Genética en Trastornos del Desarrollo: Hallazgos en Dislexia y Trastorno por Déficit de Atención e Hiperactividad

Ximena Carrasco Ch., Neuropediatra

Departamento de Pediatría Oriente, Facultad de Medicina,
Universidad de Chile
Servicio de Neurología y Psiquiatría, Hospital de Niños Luis Calvo Mackenna
&
Laboratorio de Neurociencias Cognitivas, Centro de Investigaciones Médicas,
Pontificia Universidad Católica de Chile

SOCIEDAD DE NEUROLOGÍA Y PSIQUIATRÍA DE LA INFANCIA Y ADOLESCENCIA

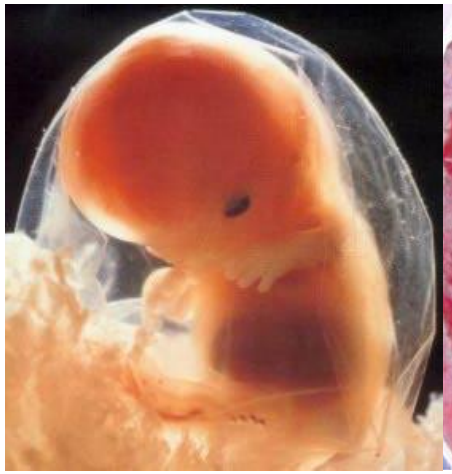
El Desarrollo Psicomotor Normal y sus Trastornos

Definición:

El desarrollo es el proceso de cambio que va experimentando cada sujeto en el transcurso del tiempo, dentro de la continuidad que implica ser y mantenerse como un ser único e identificable. El desarrollo se refiere, específicamente, a la adquisición y perfeccionamiento de competencias cognitivo/conductuales que sirven para que el individuo se desenvuelva exitosamente en su contexto particular, antes y después de su nacimiento (mayoritariamente en forma postnatal) y que culmina en el ser adulto.

Es un cambio con sentido (↑): adquisición y optimización de funciones de acuerdo al contexto.

Continuidad del desarrollo: Embrionario → Fetal → Postnatal

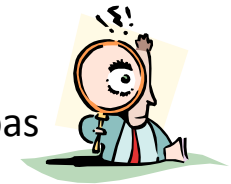


¿Qué aspectos del encéfalo no están listos al nacer?

- ❖Neuropila (dendritas principalmente)
- ❖Sinapsis (formación, poda, sintonía fina)
- ❖Mielina
- ❖Grandes redes (sustentables y eficientes)

Desarrollo cognitivo, emocional y conductual

Como una torre de bloques…
El desarrollo puede fracasar por fallas en cualquiera de las etapas



Continuidad del desarrollo postnatal y aprendizaje

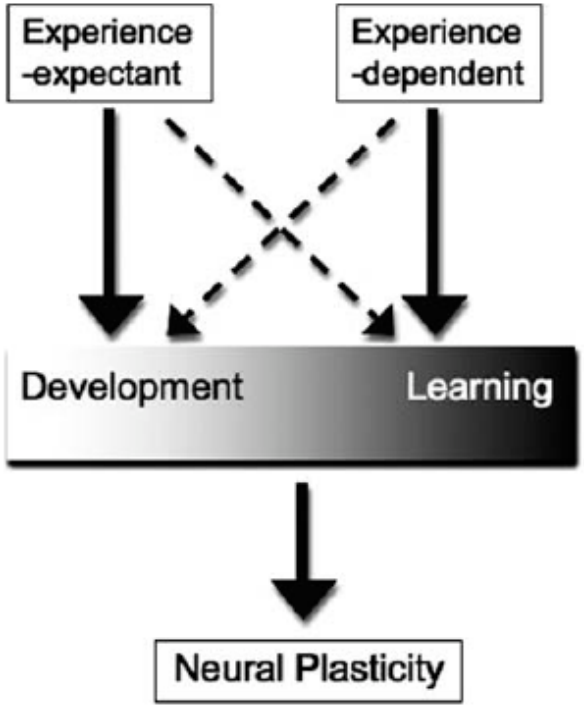


Figure 1.

This working model illustrates that development and learning exist on a continuum, as each independently and simultaneously influence neural plasticity. While development is largely guided by experience-expectant mechanisms, it also receives input from experience-dependent mechanisms. Similarly, learning is mostly guided by experience-dependent mechanisms, but also receives experience-expectant input (72 × 72 DPI).

◆ Neural Plasticity of Development and Learning ◆
Adriana Galván
Department of Psychology, Brain Research Institute, University of California, Los Angeles, California
Hum Brain Mapp 31:879–890, 2010.

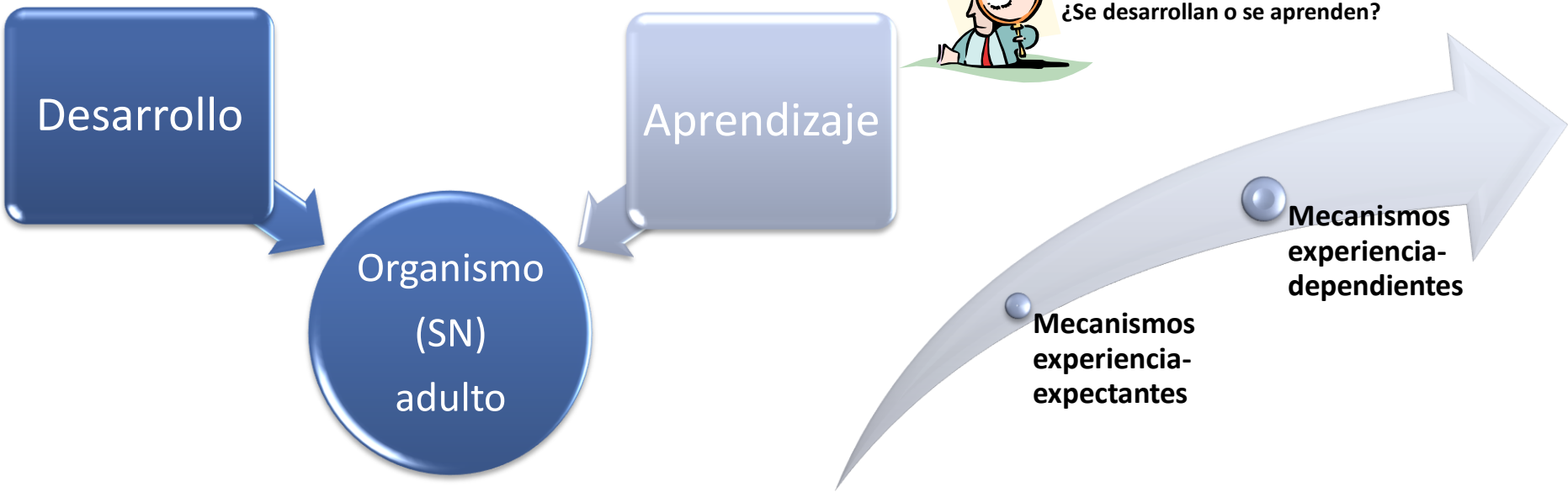
Continuidad: Desarrollo → Aprendizaje

Desarrollo → Experiencia-Expectante

Greenough, 1987: Mecanismos de plasticidad del desarrollo, experiencia-expectantes, utilizan información ambiental común a todos los miembros de la especie a lo largo de la evolución; poseen un *timing* específico. Si el desarrollo es normal, seguirá la "norma filogenética".

Aprendizaje → Experiencia-Dependiente

Los mecanismos de plasticidad que subyacen al aprendizaje, experiencia-dependientes, son sensibles a la experiencia individual y no están limitados temporalmente. Son "ontogenéticos".



◆ Neural Plasticity of Development and Learning ◆

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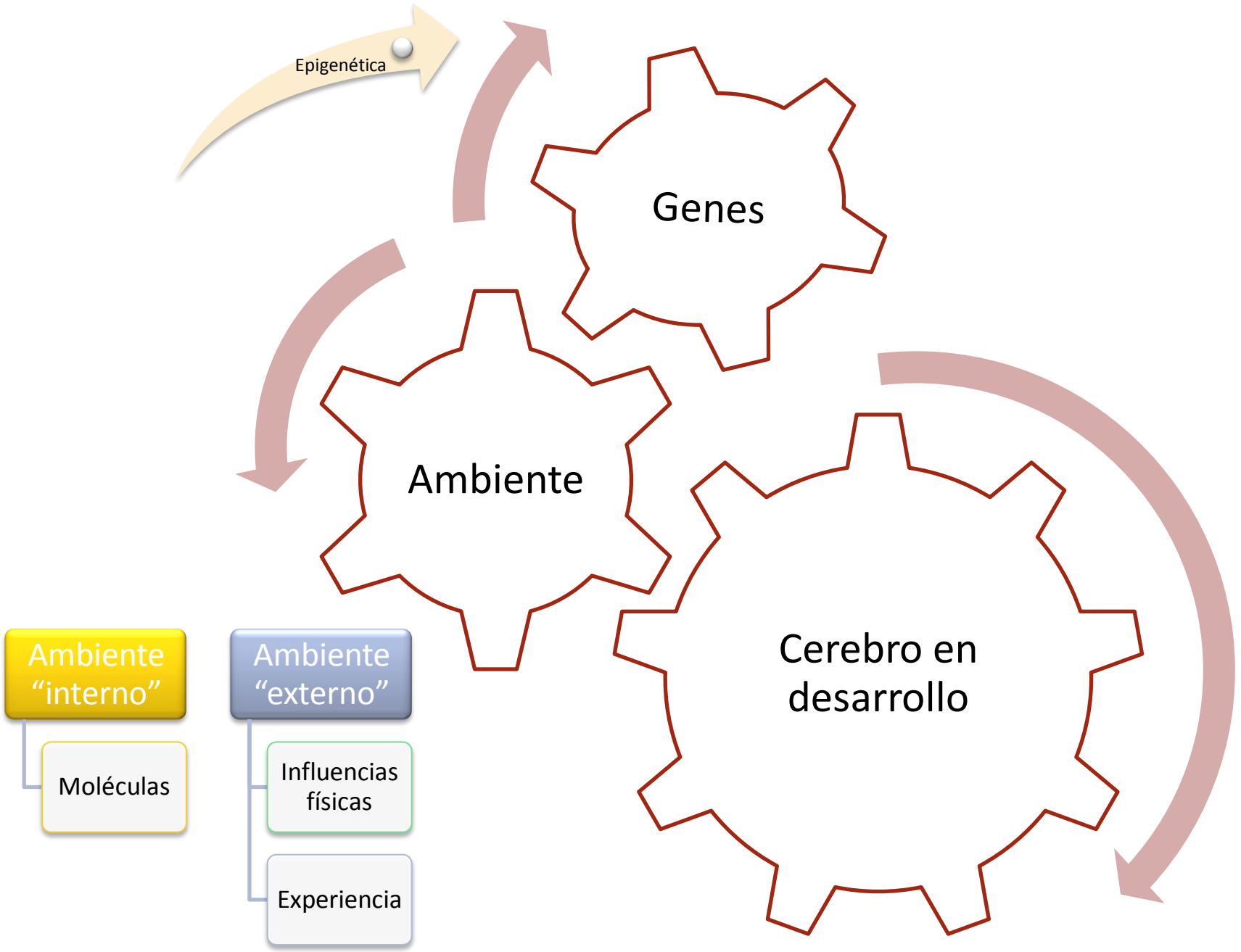
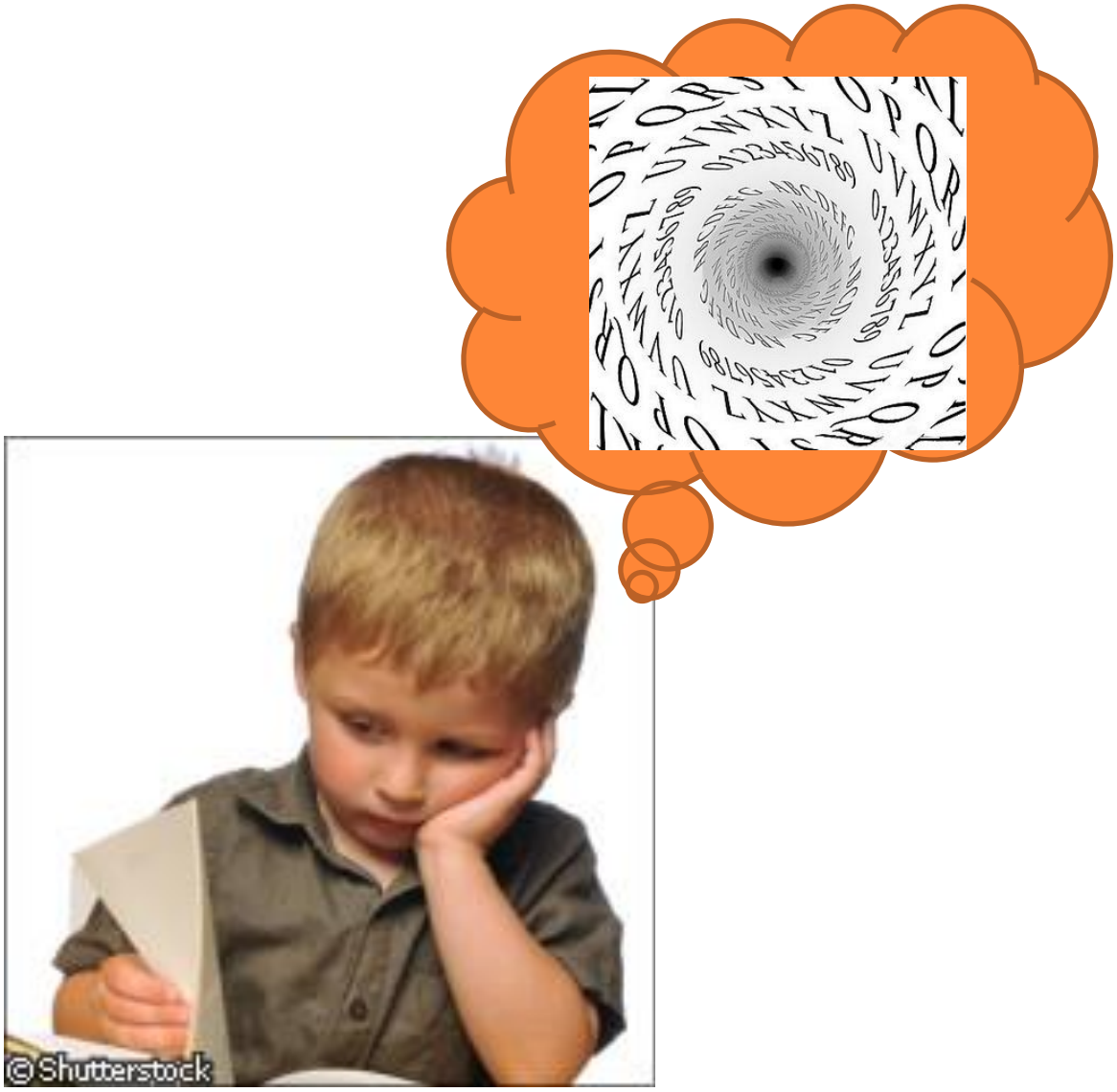

Epigenética
Genes
Ambiente
Cerebro en desarrollo
Ambiente "interno"
Moléculas
Ambiente "externo"
Influencias físicas
Experiencia

Genética en la Dislexia del Desarrollo



Dislexia del Desarrollo: Conceptos básicos

La Dislexia consiste en una dificultad severa y específica en el proceso de adquisición de la lectura, que no se corresponde con las habilidades cognitivas y circunstancias educacionales del niño, y no se explica por otro cuadro neurológico.

La base cognitiva del trastorno sería, según la visión más actualizada, un "déficit fonológico", manifestado en tres aspectos:

1) Deficiente "conciencia fonológica" (representación y procesamiento mental de los sonidos del lenguaje).
2) Pobre memoria verbal de corto plazo (memoria de trabajo fonológica).
3) Lenta recuperación lexical de palabras para la articulación del lenguaje.

El establecimiento de las estructuras fonológicas acontece en el lactante, en el primer año de vida. Suele coexistir con Trastorno del desarrollo del lenguaje y con otros trastornos del desarrollo (TDAH, Discalculia, Dispraxia), por lo que probablemente comparten mecanismos fisiopatológicos y etiológicos (genéticos).

Otras teorías han planteado la existencia de un déficit en el procesamiento auditivo, visual o motor, lo que no se contradice del todo con lo anterior y que podrían explicar algunos casos de dislexia.

Desarrollo fonológico en el lactante

Los bebés nacen con la habilidad de detectar diferencias fonéticas de todos los lenguajes , pero antes de los 12 meses han aprendido con la experiencia, de modo implícito e informal, una capacidad fonética lenguaje-específica para la lengua nativa, lo que sirve de base al aprendizaje de palabras.

