Correlati cerebrali dell'ADHD: update e potenziali applicazioni cliniche

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Azienda Ospedaliera S. Andrea

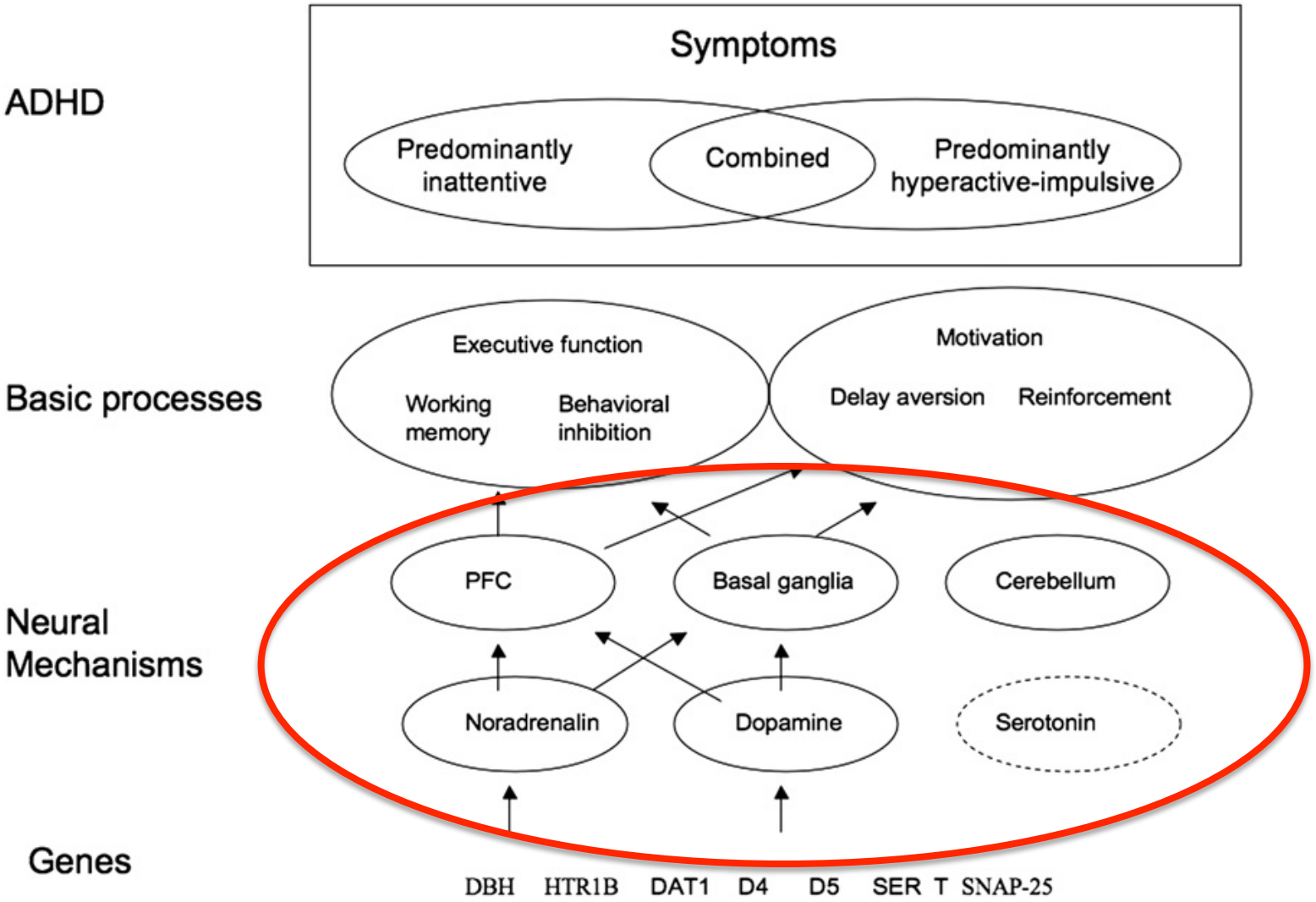

Fig. 1. Illustration of relation between levels of organization. See text for explanation.

