol 2000; 42: 470-475.

Tucker DM, Liotti M. Neuropsychological mechanisms of anxiety and depression. In Handbook of Neuropsychology (F Boller and J Grafman, Eds), 1989 (3) 443-475. Elsevier, Amsterdam.

Tucker DM, Luu P, Pribram KH. Social and emotional self-regulation. Ann N Y Acad Sci1995 Dec; 15(769):213-39.

Vasileiadis GT, Thompson RT, Han VK, Gelman N. Females follow a more "compact" early human brain development model than males. A case-control study of preterm neonates. Pediatr Res. 2009 Nov;66(5):551-5.

Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulated cortex: The anterior executive and posterior evaluative regions. Cereb Cortex 1992; 359: 490-506.

Vogt BA, Nimchinsky EA, Vogt LJ, Holf PR. Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. J Comp Neurol 1995; 359: 490-506.

Walhovd KB, Fjell AM, Reinvang I, Lundervold A, Dale AM, Eilertsen DE et al. Effects of age on volumes of cortex, white matter and subcortical structures. Neurobiol Aging. 2005 Oct;26(9):1261-70

Warrier C, Wong P, Penhune V, Zatorre R, Parrish T, Abrams D et al. Relating structure to function: Heschl's gyrus and acoustic processing. J Neurosci. 2009 Jan 7;29(1):61-9.

Watkins KE, Paus T, Lerch JP, Zijdenbos A, Collins DL, Neelin P et al. Structural asymmetries in the human brain: A voxel-based statistical analysis of 142 MRI scans. Cereb Cortex 2001;11:868–877.

Wernicke C. Der apasische Symptomenkomplex: eine psychologische Studie auf anatomischer Basis (Cohn und Welgert, Breslau, 1874).

Wilke M, Krägeloh-Mann I, Holland SK. Global and local development of gray and white matter volume in normal children and adolescents. Exp Brain Res. 2007 Apr;178(3):296-307.

Witelson SF, Pallie W. Left hemisphere specialization for language in the newborn. Neuroanatomical evidence of asymmetry. Brain 1973 Sep; 96(3):641-6.

Witelson SF, Kigar DL. Sylvian fissure morphology and asymmetry in men and women: Bilateral differences in relation to handedness in men. J Comp Neurol 1992; 323: 326-340.

Williams RW, Herrup K. The control of neuron number. Annu Rev Neurosci. 1988;11:423-53.

Wolpert L. Development of the asymmetric human. European Review 2005; 13: 97-103.

Wright CI, Williams D, Feczko E, Barrett LF, Dickerson BC, Schwartz CE, Wedig MM. Neuroanatomical correlates of extraversion and neuroticism. Cereb Cortex. 2006 Dec;16(12):1809-19

Yakovlev PI, Rakic P. Patterns of decussation of bulbar pyramids and distribution of pyramidal tracts on two sides of the spinal cord. Trans Am Neurol Assoc 1966;91:366–367.

Yakovlev PI, Lecours AR (1967). The myelogenetic cycles of regional maturation of the brain. In: Minkowski A (ed). Regional Development of the Brain in Early Life. Blackwell Scientific Publications: Boston. pp 3–70.

Yücel M, Stuart GW, Maruff P, Velakoulis D, Crowe SF, Savage G et al. Hemispheric and gender-related differences in the gross morphology of the anterior cingulated/ paracingulate cortex in normal volunteers: An MRI morphometric study. Cereb Cortex 2001; 11: 17-25.

Zangwill OL. Speech and the minor hemisphere. Acta Neurol Psychiatr Belg. 1967 Nov;67(11):1013-20

Zatorre RJ. On the representation of multiple languages in the brain: old problems and new directions. Brain Lang 1989; 36(1): 127-47.

Zatorre RJ, Belin P, Penhune VB. Structure and function of auditory cortex: music and speech. Trends Cogn Sci. 2002 Jan 1;6(1):37-46.

Zuckerman M, Kuhlman DM, Thornquist M, Kiers H. Five (or three): Robust questionnaire scale factors of personality without culture. Personality and Individual Differences 1991; 12, 929-941.