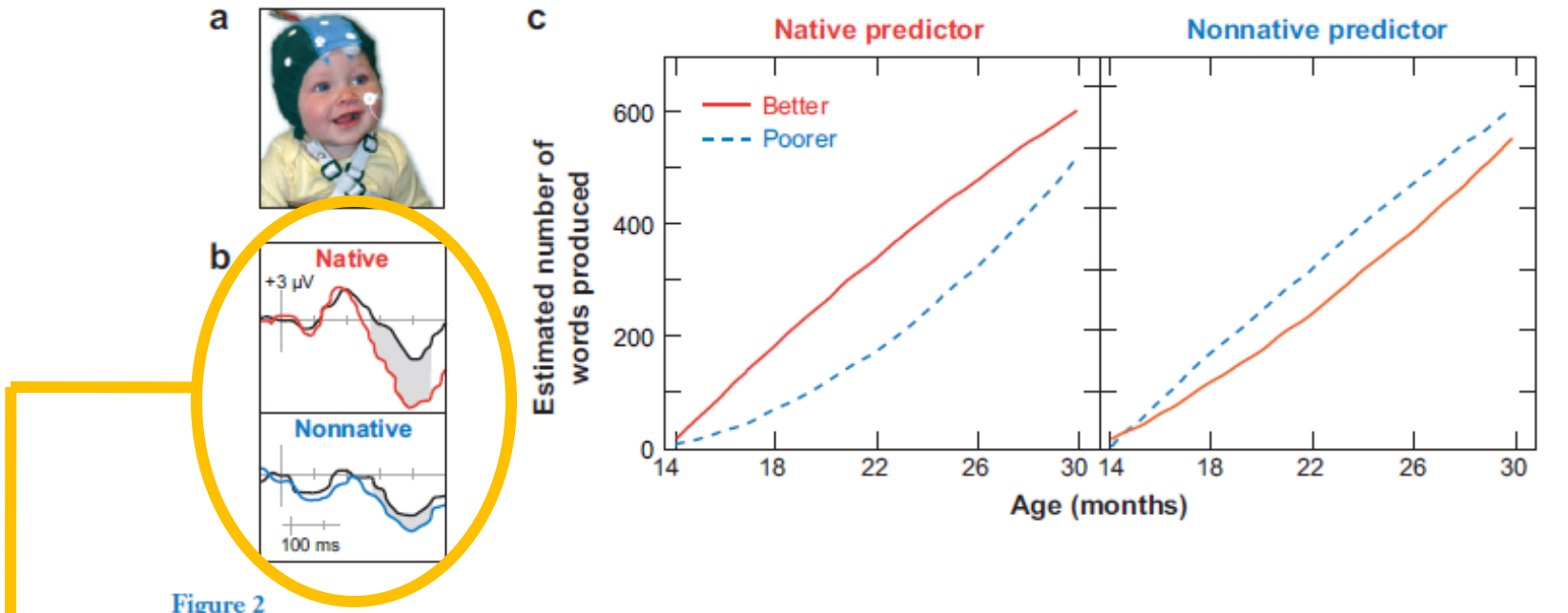
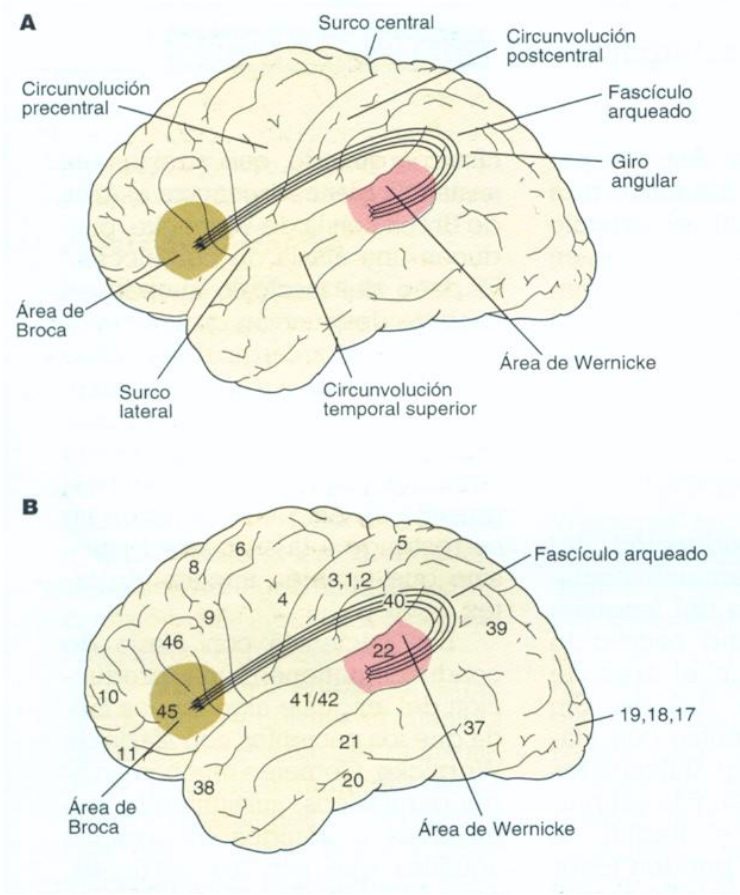


Figure 2

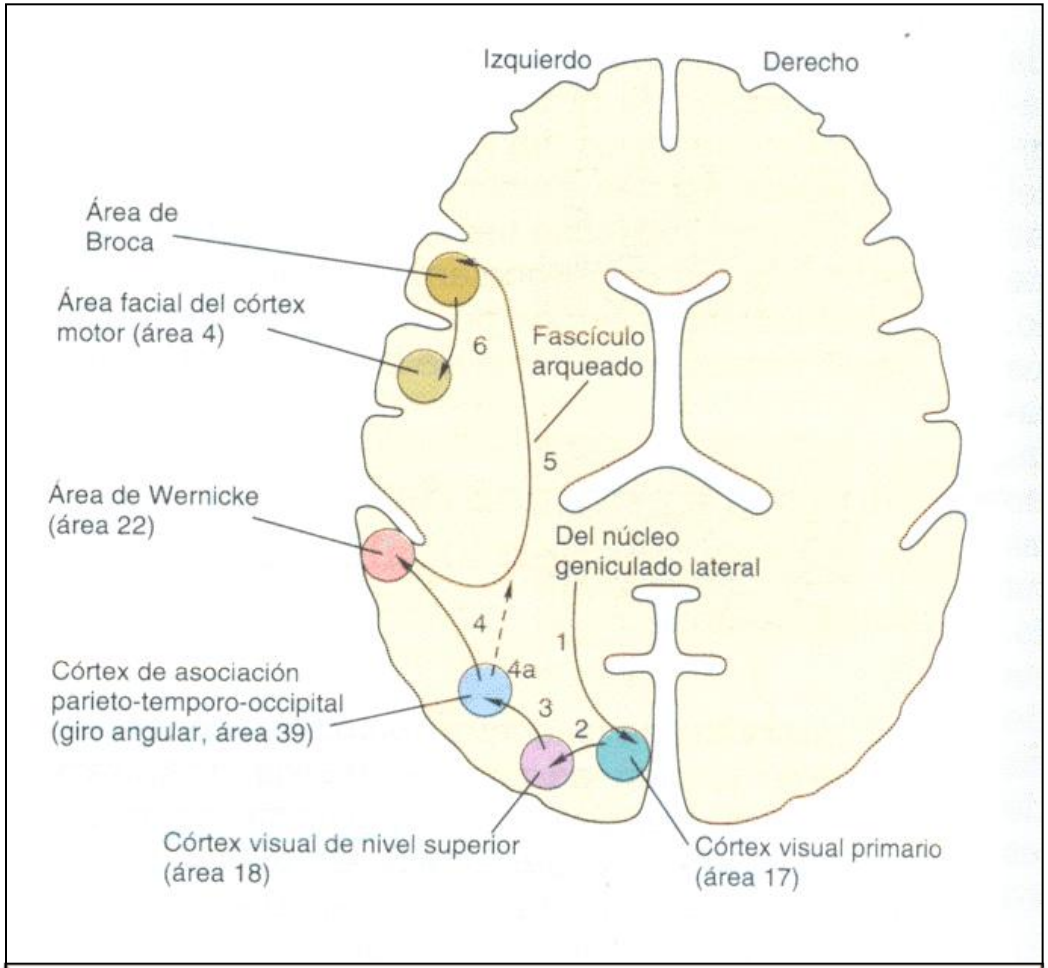
(*a*) A 7.5-month-old infant wearing an ERP electrocap. (*b*) Infant ERP waveforms at one sensor location (CZ) for one infant are shown in response to a native (English) and nonnative (Mandarin) phonetic contrast at 7.5 months. The mismatch negativity (MMN) is obtained by subtracting the standard waveform (*black*) from the deviant waveform (English = *red*; Mandarin = *blue*). This infant's response suggests that native-language learning has begun because the MMN negativity in response to the native English contrast is considerably stronger than that to the nonnative contrast. (*c*) Hierarchical linear growth modeling of vocabulary growth between 14 and 30 months for MMN values of +1SD and −1SD on the native contrast at 7.5 months (*c*, *left*) and vocabulary growth for MMN values of +1SD and −1SD on the nonnative contrast at 7.5 months (*c*, *right*). Analyses show that both contrasts predict vocabulary growth but that the effects of better discrimination are reversed for the native and nonnative contrasts. (From Kuhl et al. 2008)

Existe una modificación neural, evidenciable a través de metodologías de las neurociencias cognitivas, cuando aún la manifestación conductual es relativamente discreta

Dislexia del Desarrollo: Bases Neurobiológicas



Áreas básicas del lenguaje



Modelo de Wernicke-Geschwind: Vías implicadas en la verbalización de una palabra escrita.

Dislexia del Desarrollo: Bases Neurobiológicas

CHILDHOOD DEVELOPMENTAL DISORDERS

PERSPECTIVE

nature neuroscience VOLUME 9 | NUMBER 10 | OCTOBER 2006

From genes to behavior in developmental dyslexia

Albert M Galaburda, Joseph LoTurco, Franck Ramus, R Holly Fitch & Glenn D Rosen

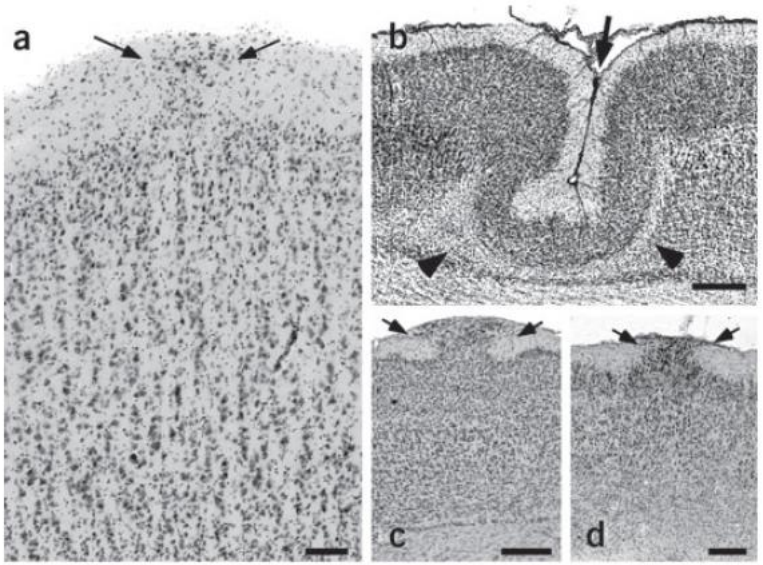
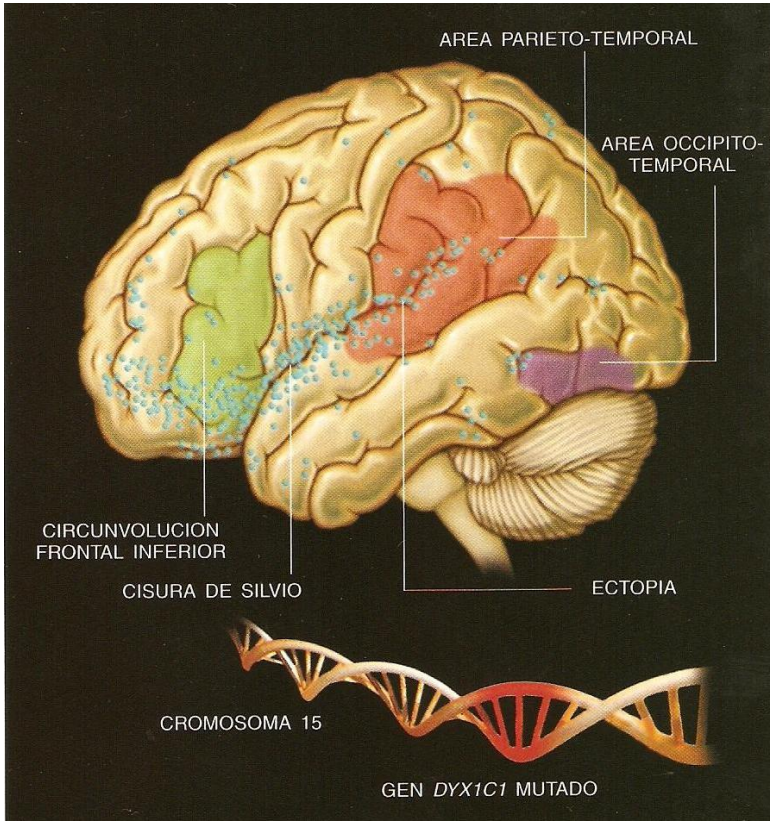


Figure 2 Human and animal neocortical malformations. (**a**) Molecular layer ectopia (arrows) in neocortical layer I of a human dyslexic. Scale bar, 100 μm. (**b**) Induced microgyria in a rat. This malformation, induced by placing a freezing probe onto the skull of a newborn rat, is generally characterized by the presence of a microsulcus (arrow) and a lamina dissecans (arrowheads). Scale bar, 300 μm. (**c**) Spontaneous molecular layer ectopia (arrows) in an immune-defective mouse. Scale bar, 250 μm. (**d**) Molecular layer ectopia (arrows) induced in a rat by *in utero* electroporation of RNAi targeted against *Dyx1c1*. Scale bar, 250 μm.



Dislexia del Desarrollo: Bases Neurobiológicas

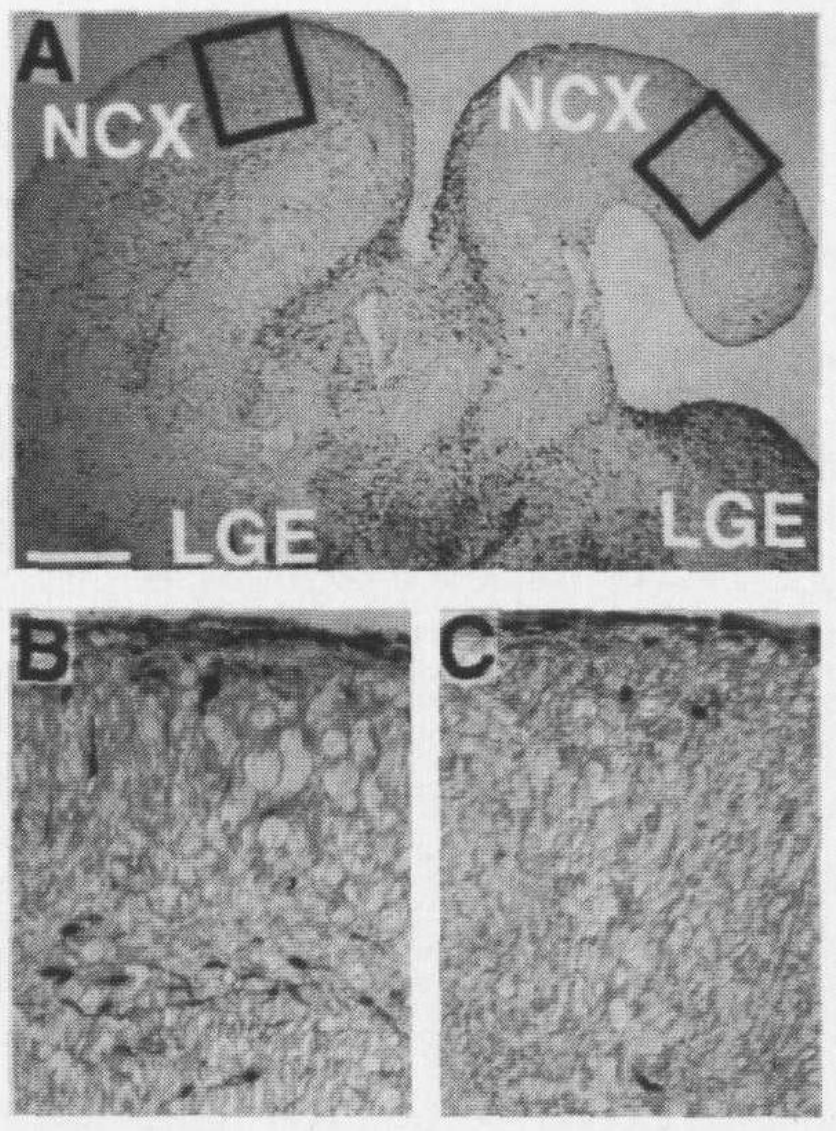
Interneuron Migration from Basal Forebrain to Neocortex: Dependence on *Dlx* Genes

S. A. Anderson, D. D. Eisenstat, L. Shi, J. L. R. Rubenstein*

Although previous analyses indicate that neocortical neurons originate from the cortical proliferative zone, evidence suggests that a subpopulation of neocortical interneurons originates within the subcortical telencephalon. For example, γ-aminobutyric acid (GABA)–expressing cells migrate in vitro from the subcortical telencephalon into the neocortex. The number of GABA-expressing cells in neocortical slices is reduced by separating the neocortex from the subcortical telencephalon. Finally, mice lacking the homeodomain proteins DLX-1 and DLX-2 show no detectable cell migration from the subcortical telencephalon to the neocortex and also have few GABA-expressing cells in the neocortex.

Nina Ireland Laboratory of Developmental Neurobiology, Center for Neurobiology and Psychiatry, Department of Psychiatry and Programs in Neuroscience, Developmental Biology, and Biomedical Sciences, 401 Parnassus Avenue, University of California at San Francisco, CA 94143–0984, USA.