Tripp & Wickens 2009

Variations in brain anatomy (structural MRI findings)

- Significant decrease in total cerebral and cerebellar volume compared with controls
- Brain abnormalities vs controls observed in frontostriatal areas, temporoparietal lobes, basal ganglia, corpus callosum, cerebellum, amygdala, hippocampus and thalamus
- Other morphological alterations, such as cortical thinning
- Alterations in structural connectivity (DTI findings)
- Aberrant cortical development and/or delayed normal cortical maturation

Variations in brain functioning (fMRI findings)

- Significant hypoactivation in networks related to executive functions, cognition, emotion, sensorimotor functions and compensatory hyperactivations in alternate regions
- Altered/perturbed pattern of functional connectivity, particularly in the default-mode network, vs controls

Cortese 2012

Neurophysiological features

- Increased theta, and decreased beta, frequencies in EEG recordings vs controls (elevated theta/beta power ratios)
- Less pronounced responses and longer latencies of event-related potentials, particularly P300, vs controls

Neurochemical factors

- Involvement of dopaminergic and adrenergic systems
  - Decreased availability of DA receptor isoforms and increased DAT binding vs controls
  - Current ADHD drug therapies block DA and NE reuptake and/or promote their release
- Serotonergic and cholinergic systems may also be involved

Genetic and environmental factors

- Heritability of ADHD: ~60–75%
- Involvement in ADHD of genes coding for isoforms of the DA receptor, DA beta-hydroxylase, synaptosomal-associated protein 25, the serotonin transporter and the serotonin 1B receptor
- Pre-, peri- and post-natal environmental factors account for ~20–25% of the aetiology of ADHD
  - Most reliable associations with low birth weight/prematurity and exposure to maternal smoking *in utero*
- Likely contribution to ADHD aetiology of G × E interactions (epigenetic changes in gene expression caused by specific environmental factors)

Cortese 2012

Variations in brain anatomy (structural MRI findings)

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Cortese 2012

Biomarkers

TABLE 1 Summary of Significant Standard Mean Difference Meta-analyses Findings

Source	Biomarkers Symbol	d	*p*	Significant after Bonferroni correction?	Significant Heterogeneity?	Publication Bias?	Associated with Drug Response?	Associated with Symptoms Severity?	Associated with Neurophysiological/ Cognitive functioning?
Urine	NE	0.41	.003	Yes	No	No	Yes: ↓	Yes	No
Urine	MHPG	−0.43	.002	Yes	Yes	No	Yes: ↓	Yes	No
Platelet	MAO	−1.05	<.0001	Yes	Yes	No	Yes: ↑	Yes	No
Urine	NM	0.51	.05	No	Yes	No	No	No	No
Urine	M	0.45	.009	No	No	No	No	No	No
Serum	ferritin (iron stores)	−0.86	.01	No	Yes	No	No	Yes	Yes
Serum/plasma/urine	Zn	−0.88	.0003	Yes	Yes	No	No	Yes	Yes
Saliva	Cortisol	−0.31	.0001	Yes	No	No	Yes: ↑	Yes	No

Note: MAO = Monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylethylene glycol; M = Metanephrine; NE = Norepinephrine; NM = Normetanephrine; Zn = Zinc.

Scassellati et al. 2012

Kynurenines

	ADHD (n =102)	Controls (n=62)	p	FDR
Tryptophan (ng/ml)	8914.9 ± 1776.3	8038.6 ± 2219.6	0.01*	0.025
Kynurenic acid (ng/ml)	3.2 ± 0.9	3.6 ±1.4	0.03*	0.031
Xanthurenic acid (ng/ml)	1.4 ± 0.5	1.6 ± 0.6	0.04*	0.037
Anthranilic acid (ng/ml)	9.6 ± 7.3	24.0 ± 8.9	<0.001*	0.006
3-Hydroxyanthranilic acid (ng/ml)	4.57 ± 3.01	3.62 ± 2.02	0.15	0.050
Kynurenine (ng/ml)	440.3 ± 158.6	296.0 ± 148.7	<0.001*	0.012
Quinolinic acid(ng/ml)	33.8 ± 10.1	31.3 ± 8.6	0.10	0.044
Kynurenine/Tryptophan Ratio	0.05 ± 0.02	0.04 ± 0.02	<0.001*	0.019

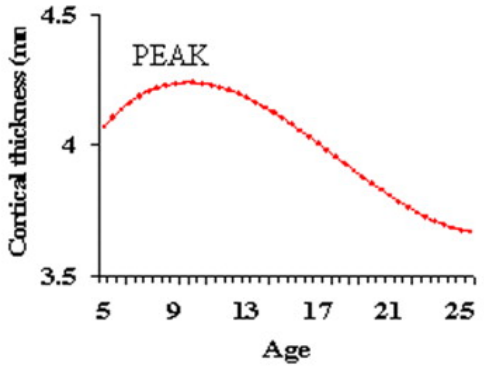
Data are expressed as mean ± standard deviation.
* Student's t-Test.
Abbreviations: Attention Deficit Hyperactivity Disorder (ADHD).
FDR: *p* value from Benjamini- Hochberg method control for false discovery rate (FDR).