SCIENCE • VOL. 278 • 17 OCTOBER 1997



Dislexia del Desarrollo: Genes

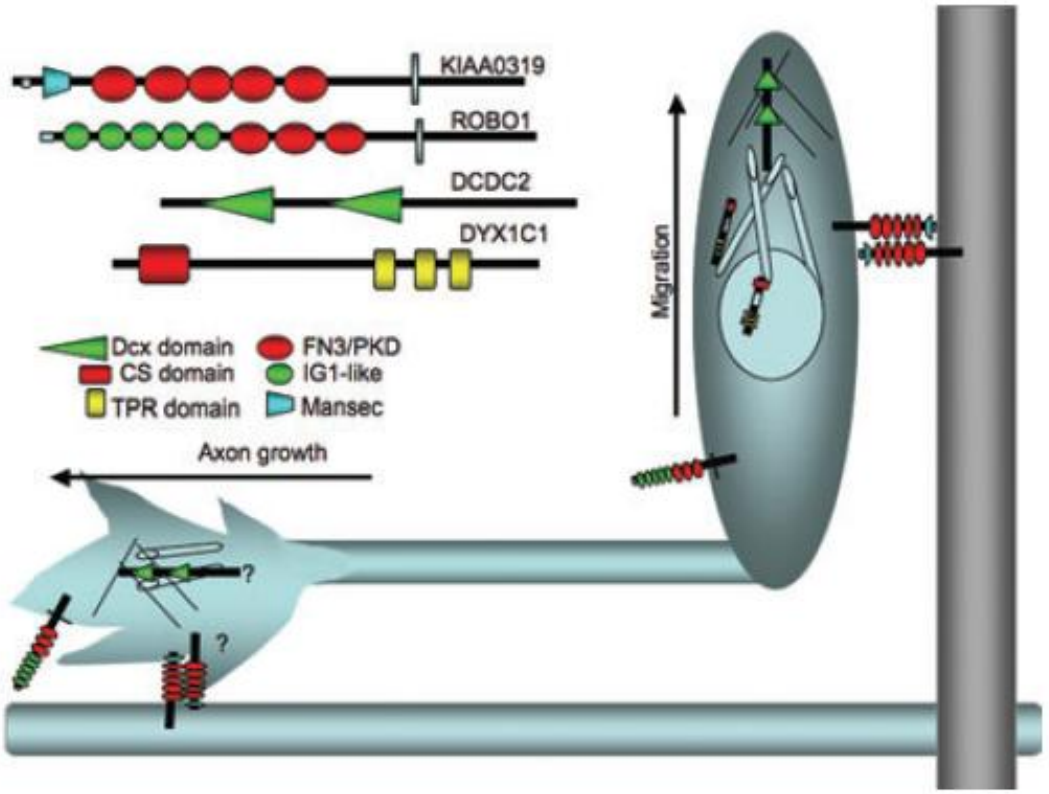


Figure 1 Protein domains and possible functions. KIAA0319 and ROBO1 serve as transmembrane adhesion molecules and receptors that guide axons to appropriate targets. DCDC2, and perhaps DYX1C1, are proposed to act as downstream targets that then serve to modulate changes in cytoskeletal dynamic processes involved in the motility of developing neurons. Critical future studies must now address whether there are links between the functions of these proteins in migration and axonal pathfinding.

Dislexia del Desarrollo: Bases Neurobiológicas

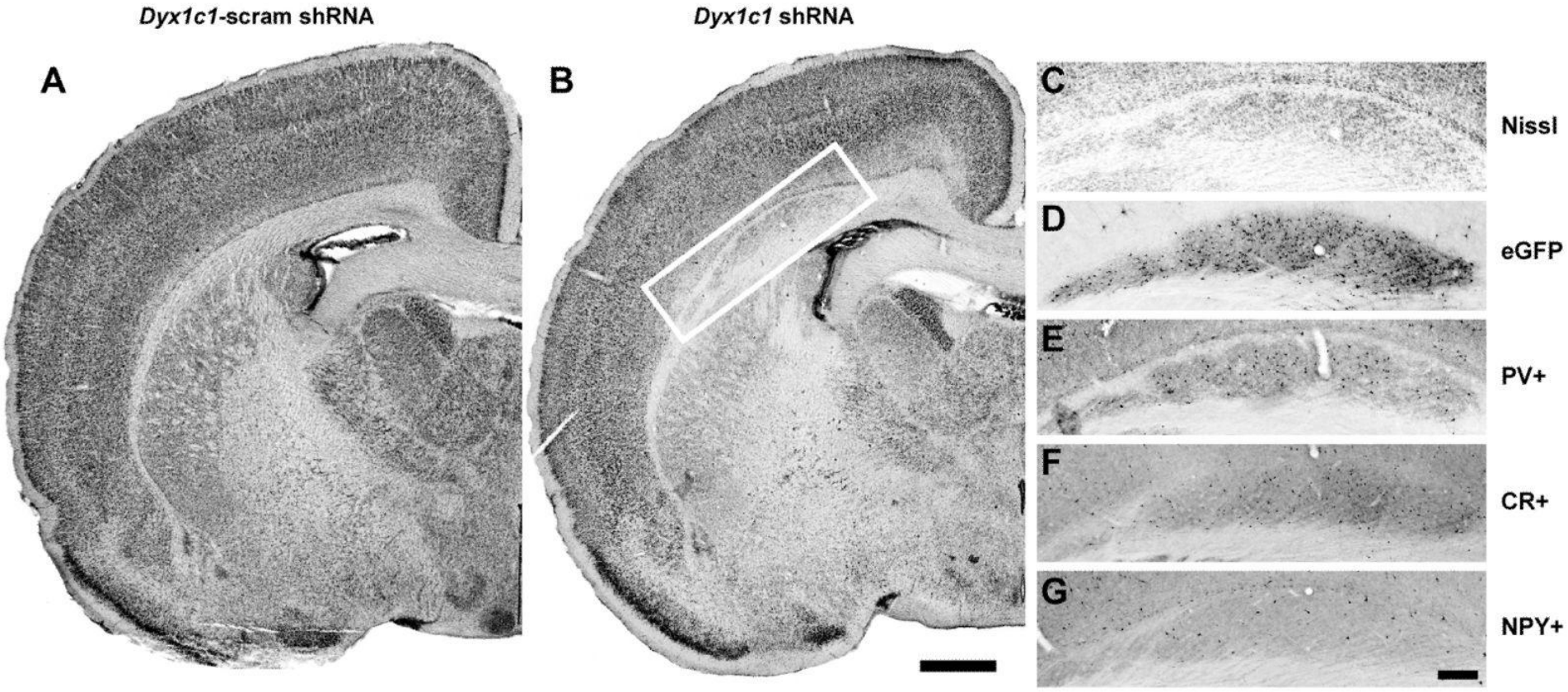


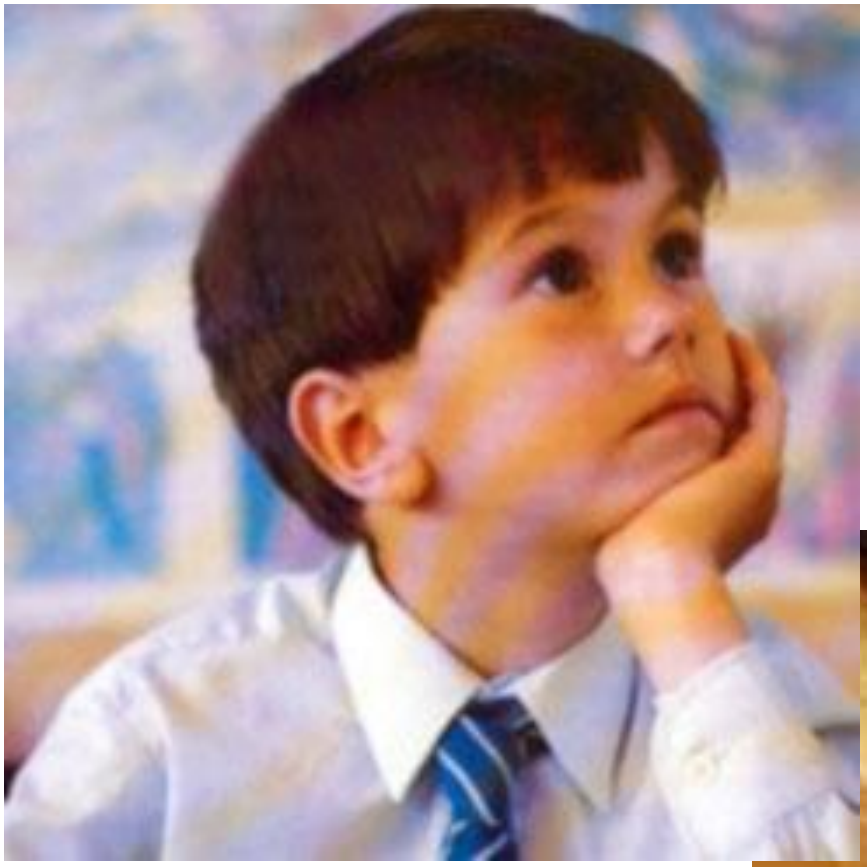
Figure 2.
GABAergic neurons in white matter heterotopias following *in utero* electroporation of *Dyx1c1* shRNA. **A.** Low power photomicrograph of Nissl-stained section from a rat embryonically transfected with *Dyx1c1*-scram shRNA (control condition). There are no heterotopias visible (compare with B). **B.** Low power photomontage of Nissl-stained section from a rat embryonically transfected with *Dyx1c1* shRNA + GFP illustrating large collection of heterotopic neurons in the white matter. White box illustrates enlarged area in panel C. Bar for A and B = 1 mm. **C.** High power photomontage of the Nissl-stained collection of heterotopic neurons shown in panel B. **D.** High-power photomontage of section adjacent to panel C immunohistochemically stained for GFP. Comparing with panel C indicates that there are large numbers of non-transfected neurons in the heterotopia. **E-G.** High-power photomontage of sections adjacent to panel C immunohistochemically stained for PV (E), CR (F), and NPY (G). The presence of these GABAergic interneurons in the heterotopia is supportive of non-cell autonomous effects of *Dyx1c1* shRNA transfection. Bar = 250 μm.

THE EFFECTS OF EMBRYONIC KNOCKDOWN OF THE CANDIDATE DYSLEXIA SUSCEPTIBILITY GENE HOMOLOGUE *DYX1C1* ON THE DISTRIBUTION OF GABAERGIC NEURONS IN THE CEREBRAL CORTEX

Timothy A. Currier*, **Mikel A. Etchegaray***, **Joshua L. Haight***, **Albert M. Galaburda**, and **Glenn D. Rosen**†
Dyslexia Research Laboratory, Division of Behavioral Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA 02215

Neuroscience. 2011 January 13; 172: 535–546.

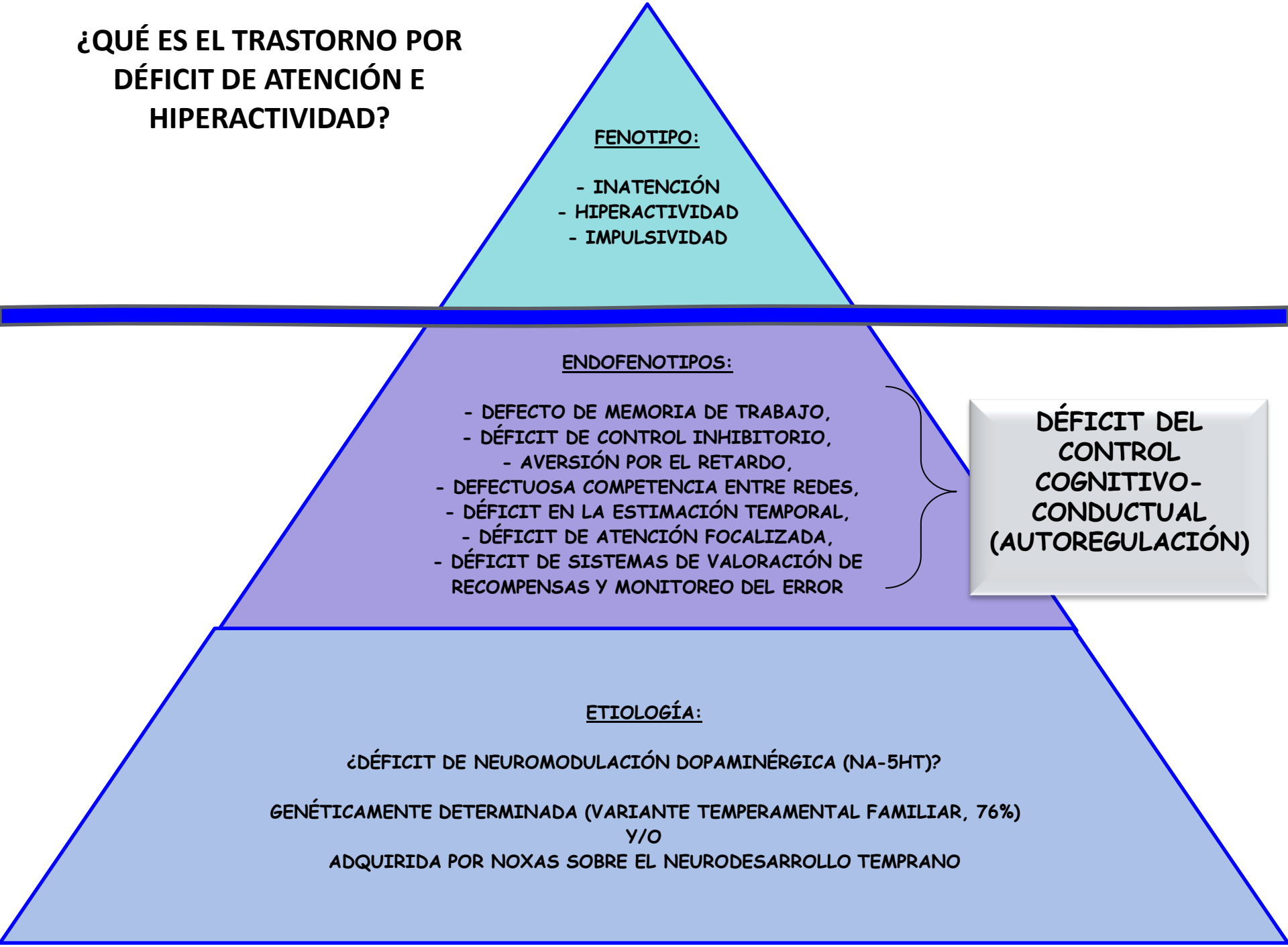
Genética en el Trastorno por Déficit de Atención e Hiperactividad (TDAH)



TDAH: Bases Neurobiológicas

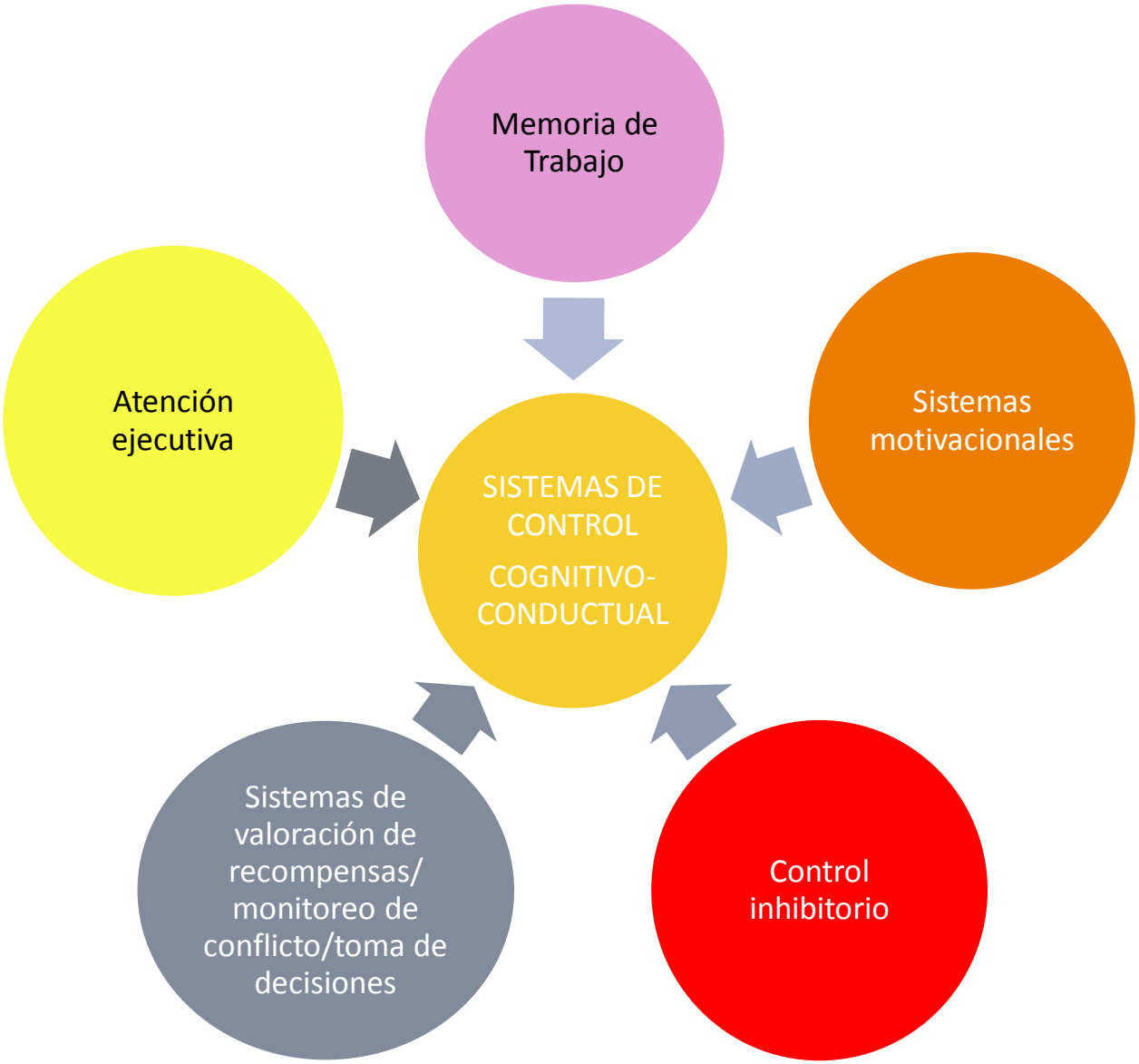
¿Es el Trastorno por Déficit de Atención e Hiperactividad una falla de la atención primariamente?

¿QUÉ ES EL TRASTORNO POR DÉFICIT DE ATENCIÓN E HIPERACTIVIDAD?



Bases Neurobiológicas del TDAH: Conducta Orientada a Metas

Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación



Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación

Linear Age-Correlated Functional Development of Right Inferior Fronto-Striato-Cerebellar Networks During Response Inhibition and Anterior Cingulate During Error-Related Processes

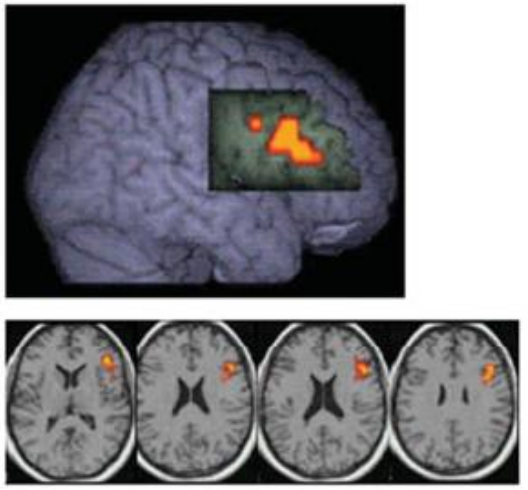
Katya Rubia,* Anna B. Smith, Eric Taylor, and Michael Brammer

Department of Child Psychiatry, Institute of Psychiatry, London SE5 8AF, United Kingdom

Human Brain Mapping 28:1163–1177 (2007)

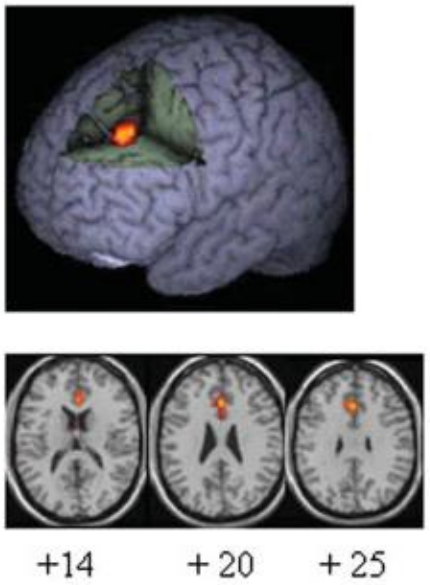
Brain regions of increased activation in adults compared to children/adolescents ($P < 0.01$) during (**a**): successful stop trials contrasted with unsuccessful stop trials. Shown is increased activation in right inferior prefrontal cortex (BA 47/45/44) in adults compared with children/adolescents in 3D and in the horizontal sections. (**b**) Unsuccessful stop trials contrasted with go-trials. Shown is increased activation in adults compared with children/adolescents in rostral anterior cingulate gyrus (BA 24) in 3D and in the horizontal sections. For the horizontal sections, the z-coordinate is indicated in distance (mm) from the anterior-posterior-commissure. The left side of the brain corresponds to the left side of the image. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

a) Successful – unsuccessful stop trials



+10 + 14 + 20 +25

b) Unsuccessful stop trials – go trials



+14 + 20 + 25

Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación

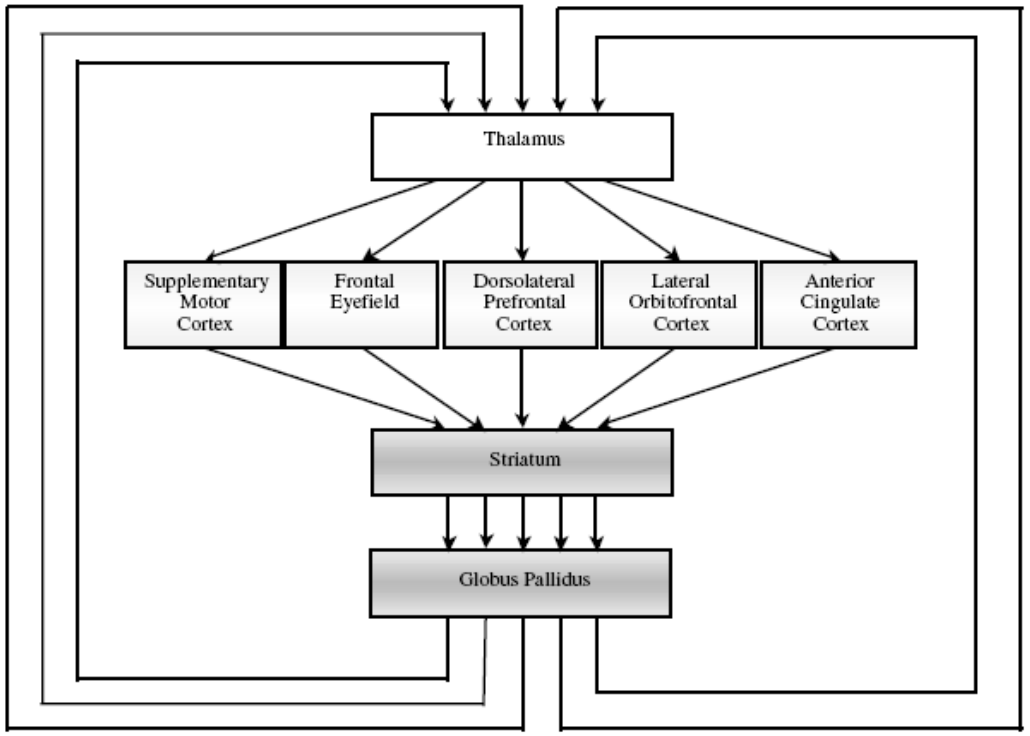


Fig. 1. Frontal-subcortical circuits between the PFC and basal ganglia (after Alexander et al., 1986).

Cortico-subcortical contributions to executive control

Katrin Heyder, Boris Suchan, Irene Daum *

Department of Neuropsychology, Faculty of Psychology, Institute of Cognitive Neuroscience, Ruhr-University of Bochum, 44780 Bochum, Germany

Acta Psychologica 115 (2004) 271–289

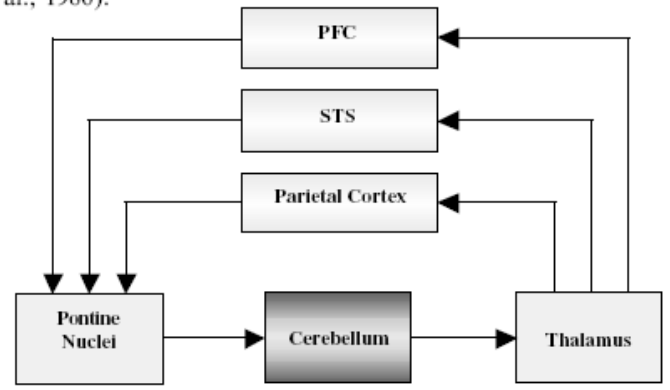


Fig. 2. Connections between the cerebellum and the neocortex (after Schmahmann, 1997). PFC = prefrontal cortex, STS = superior temporal sulcus.

Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación

Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

JAMA, October 9, 2002—Vol 288, No. 14

F. Xavier Castellanos, MD
Patti P. Lee, MD
Wendy Sharp, MSW
Neal O. Jeffries, PhD
Deanna K. Greenstein, PhD
Liv S. Clasen, PhD
Jonathan D. Blumenthal, MA
Regina S. James, MD
Christen L. Ebens, BA
James M. Walter, MA
Alex Zijdenbos, PhD
Alan C. Evans, PhD
Jay N. Giedd, MD
Judith L. Rapoport, MD

Objective To compare regional brain volumes at initial scan and their change over time in medicated and previously unmedicated male and female patients with ADHD and healthy controls.

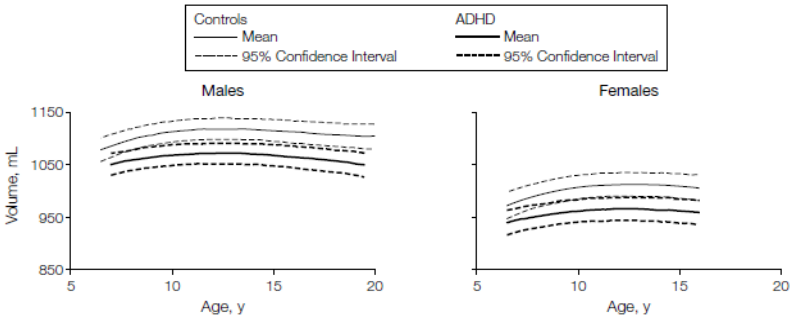
Design, Setting, and Participants Case-control study conducted from 1991-2001 at the National Institute of Mental Health, Bethesda, Md, of 152 children and adolescents with ADHD (age range, 5-18 years) and 139 age- and sex-matched controls (age range, 4.5-19 years) recruited from the local community, who contributed 544 anatomic magnetic resonance images.

Main Outcome Measures Using completely automated methods, initial volumes and prospective age-related changes of total cerebrum, cerebellum, gray and white matter for the 4 major lobes, and caudate nucleus of the brain were compared in patients and controls.

Results On initial scan, patients with ADHD had significantly smaller brain volumes in all regions, even after adjustment for significant covariates. This global difference was reflected in smaller total cerebral volumes (–3.2%, adjusted $F_{1,280}$=8.30, P=.004) and in significantly smaller cerebellar volumes (–3.5%, adjusted $F_{1,280}$=12.29, P=.001). Compared with controls, previously unmedicated children with ADHD demonstrated significantly smaller total cerebral volumes (overall $F_{2,288}$=6.65; all pairwise comparisons Bonferroni corrected, –5.8%; P=.002) and cerebellar volumes (–6.2%, $F_{2,288}$=8.97, P<.001). Unmedicated children with ADHD also exhibited strikingly smaller total white matter volumes ($F_{2,288}$=11.65) compared with controls (–10.7%, P<.001) and with medicated children with ADHD (–8.9%, P<.001). Volumetric abnormalities persisted with age in total and regional cerebral measures (P=.002) and in the cerebellum (P=.003). Caudate nucleus volumes were initially abnormal for patients with ADHD (P=.05), but diagnostic differences disappeared as caudate volumes decreased for patients and controls during adolescence. Results were comparable for male and female patients on all measures. Frontal and temporal gray matter, caudate, and cerebellar volumes correlated significantly with parent- and clinician-rated severity measures within the ADHD sample (Pearson coefficients between –0.16 and –0.26; all P values were <.05).

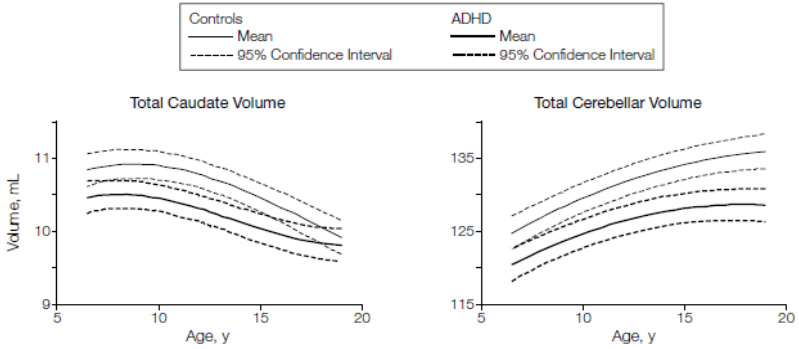
Conclusions Developmental trajectories for all structures, except caudate, remain roughly parallel for patients and controls during childhood and adolescence, suggesting that genetic and/or early environmental influences on brain development in ADHD are fixed, nonprogressive, and unrelated to stimulant treatment.

Figure 1. Predicted Unadjusted Longitudinal Growth Curves for Total Cerebral Volumes for Patients With ADHD and Controls



ADHD indicates attention-deficit/hyperactivity disorder. Curvature cubic, quadratic, and linear coefficients did not differ significantly between male and female patients, and sex did not interact significantly with diagnosis. Although all data were used in analyses, graphs of developmental curves are restricted to the central 90% of each sample's age distribution because fitted polynomial curves may be heavily influenced by outliers at the age range extremes.

Figure 2. Predicted Unadjusted Longitudinal Growth Curves for Total Caudate and Cerebellar Volume for Patients With ADHD vs Controls



ADHD indicates attention-deficit/hyperactivity disorder. Data beyond 16 years are for male patients only, because data from female patients did not exist beyond 16 years (effects ascribable to sex were assumed to be the same between ages 16-19 years as for ages 5-16 years, warranted as a single value to select the differences in intercepts [curve heights] for any case).

Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación

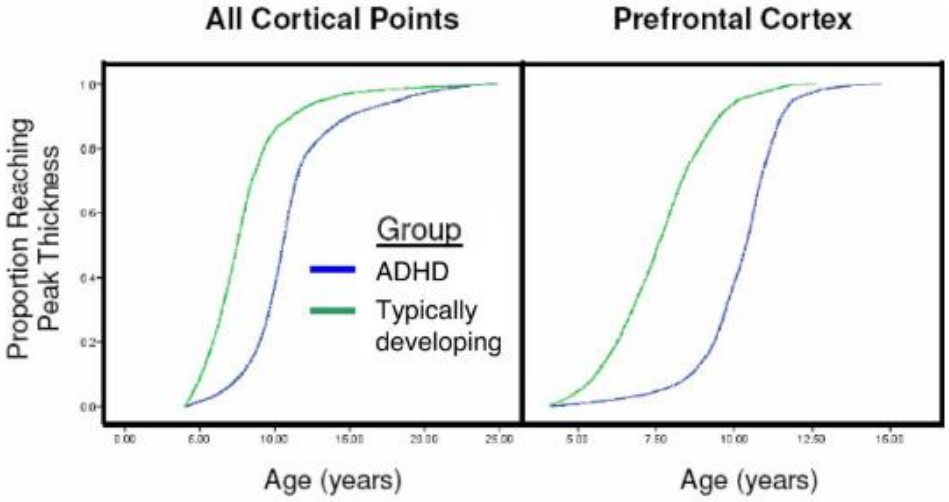
Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation

P. Shaw[†‡], K. Eckstrand[†], W. Sharp[†], J. Blumenthal[†], J. P. Lerch[§], D. Greenstein[†], L. Clasen[†], A. Evans[§], J. Giedd[†], and J. L. Rapoport[†]

[†]Child Psychiatry Branch, National Institute of Mental Health, Room 3N202, Building 10, Center Drive, Bethesda, MD 20892; and [§]Montreal Neurological Institute, McGill University, Montreal, QC, Canada H3A 2T5

Edited by Leslie G. Ungerleider, National Institutes of Health, Bethesda, MD, and approved October 5, 2007 (received for review August 17, 2007)

Fig. 3. Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (*Left*) and the prefrontal cortex (*Right*). The median age by which 50% of cortical points had attained their peak differed significantly between the groups (all $P < 1.0 \times 10^{-20}$)



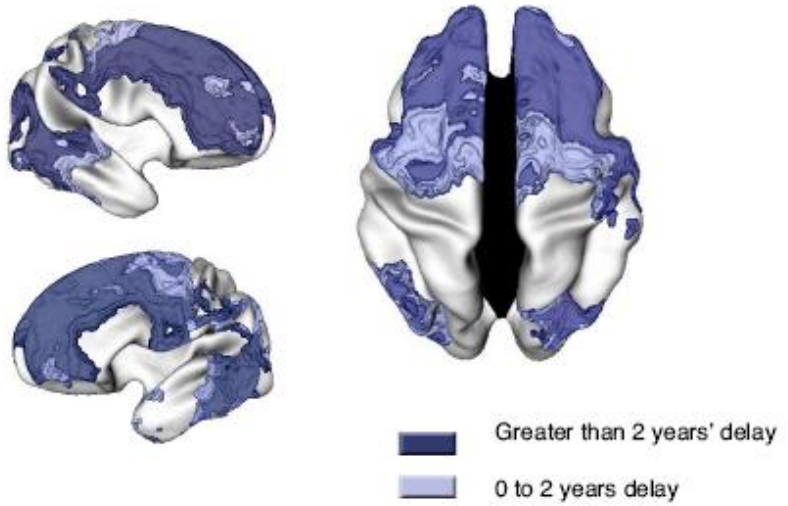


Fig. 2. Regions where the ADHD group had delayed cortical maturation, as indicated by an older age of attaining peak cortical thickness.

Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación

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NeuroImage 39 (2008) 527–537

Competition between functional brain networks mediates behavioral variability

A.M. Clare Kelly,[a] Lucina Q. Uddin,[a] Bharat B. Biswal,[b]
F. Xavier Castellanos,[a] and Michael P. Milham[a,*]

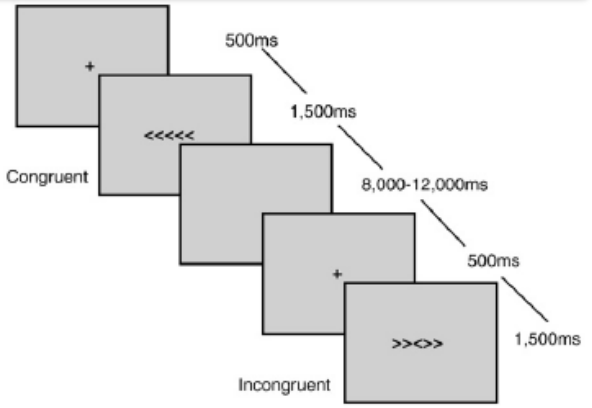


Fig. 1. The Eriksen flanker task and trial timing. The subjects' task is to identify the direction of the central arrow, ignoring the direction of the four flanking arrows.