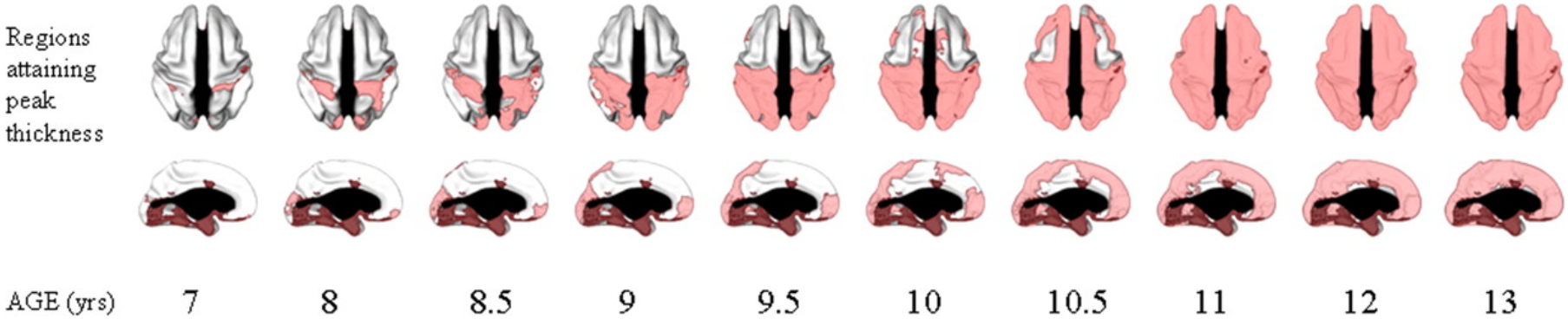
	ADHD Comorbidity (n =53)	ADHD No comorbidity (n=49)	p
Tryptophan (ng/ml)	9131.8 ± 2067.5	8680.4 ± 1350.9	0.2
Kynurenic acid (ng/ml)	3.1 ± 0.9	3.2 ±0.8	0.3
Xanthurenic acid (ng/ml)	1.4± 0.5	1.3 ± 0.4	0.6
Anthranilic acid (ng/ml)	9.3±7.3	9.8 ± 7.3	0.7
3-Hydroxyanthranilic acid (ng/ml)	4.06 ±2.5	4.34 ± 2.6	0.6
Kynurenine (ng/ml)	445.7±139.8	434.4 ±178.05	0.7
Quinolinic acid (ng/ml)	33.2± 9.7	34.3± 10.6	0.6
Kynurenine/Tryptophan Ratio	0.05± 0.02	0.05± 0.02	0.9

Data are expressed as mean ± standard deviation.
* Student's t-Test.
Abbreviations: Attention Deficit Hyperactivity Disorder (ADHD)