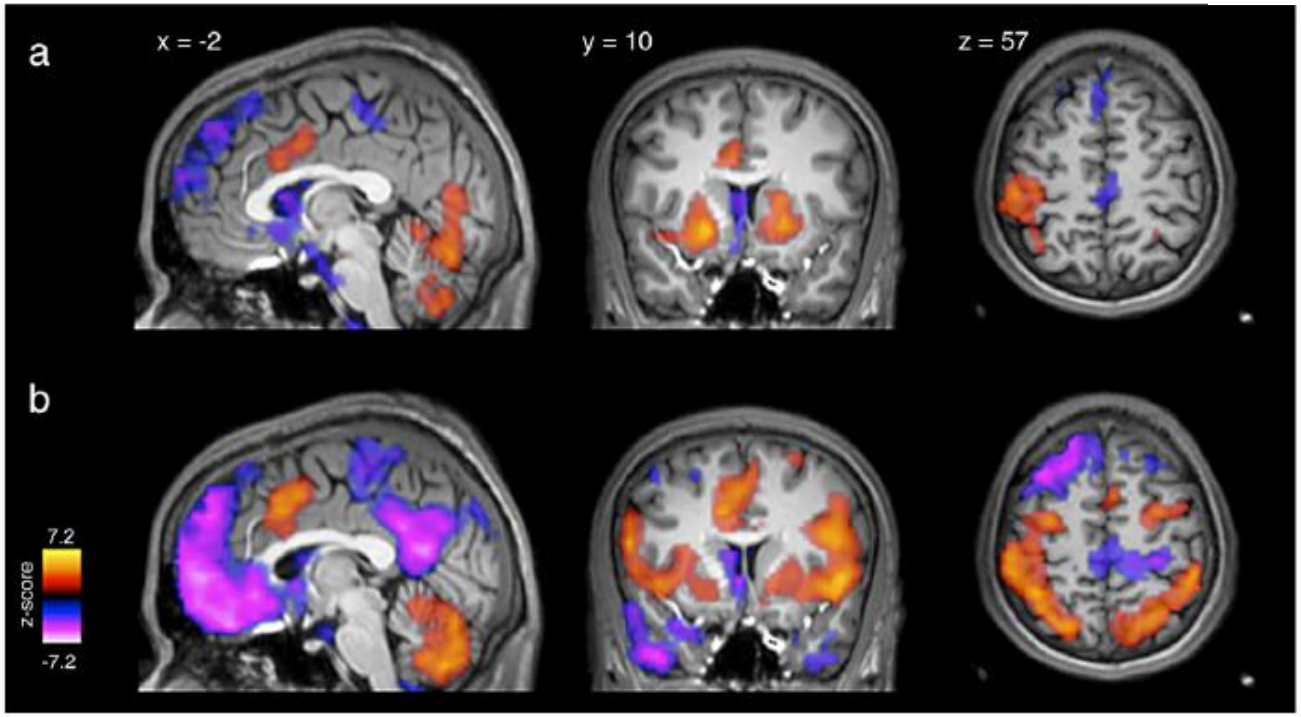


Fig. 2. Z-score thresholded maps (neurological convention) of activation (yellow–red) and deactivation (blue–white) related to the congruent (a) and incongruent (b) trials of the flanker task.

Bases Neurobiológicas del TDAH: Control Conductual/Autoregulación

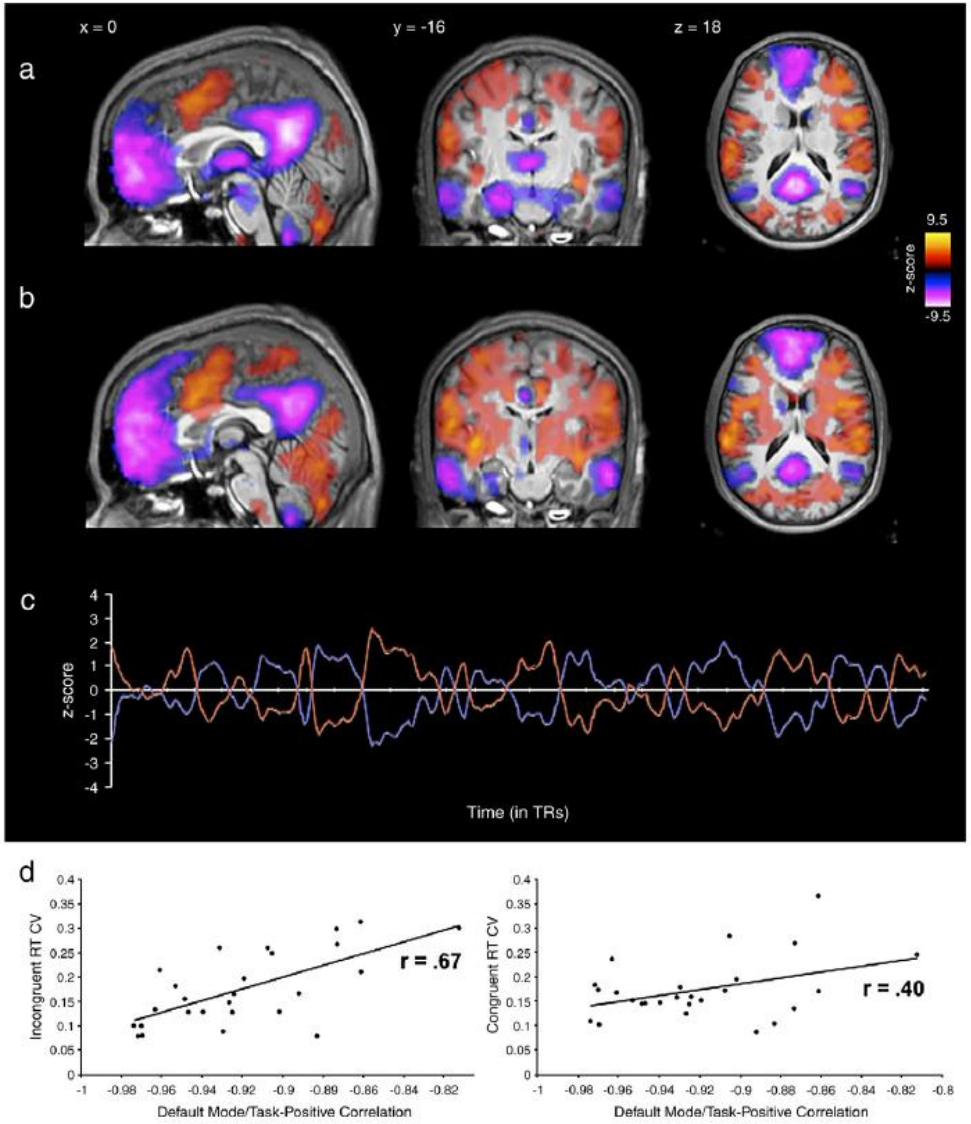
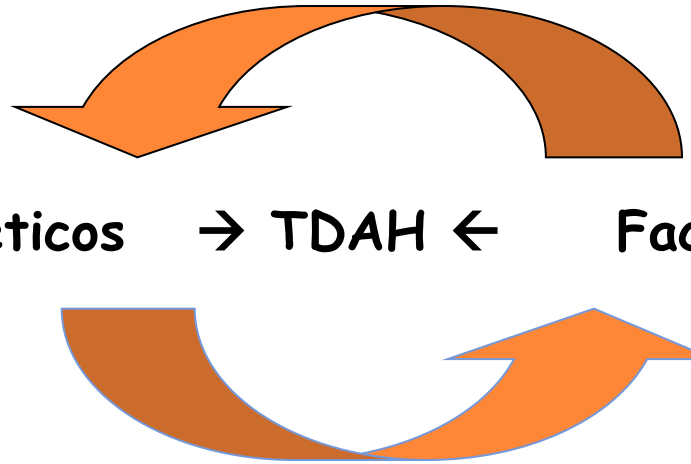


Fig. 3. (a) Primary 5-seed GLM analysis z-score thresholded maps (neurological convention) of the default mode (blue–white) and task-positive (yellow–red) networks ($p<0.05$, corrected); (b) confirmatory ICA z-score thresholded maps of the default mode (blue–white) and task-positive (yellow–red) networks ($p<0.05$, corrected); (c) default mode and task-positive antiphase timeseries for one subject with near perfect negative correlation ($r=-0.97$); (d) the stronger the negative correlation between spontaneous activity in the default mode network and the task-positive attentional network, the more consistent the behavioral performance, as measured by RT coefficient of variation (RT CV) on incongruent and congruent trials.

Bases Neurobiológicas del TDAH: Etiología



Factores genéticos → TDAH ← Factores ambientales

Múltiples genes candidatos

- Tabaquismo materno durante el embarazo.
- Stress materno en el embarazo.
- Lesión cerebral traumática.
- Lesión vascular cerebral (>si compromete estriado).
- Daño cerebral perinatal (>si compromete estriado).
- Deprivación temprana severa.
- Adversidad familiar psicosocial.

Bases Neurobiológicas del TDAH: Etiología

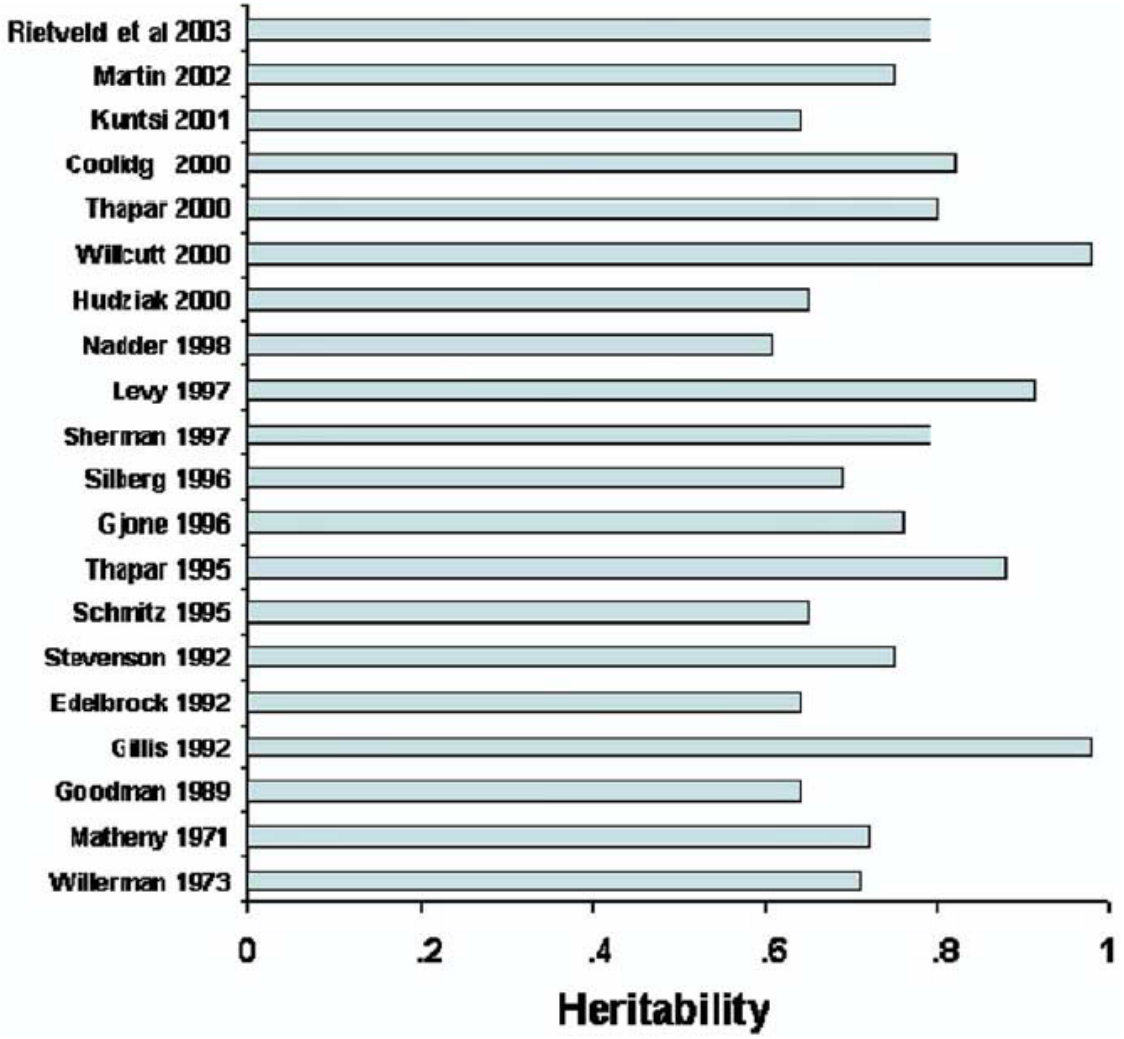


Figure 1. Estimated heritability of attention-deficit/hyperactivity disorder, based on pooled results from 20 twin studies.

Heredabilidad Promedio 76%

S.V. Faraone et al

BIOL PSYCHIATRY 2005;57:1313–1323

Bases Neurobiológicas del TDAH: Genes candidatos

Gene	Published negative associations	Published positive associations
Catecholamines		
COMT	7	1
Catecholamines: dopamine		
DAT1 (SLC6A3)	9	17
DRD1		2
DRD2	2	1
DRD3	1	
DRD4	10	21
DRD5	3	2
DBH	3	4
TH	1	
DARPP-32	1	
NR4A2		1
Catecholamines: norepinephrine		
NET1 (SLC6A2)	3	2
ADRA2A	1	5
ADRA2C	1	
ADRB2		1
PNMT		1
Other monoamines		
MAOA	3	5
MAOB	2	1
Other monoamines: serotonin		
5-HTT (SLC6A4)	5	4
5HTB1	1	2
5HTR2A	3	3
5HTR2B	1	
HTR4		1
TPH	1	1
TPH2	1	3
DDC	1	1
Other neurotransmitter systems: acetylcholine		
CHRNA4		1
CHRNA7	1	
Other genes		
SNAP25	1	4
BDNF	2	2
GDNF	2	
NGF	1	
NT3	1	
GRIN2A		1
FGF10	1	
ISL1	1	
HCN1	1	
ITGA1	1	
HLA-DRB1	1	
SLC1A3	1	1
CLOCK		1
ARRB2		1
SYP		1
HES1		1
FADS2		1
IL-1		1
AR		1
LIN-7		1

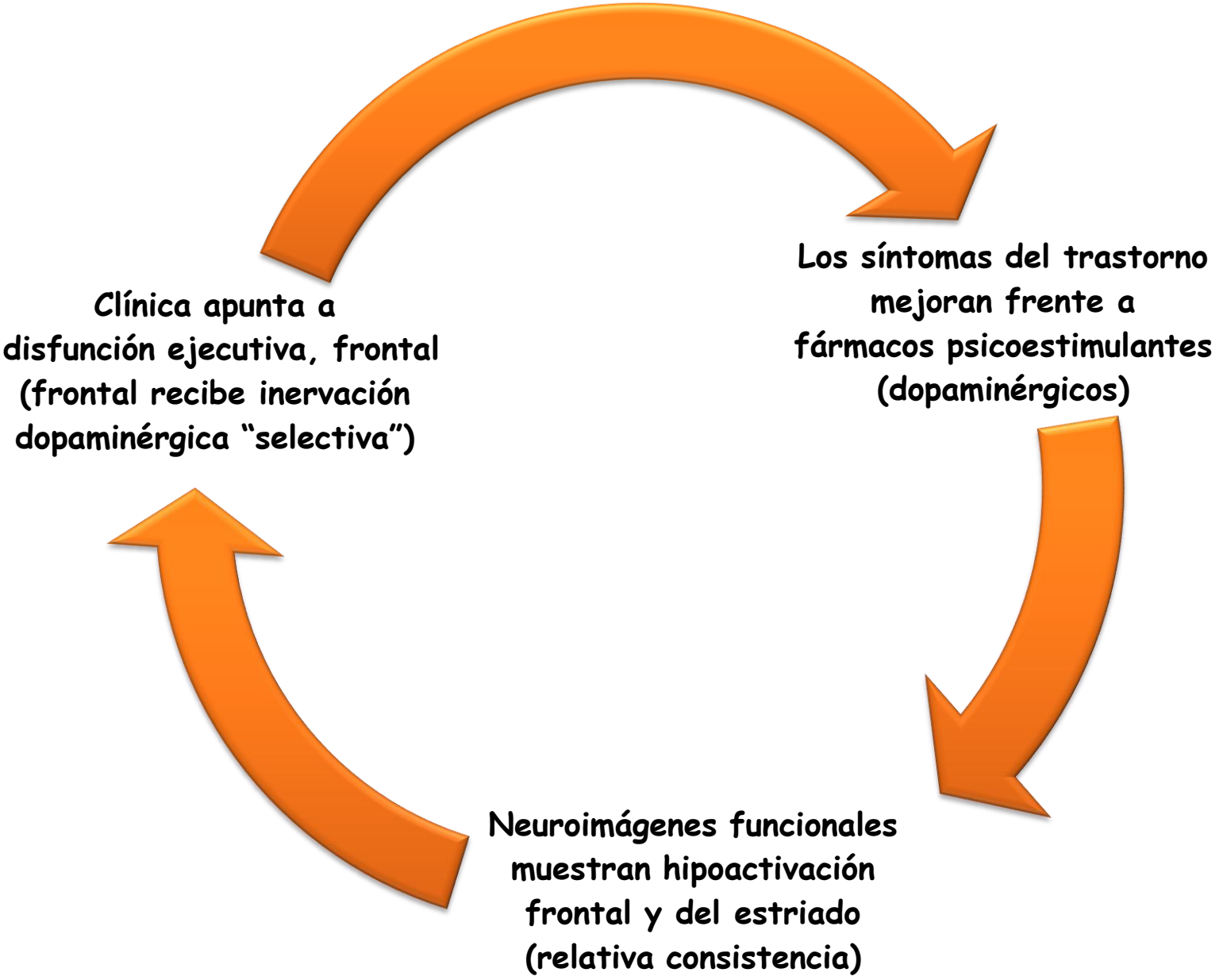
Expression in the brain of genes associated with ADHD in at least two studies