Evangelisti M, De Rossi P et al. 2017

Neurosviluppo corticale





Shaw et al. 2008

Childhood Psychiatric Disorders as Anomalies in Neurodevelopmental Trajectories

Philip Shaw,* Nitin Gogtay, and Judith Rapoport

Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland

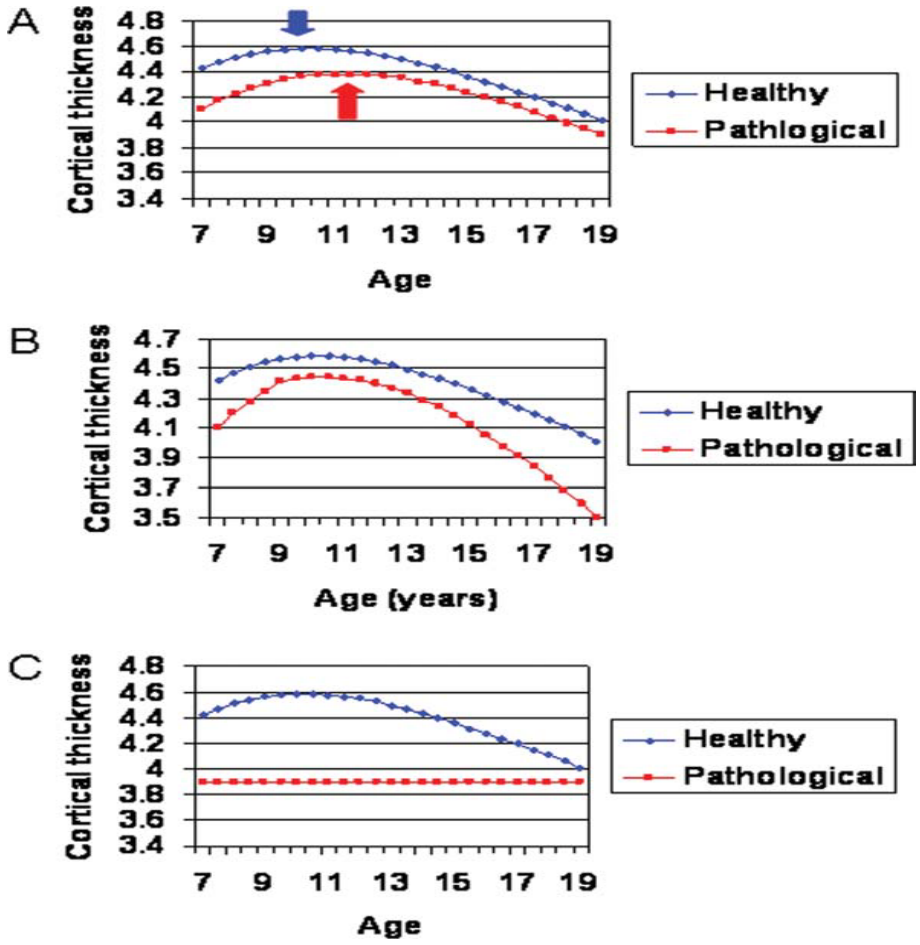
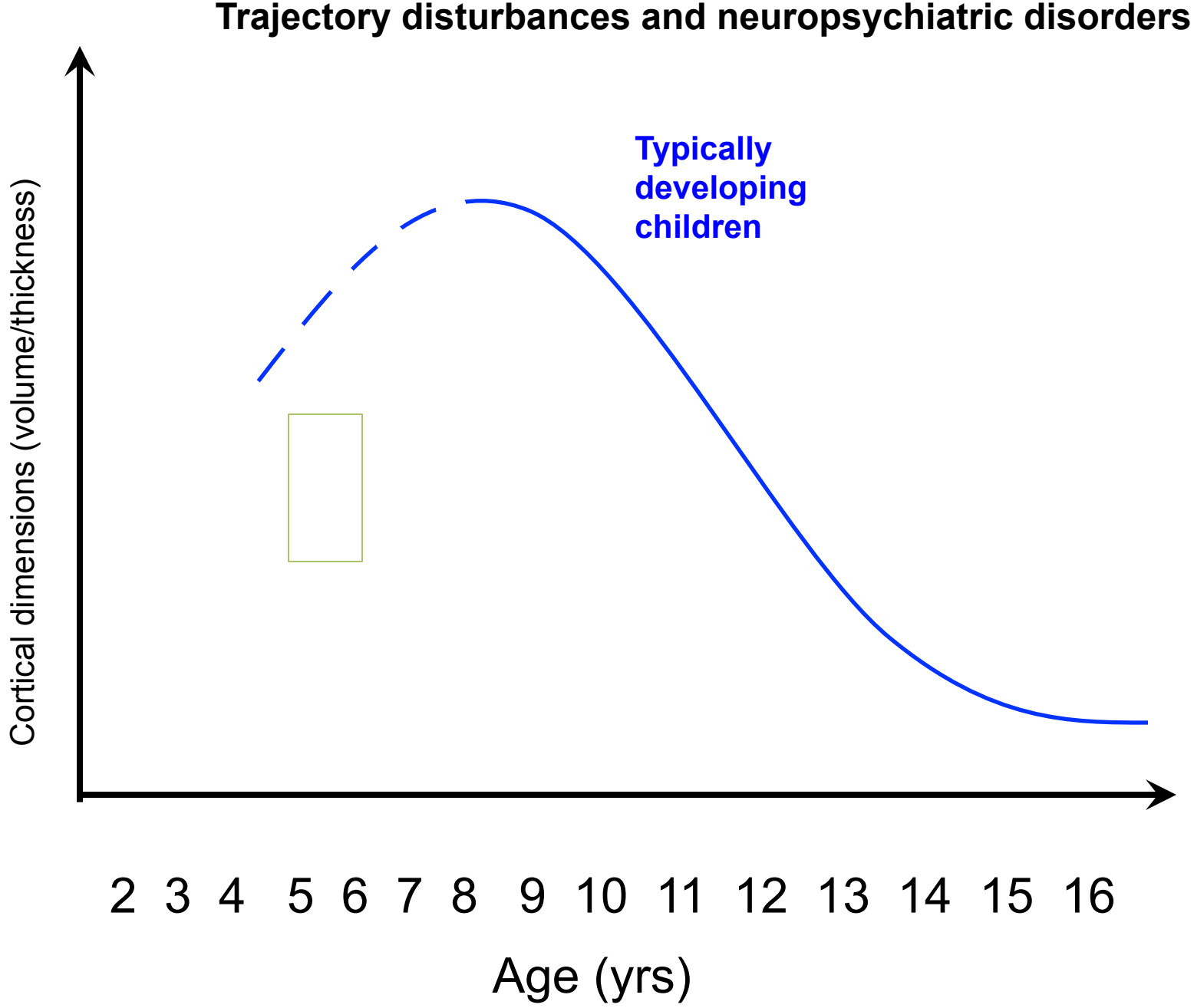
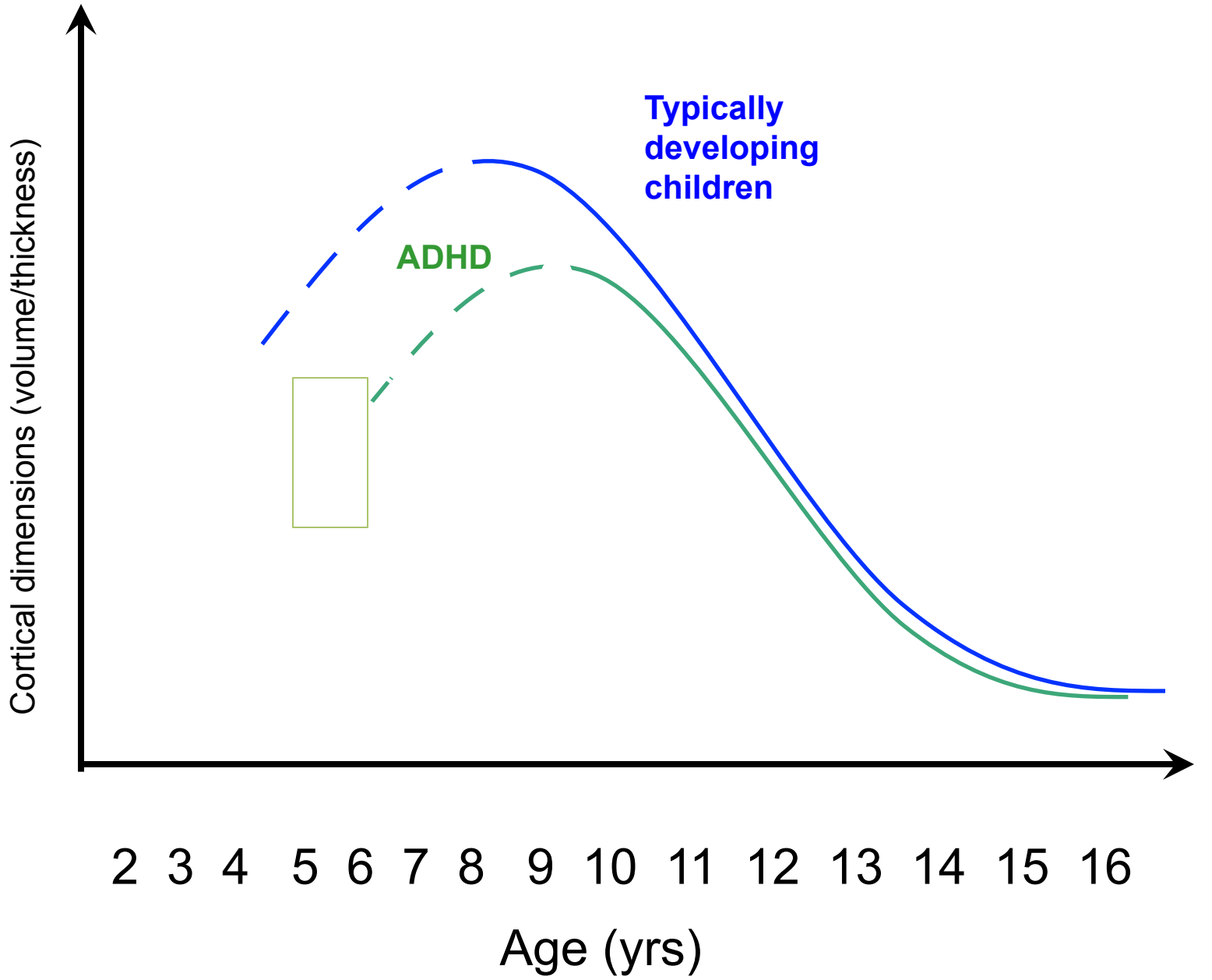