Candidate gene (locus)	Expression in mouse	Expression in human	Additional expression or protein localization
Catecholamines: dopamine			
SLC6A3/DAT1 (5p15)	Midbrain	Whole brain moderate expression	Striatum (Garris and Wightman, 1994). Midbrain (Brookes et al., 2007; Giros et al., 1992; Shimada et al., 1992). Temporal lobe, cerebellum (Mill et al., 2002). Prefrontal cortex (Garris and Wightman, 1994). Amygdala (Garris and Wightman, 1994)
DRD1 (5q35)	High expression in striatum, amygdala, olfactory areas, hippocampus	Whole brain high expression, particularly caudate nucleus and prefrontal cortex	Striatum (Augood et al., 2000; Hurd et al., 2001). Frontal cortex (Hurd et al., 2001)
DRD4 (11p15)	Whole brain, enriched in ventral striatum, retro hippocampal region, olfactory areas, amygdala	Moderate expression in prefrontal, parietal and temporal lobes, cingulate cortex, cerebellum, basal ganglia	Prefrontal cortex (De La Garza and Madras, 2000; Noaín et al., 2006; Primus et al., 1997). Hippocampus (De La Garza and Madras, 2000; Primus et al., 1997). Hypothalamus, thalamus, entorhinal cortex, lateral septal nucleus (Mrzljak et al., 1996; Primus et al., 1997). Globus pallidus (Mrzljak et al., 1996)
DRD5 (4p16)	Whole brain high expression and receptor density	Whole brain moderate expression	Cerebellum, substantia nigra, hypothalamus, striatum, cerebral cortex, nucleus accumbens, hippocampus and olfactory tubercle (Beischlag et al., 1995; Khan et al., 2000)
DBH (9q34)	Medulla, pons	Whole brain moderate expression	Noradrenergic brain stem nuclei, sympathetic ganglion neurons (Hoyle et al., 1994) and hypothalamus, substantia nigra (Westlund et al., 1988)
Catecholamines: norepinephrine			
SLC6A2/NET1 (16q12)	Very low expression and receptor density in the brain	Whole brain moderate expression	Locus coeruleus (Eymin et al., 1995). Amygdala (Smith and Porrino, 2008)
ADRA2A (10q25)	Very low expression and receptor density in the brain	Moderate expression whole brain.	Cerebellum (Schambra et al., 2005)
Other monoamines			
MAOA (Xp11)	Moderate expression in pallidum	Moderate expression whole brain. High expression in thalamus, amygdala, occipital lobe and prefrontal cortex	Hypothalamus, nucleus coeruleus, substantia nigra (Westlund et al., 1988)
Serotonin			
SLC6A4, 5-HTT (17q11)	Limited expression and density in striatum and amygdala, pons, medulla, midbrain	Moderate whole brain expression	Midbrain, pons (Lim et al., 2006). Amygdala (O'Rourke and Fudge, 2006)
5HT1B (6q14)	High expression in striatum and cerebellum	Moderate expression in whole brain. High expression in prefrontal cortex and amygdala	NI raphe (Bidmon et al., 2001). Substantia nigra, globus pallidus, striatum, amygdala, hippocampus, and the cerebral cortex (Varnäs et al., 2001)
5HTR2A (13q14)	Very low expression and receptor density in the brain	High expression in the whole brain, particularly the prefrontal cortex	Prefrontal cortex (De Almeida and Mengod, 2007; Hall et al., 2000)
TPH2 (12q21)	Very low expression and receptor density in the brain	Whole brain moderate expression. High expression in cingulate cortex and globus pallidus	Raphe nuclei (Zill et al., 2007). Pons (Lim et al., 2007)
Other			
SNAP25 (20p11.2)	Whole brain high expression and receptor density	Whole brain high expression	Whole brain high expression (Garbelli et al., 2008)

The frontal lobes include prefrontal and orbitofrontal cortex. The basal ganglia include putamen, caudate nucleus, nucleus accumbens, globus pallidus, subthalamic nucleus and substantia nigra. The diencephalon includes thalamus, hypothalamus , subthalamus and pretectum. The Midbrain includes internal structures such as the raphe nuclei, the red nucleus and the reticular formation (including the locus coeruleus).

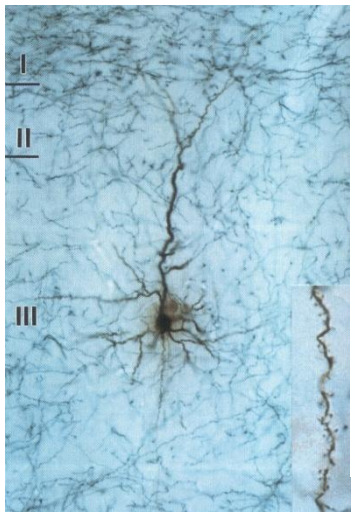
S. Durston et al. / Neuroscience and Biobehavioral Reviews 33 (2009) 674–689

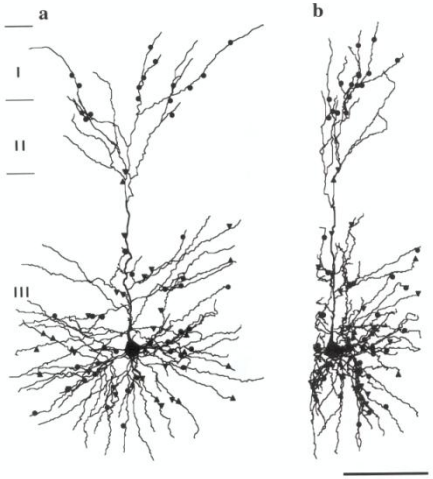
Bases Neurobiológicas del TDAH: Teoría dopaminérgica

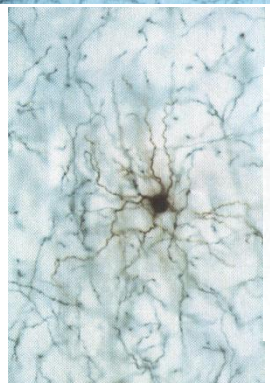


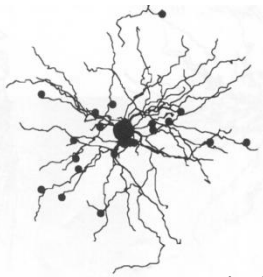
Bases Neurobiológicas del TDAH: Teoría dopaminérgica

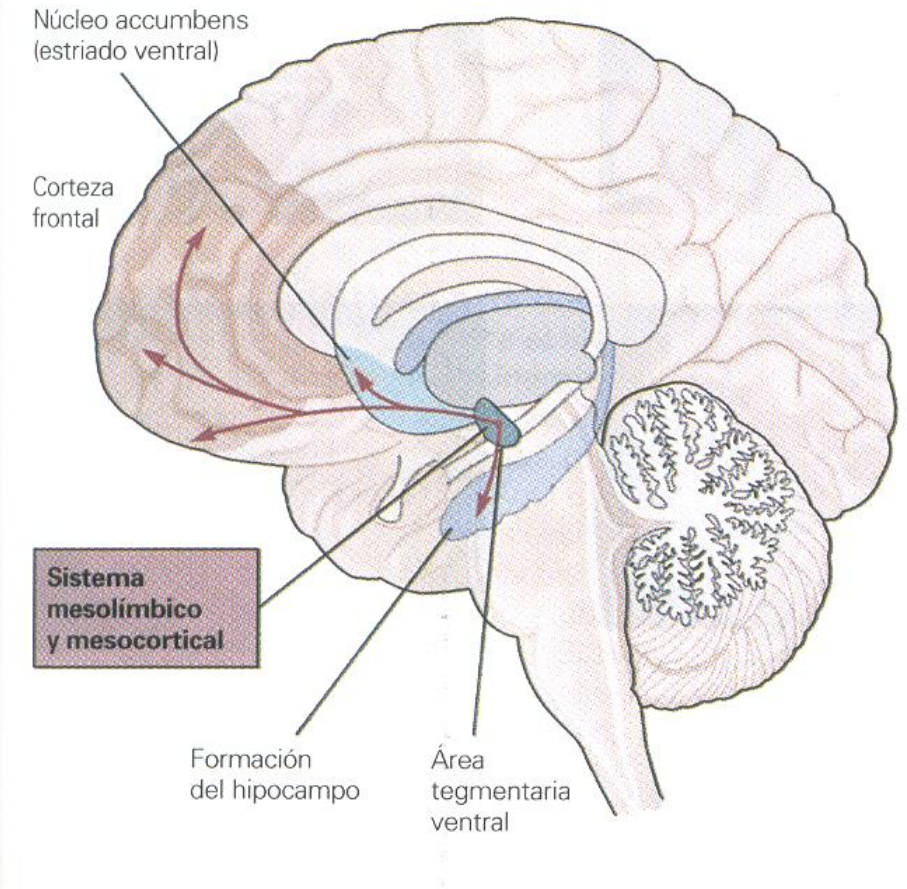
"Los axones dopaminérgicos forman un impresionante plexo en PFC de primates y humanos".











Krimer, L., Jakab, R. & Goldman-Rakic, P. The Journal of Neuroscience, 1997, 17(19): 7450-61.

Rol del sistema meso-cortical y meso-límbico dopaminérgico:

Modulación del input excitatorio a las neuronas de la PFC (piramidales principalmente)

Bases Neurobiológicas del TDAH: Teoría dopaminérgica

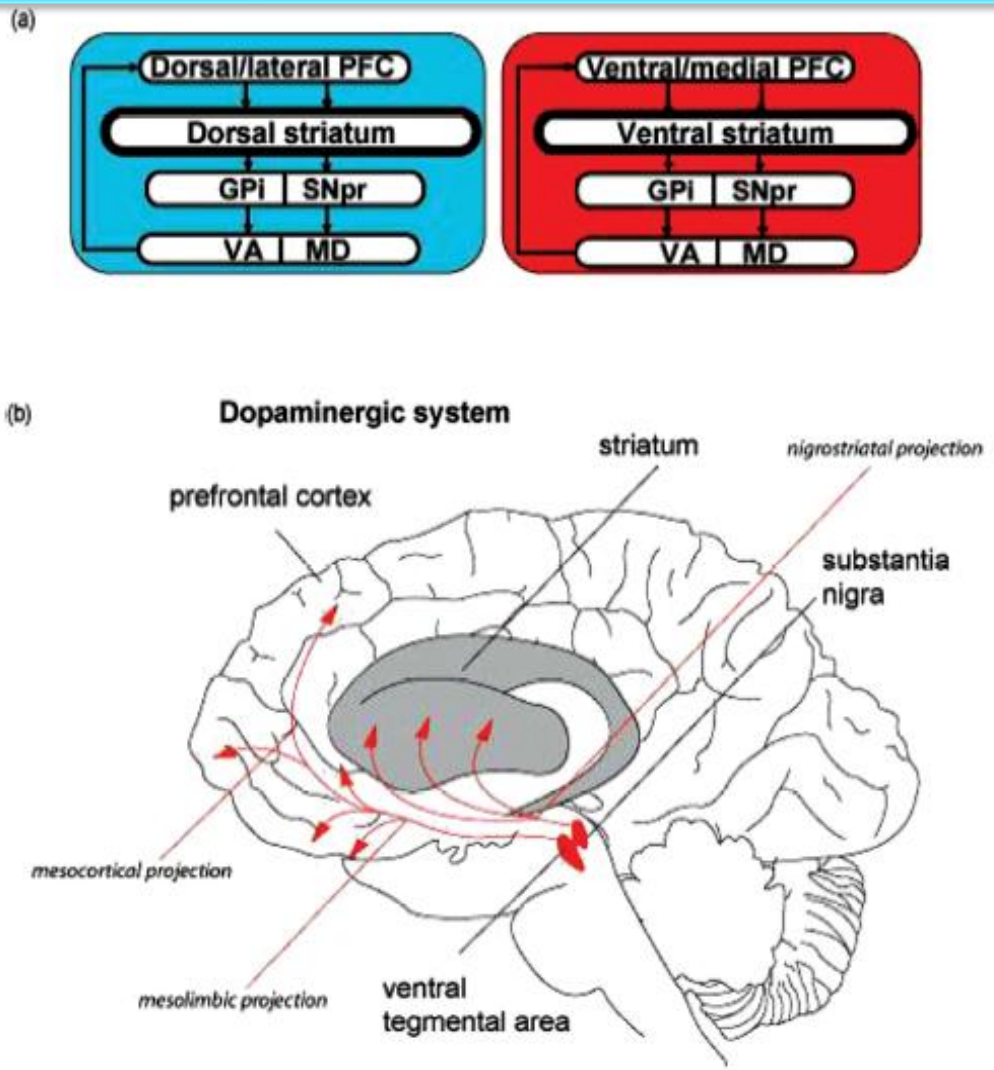


Fig. 1. (*a*) Functionally distinct dorsal and ventral frontostriatal circuits. (*b*) Major dopamine projections.

Role of Dopamine in the Motivational and Cognitive Control of Behavior
Roshan Cools
Neuroscientist 2008; 14; 381

Bases Neurobiológicas del TDAH: Teoría dopaminérgica

Sagvolden et al.: A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD)

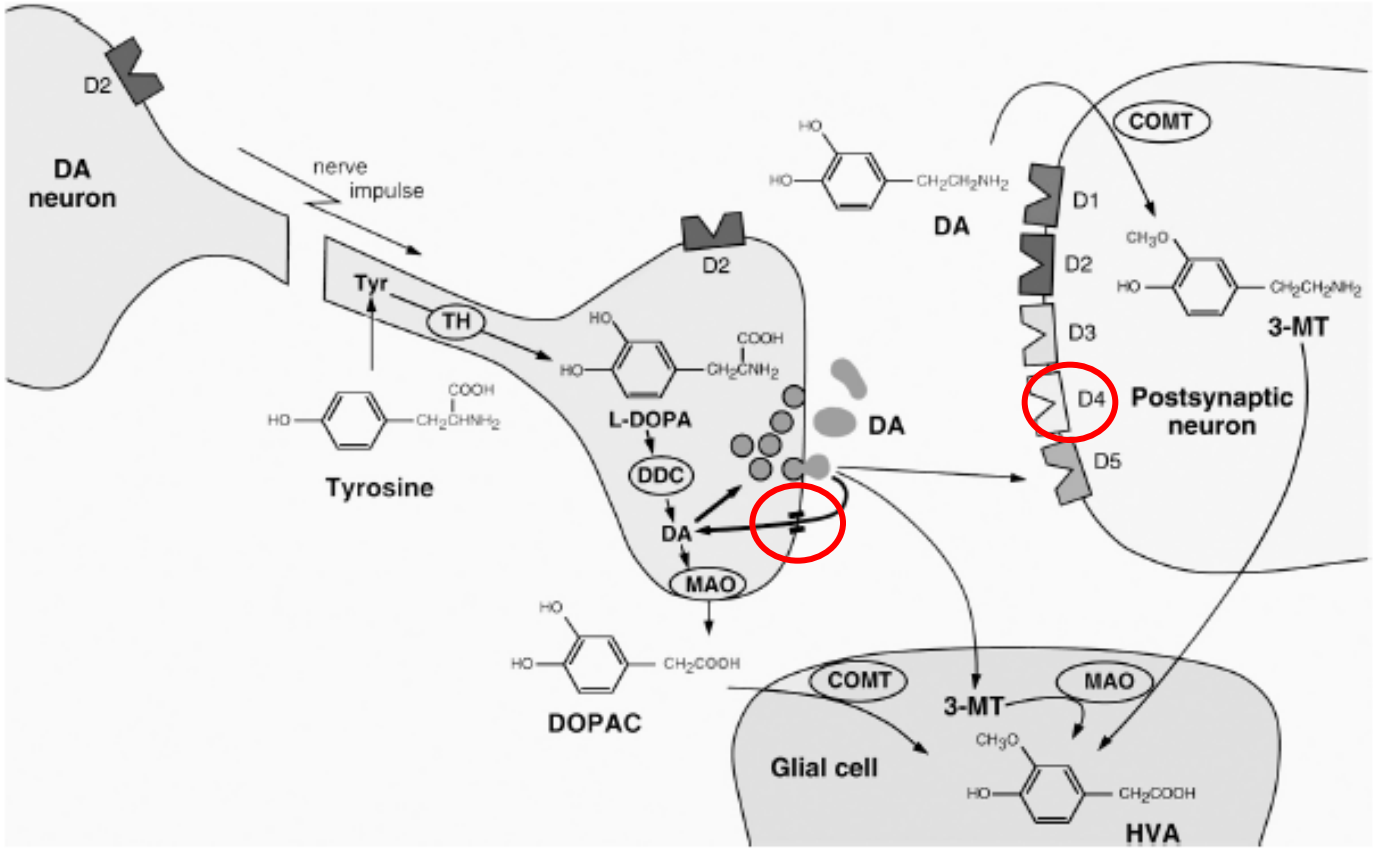
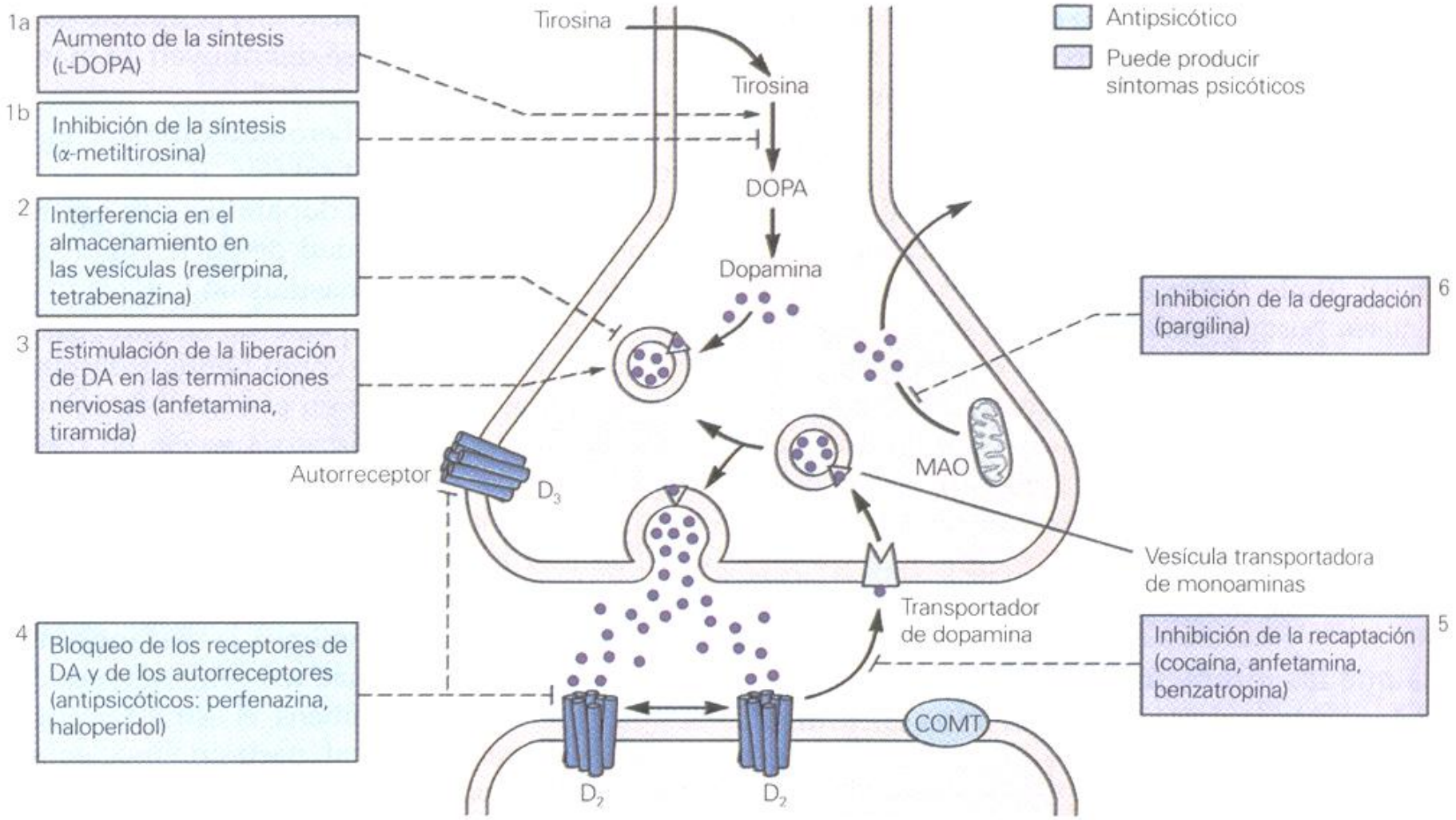


Figure 3. Neurons and glial cell showing dopamine synthesis, metabolism, and typical positions of dopamine receptors. Note that D1/5 and D2/3/4 receptors are not generally colocalized on the same neuron as they have opposite effects. Abbreviations: 3MT = 3-methoxy-tyramine, COMT = catechol-O-methyl transferase, D1–D5 = dopamine receptors 1 through 5, DA = dopamine, DDC = DOPA decar-boxylase, HVA = homovanillic acid, MAO = monoamine oxidase, TH = tyrosine hydroxylase, Tyr = tyrosine. (Modified after Waters 1995.)

Bases Neurobiológicas del TDAH: Teoría dopaminérgica



Bases Neurobiológicas del TDAH: Teoría dopaminérgica

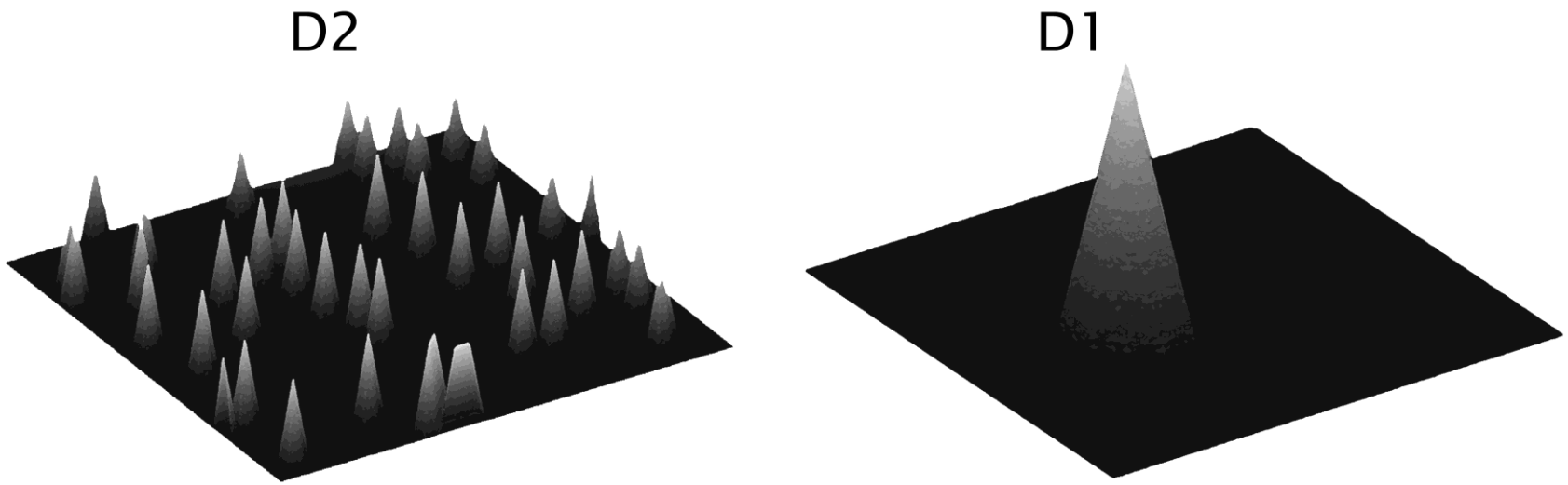
Progress in Neurobiology 74 (2004) 1–57

www.elsevier.c

The principal features and mechanisms of dopamine modulation in the prefrontal cortex

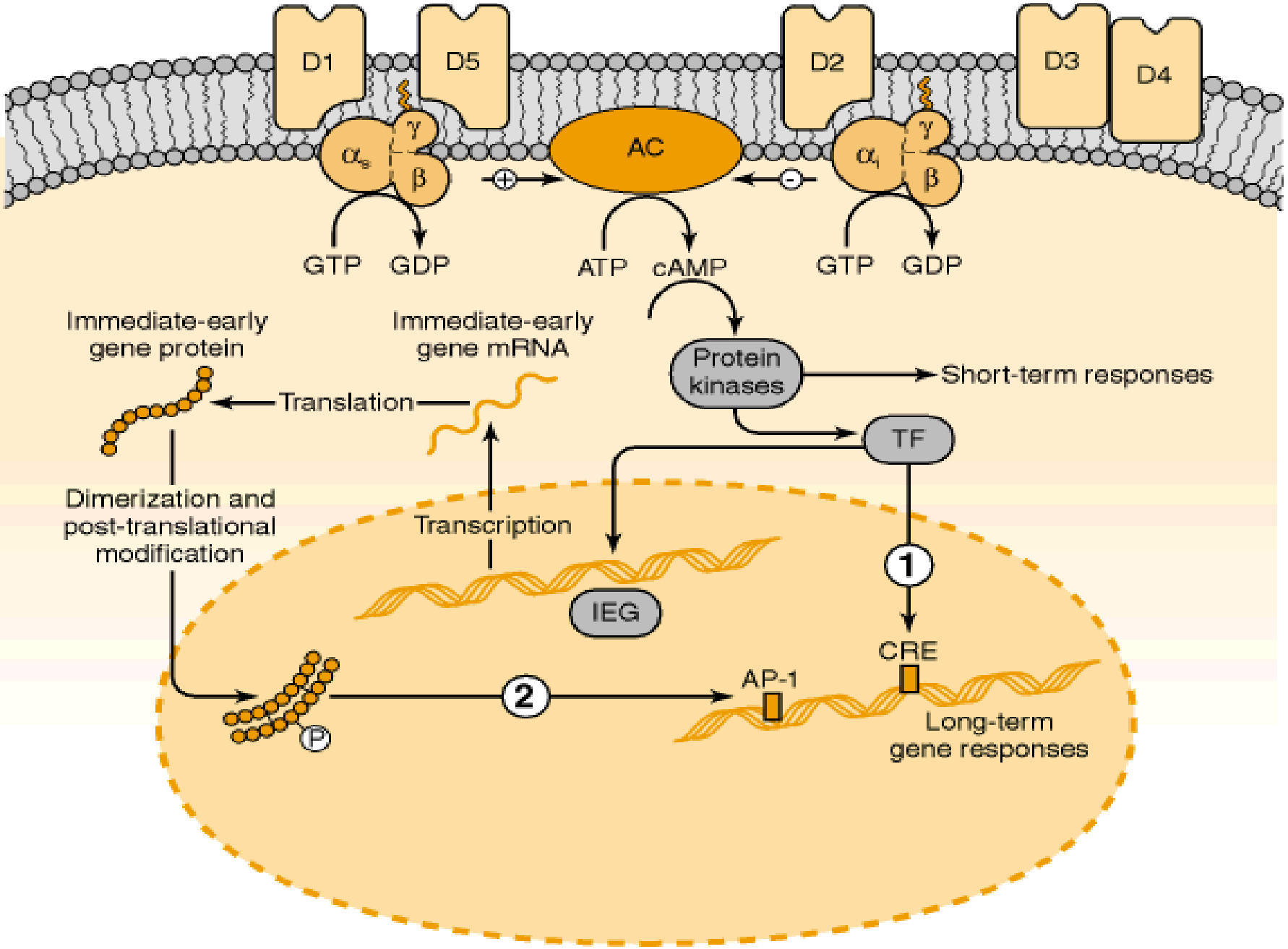
Jeremy K. Seamans[a,*], Charles R. Yang[b,1]

[a]*Department of Physiology, MUSC, 173 Ashley Avenue, Suite 403, Charleston, SC 29425, USA*
[b]*Neuroscience Discovery, Lilly Corporate Center, Indianapolis, IN 46285-0510, USA*



Cortical landscapes of activity under the influences of D2 receptor activity (tonic DA liberation) and D1-receptor activity (phasic DA liberation). The D2-state promotes the activation of multiple representations, while the D1-state produces a generalized inhibition, and allows the activation of very few networks (de Seamans and Yang, 2004; Aboitiz, 2009).

Bases Neurobiológicas del TDAH: Teoría dopaminérgica

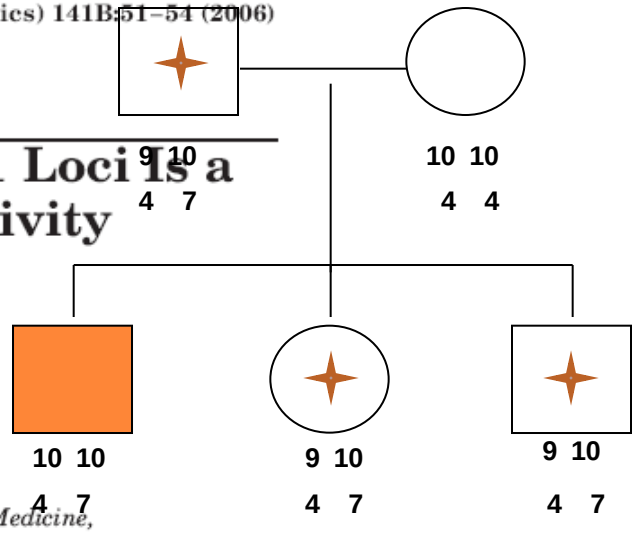


American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 141B:51–54 (2006)

Genotypic Interaction Between DRD4 and DAT1 Loci Is a High Risk Factor for Attention-Deficit/Hyperactivity Disorder in Chilean Families

Ximena Carrasco,[1] Paula Rothhammer,[2,3] Mauricio Moraga,[2] Hugo Henríquez,[2] Ranajit Chakraborty,[4] Francisco Aboitiz,[3] and Francisco Rothhammer[2,5]*

[1]*Hospital Calvo Mackenna, Santiago, Chile*
[2]*Programa de Genética Humana, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile*
[3]*Departamento de Psiquiatría y Centro de Investigaciones Médicas, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*
[4]*Center for Genome Information, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio*
[5]*CIHDE Universidad de Tarapacá, Arica, Chile*



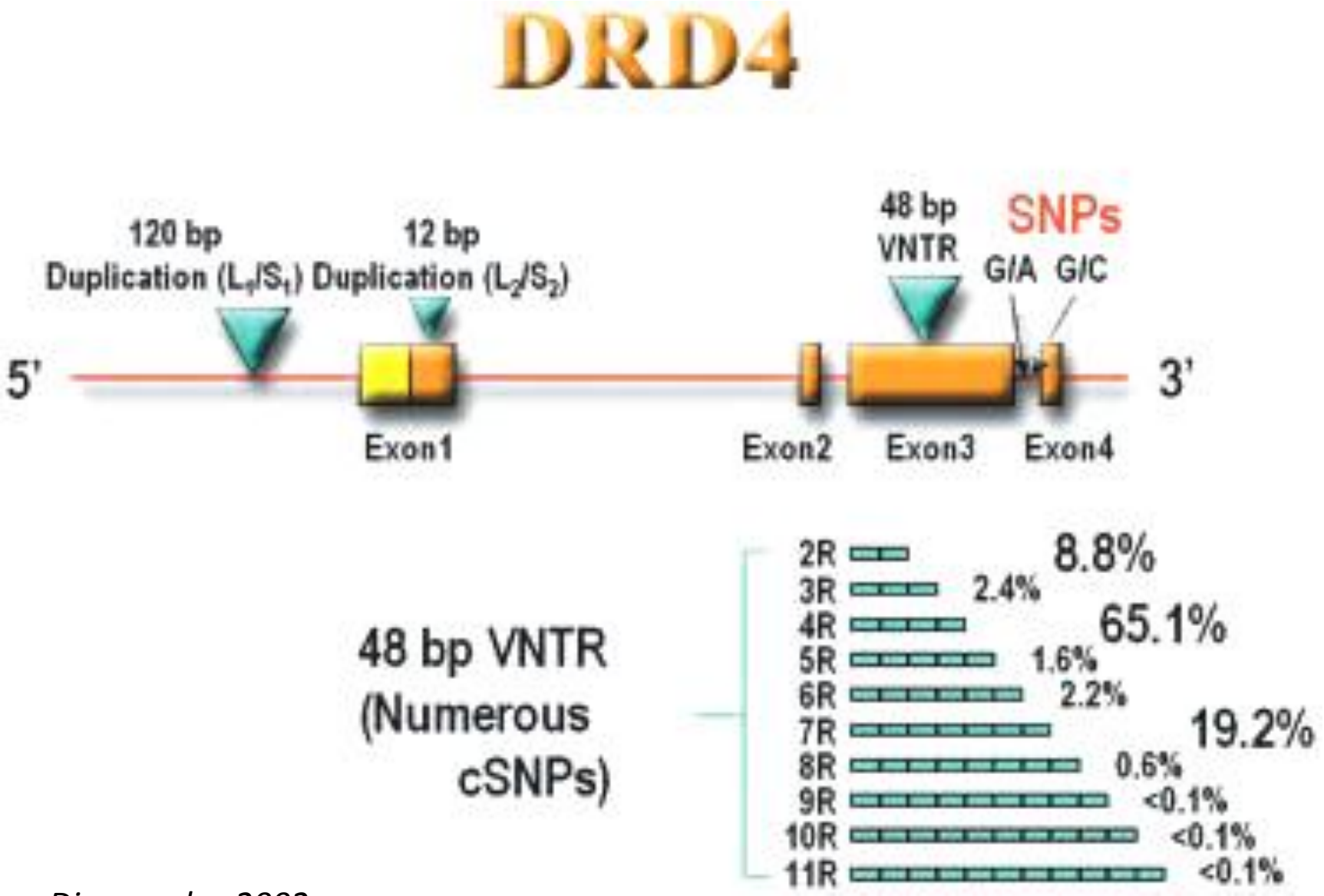
Attention-deficit/hyperactivity disorder, ADHD [MIM 126452], is a common, highly heritable neurobiological disorder of childhood onset, characterized by hyperactivity, impulsiveness, and/or inattentiveness. As part of an ongoing study of ADHD, we carried out a family-based discordant sib-pair analysis to detect possible associations between dopamine receptor D4 (DRD4) and dopamine transporter 1 (DAT1) polymorphisms and ADHD in Chilean families. Both loci individually classified as homozygotes or heterozygotes for the DRD4 7-repeat and DAT1 10-repeat alleles, did not exhibit genotype frequency differences between affected children and their healthy siblings (Fisher's exact test $P > 0.25$ in both cases). However, the simultaneous presence of both DRD4 7-repeat heterozygosity and DAT1 10 allele homozygosity were significantly higher (34.6%) in cases (26), compared with their unaffected siblings (25) (4%; Fisher's exact test $P = 0.0096$; odds-ratio, OR = 12.71). Increased density of dopamine transporter in ADHD brains, along with abundance of 7-repeat D4 receptors in prefrontal cortex, which is impaired in ADHD patients, make the observed gene–gene interaction worthy of further incisive studies.