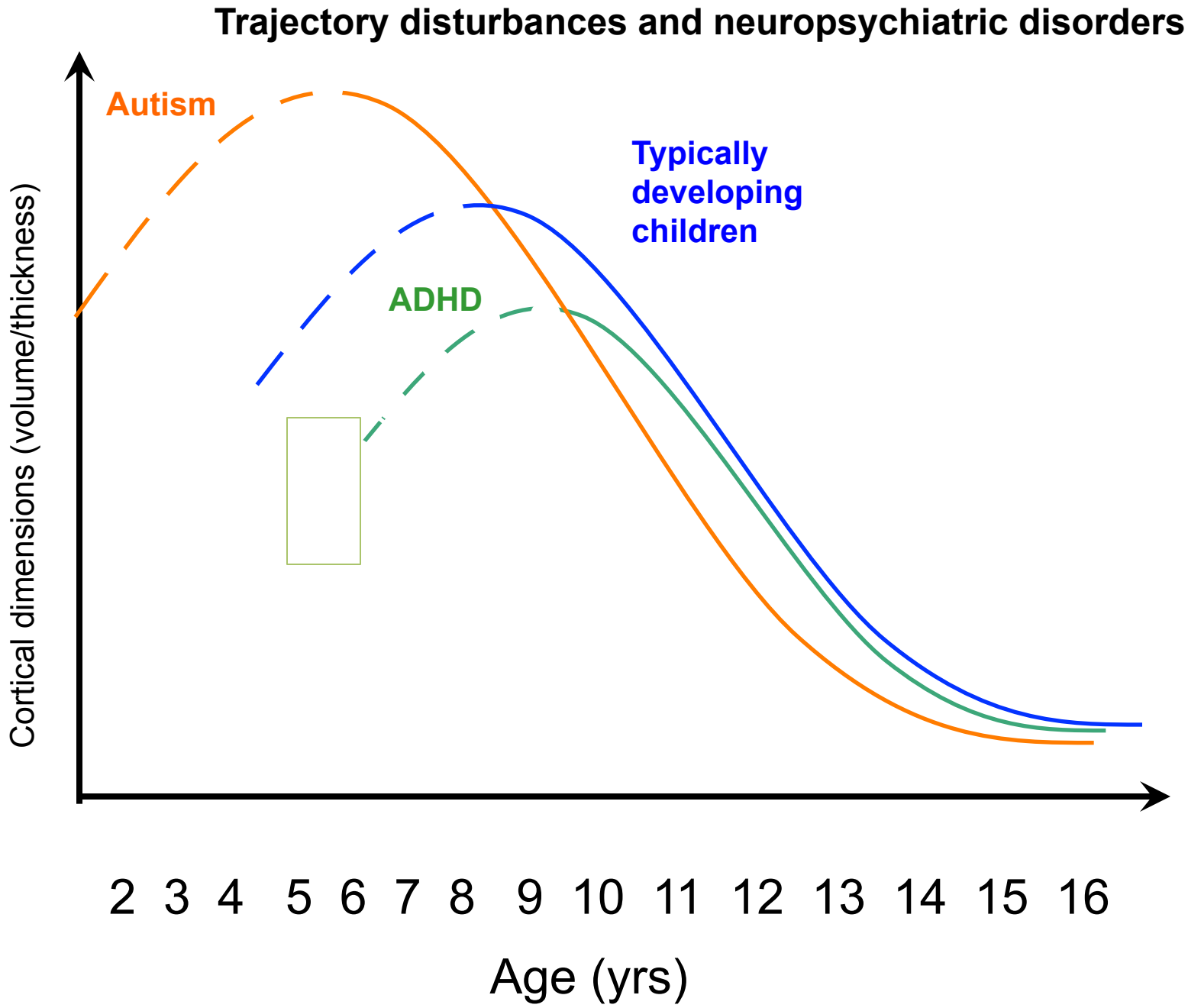
Figure 1.