TABLE I. DRD4 and DAT1 Genotype Frequencies in Cases and Controls

Genotypes		Frequency in		
DRD4[a]	DAT1[b]	Cases	Controls	Total
+/−	+/+	9	1	10
	+/−	1	6	7
−/−	+/+	7	10	17
	+/−	9	8	17
Total		26	25	51

[a]+/− denotes heterozygotes for the DRD4 7-repeat allele and −/− are genotypes not carrying the 7-repeat allele; no individual was homozygous for the 7-repeat allele in cases or controls.
[b]+/+ denotes homozygosity for the 10-repeat allele at the DAT1 locus and +/− for individuals with one copy of the 10-repeat allele; all individuals in the sample of cases and controls carried at least one 10-repeat allele in their genotypes.

Bases Neurobiológicas del TDAH: Gen DRD4



Ding y cols., 2002.

Bases Neurobiológicas del TDAH: Gen DRD4

DRD4:

11p15.5

25 alelos; 18 variantes aminoacídicas, la mayoría por VNTRs de 48 pb en el exón 3 (16 aa), con diferentes haplotipos. 7R se asocia a ADHD.

Exón 3 codifica loop citiplasmático de unión a proteína Gi.

DRD4-7R, menor afinidad.

Localización en neuronas GABAérgicas de PFC, N Acc, vermis cerebeloso ventral.

Am. J. Hum. Genet. 74:931–944, 2004

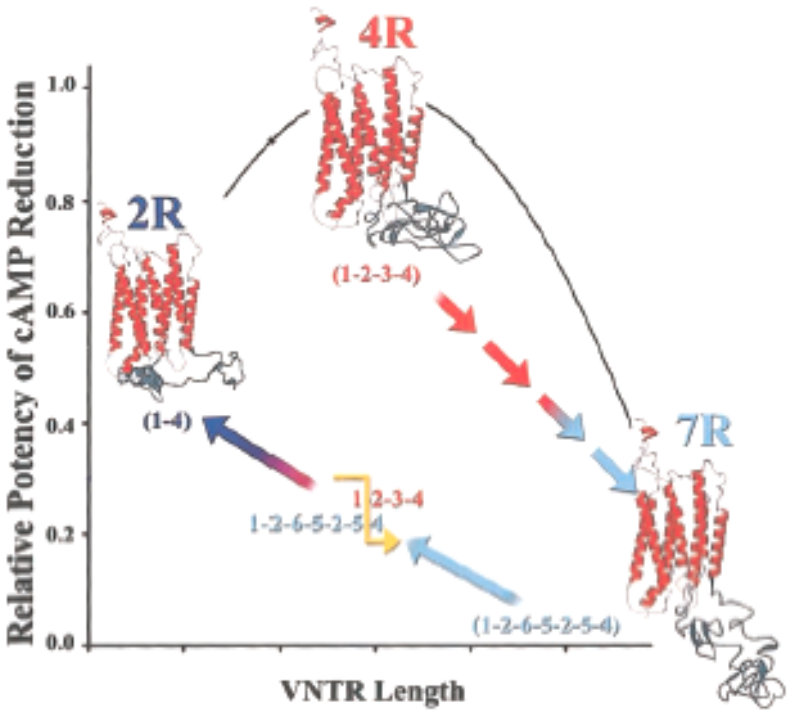
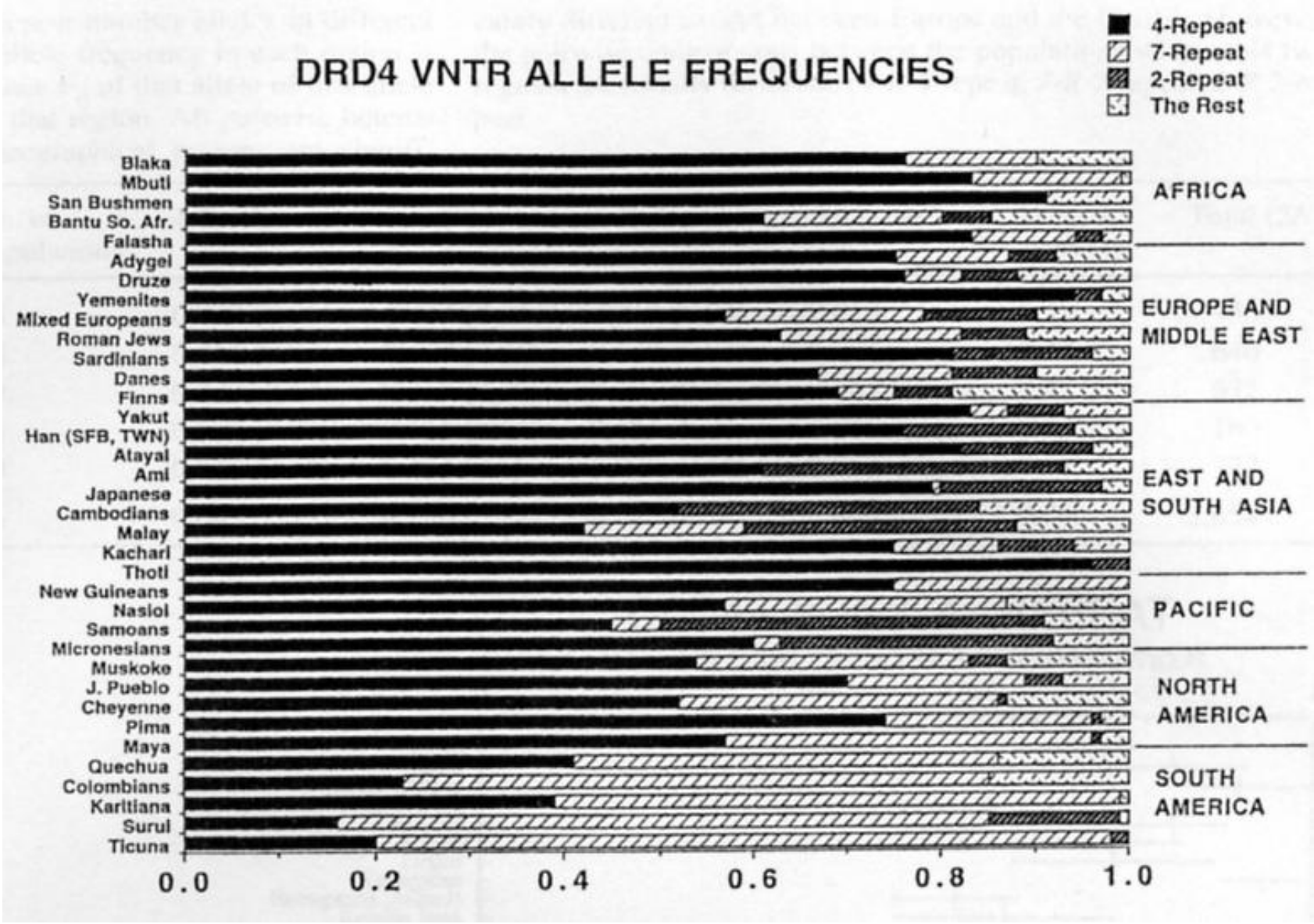


Figure 3 A diagrammatic model for *DRD4* variant selection. DRD4 2R, 4R, and 7R protein variants are shown diagrammatically, aligned on a scale of relative efficiency for cAMP reduction. These values were calculated from the data of Asghari et al. (1995), normalized to 4*R* = 1.0. Haplotype nomenclature (i.e., 1-2-3-4) appears as proposed elsewhere (Ding et al. 2002). The unusual derivation of the 7R allele from the ancestral 4R allele (~40,000–50,000 years ago) and its increase in prevalence are indicated by red to turquoise arrows. The subsequent derivation of the 2R allele from a 7R/4R recombination is indicated by turquoise to blue arrows.

Bases Neurobiológicas del TDAH: Gen DRD4



F-M Chang et al. Hum. Genet. 1996; 98: 91-101.

Población de Santiago 27% *(Vieyra y cols. 2003)*

Riesgo de déficit atencional/hiperactividad en escolares Aymara, Rapa-Nui y de Santiago de Chile. Posible contribución de polimorfismos genéticos del sistema dopaminérgico

LIZA PAZ LAGOS[1,a], CLAUDIO SILVA[2], PAULA ROTHHAMMER[4], XIMENA CARRASCO[5], ELENA LLOP[3], FRANCISCO ABOITIZ[4], FRANCISCO ROTHHAMMER[1,3]

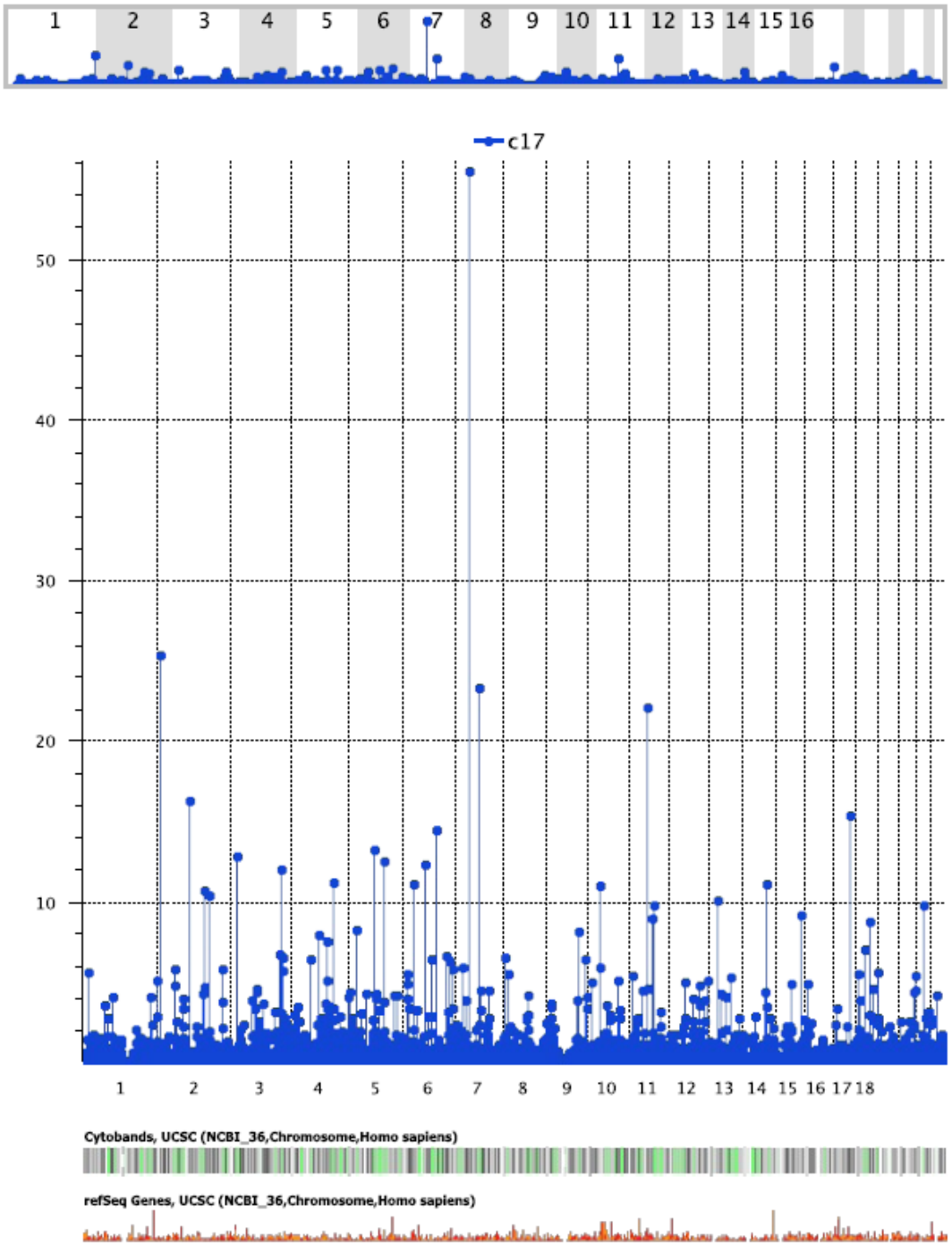
Tabla 3. Promedios y desviaciones estándar de los puntajes obtenidos en la escala de Conners según localidad y género

Población	Sexo	n	Hiperactividad	Déficit atencional	Problemas emocionales
Isla de Pascua	Femenino	249	1,76 ± 2,34	1,47 ± 1,79	0,87 ± 1,62
Isla de Pascua	Masculino	285	3,78 ± 3,08	2,61 ± 2,11	1,81 ± 2,37
Precordillera XV Región	Femenino	40	1,33 ± 1,98	1,35 ± 1,42	0,38 ± 0,84
Precordillera XV Región	Masculino	32	3,62 ± 2,83	2,41 ± 1,78	0,72 ± 1,28
Santiago	Femenino	197	1,41 ± 2,03	1,74 ± 1,80	0,73 + 1,48
Santiago	Masculino	172	2,63 ± 2,53	2,20 ± 1,76	0,76 ± 1,46

Tabla 4. Distribución de alelos de los sistemas genéticos dopaminérgicos DRD4 y DAT 1 en las localidades estudiadas

Población	n	DRD4.2	DRD4.3	DRD4.4	DRD4.5	DRD4.6	DRD4.7	DRD4.8	DRD4.9	DRD4.10
Isla de Pascua	64	0,25	0,11	0,53	0,02	0	0,10	0	0	0
Precordillera XV Región	83	0	0	0,57	0,13	0,03	0,27	0	0	0
Santiago	100	0,06	0,01	0,59	0,02	0,05	0,27	0,01	0,01	0

Población	n	DAT1.3	DAT1.5	DAT1.7	DAT1.8	DAT1.9	DAT1.10	DAT1.11	DAT1.12	DAT1.13
Isla de Pascua	64	0	0	0	0	0,12	0,87	0,01	0	0
Precordillera XV Región	83	0	0	0	0	0,05	0,95	0	0	0
Santiago	100	0	0	0	0,01	0,23	0,74	0,035	0	0



National Human Genome Research Institute

A Sequential Test Algorithm for DNA Pooling/Bootstrap-Based Studies

Jorge I. Vélez and Mauricio Arcos-Burgos

Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, US

Hierarchical Genetic Organization of Human Cortical Surface Area

Chi-Hua Chen,[1] E. D. Gutierrez,[2] Wes Thompson,[1] Matthew S. Panizzon,[1] Terry L. Jernigan,[1,2] Lisa T. Eyler,[1,3] Christine Fennema-Notestine,[1,4] Amy J. Jak,[1,5] Michael C. Neale,[6] Carol E. Franz,[1,7] Michael J. Lyons,[8] Michael D. Grant,[8] Bruce Fischl,[9] Larry J. Seidman,[10] Ming T. Tsuang,[1,5,6] William S. Kremen,[1,5,6]*† Anders M. Dale[1,4,11]*

Surface area of the cerebral cortex is a highly heritable trait, yet little is known about genetic influences on regional cortical differentiation in humans. Using a data-driven, fuzzy clustering technique with magnetic resonance imaging data from 406 twins, we parceled cortical surface area into genetic subdivisions, creating a human brain atlas based solely on genetically informative data. Boundaries of the genetic divisions corresponded largely to meaningful structural and functional regions; however, the divisions represented previously undescribed phenotypes different from conventional (non–genetically based) parcellation systems. The genetic organization of cortical area was hierarchical, modular, and predominantly bilaterally symmetric across hemispheres. We also found that the results were consistent with human-specific regions being subdivisions of previously described, genetically based lobar regionalization patterns.

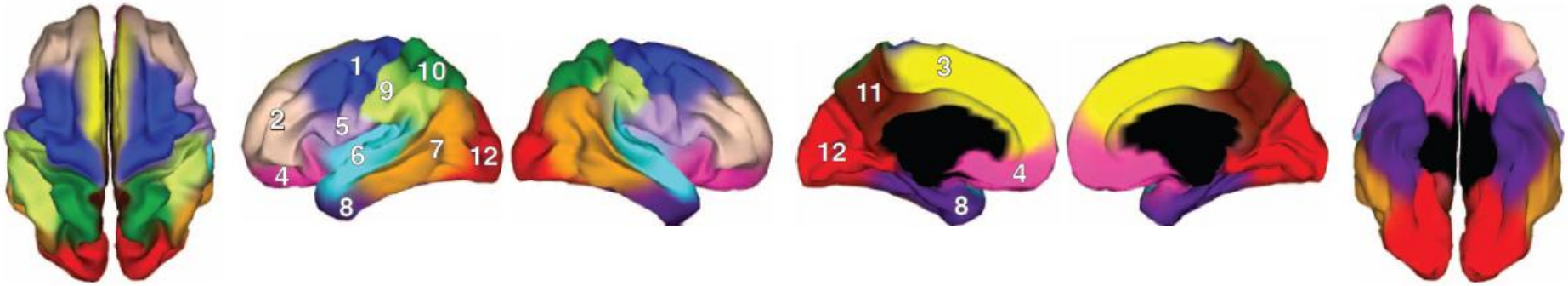


Fig. 1. Genetic clustering map for 12-cluster solution. 1, motor-premotor cortex; 2, dorsolateral prefrontal cortex; 3, dorsomedial frontal cortex; 4, orbitofrontal cortex; 5, pars opercularis and subcentral region; 6, superior temporal cortex; 7, posterolateral temporal cortex; 8, anteromedial temporal cortex; 9, inferior parietal cortex; 10, superior parietal cortex; 11, precuneus; and 12, occipital cortex. Views shown from left to right are, respectively, superior, left hemisphere lateral, right hemisphere lateral, left hemisphere medial, right hemisphere medial, and inferior.

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