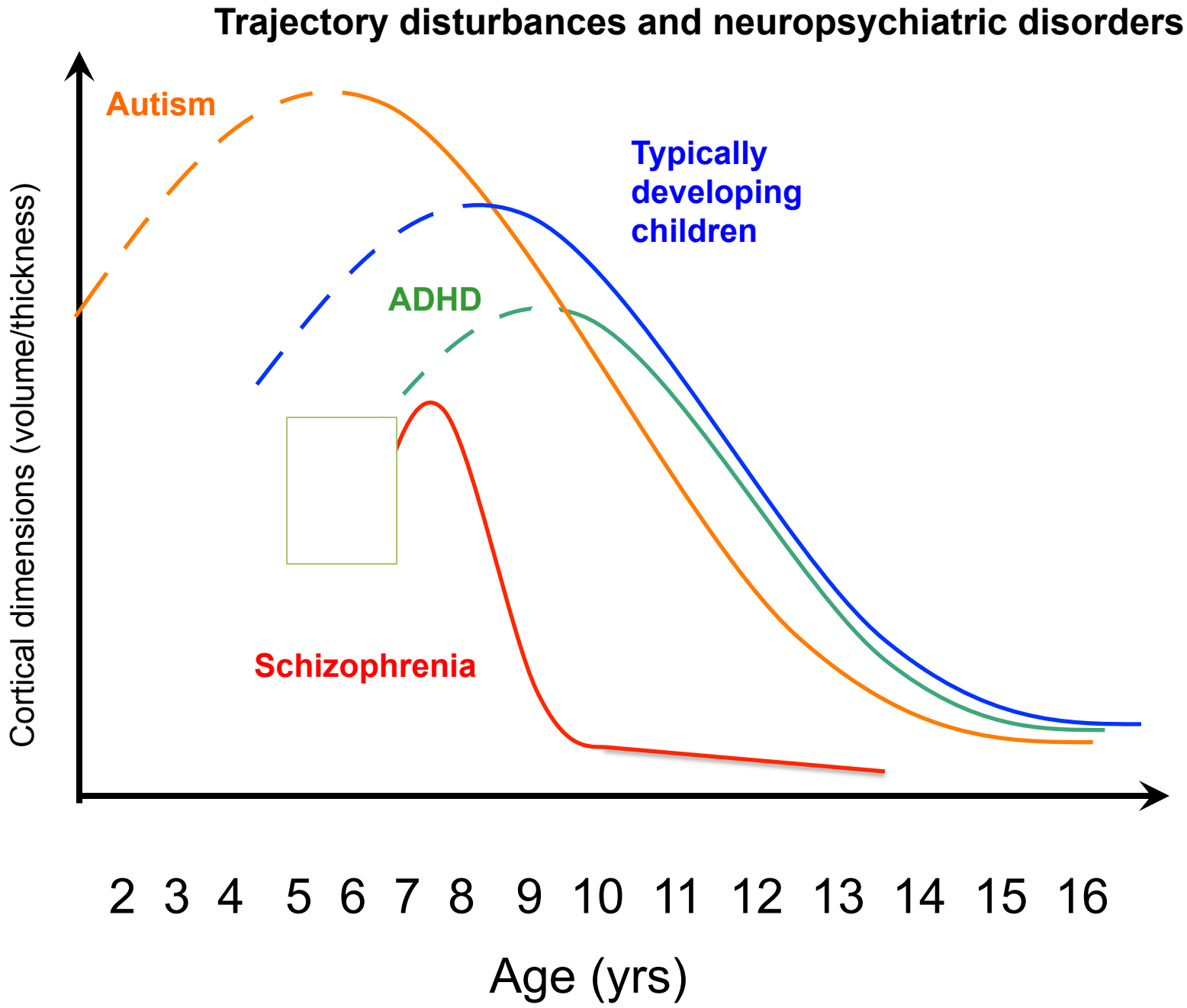
How developmental trajectories can go awry. In all examples hypothetical data representing the change in cortical thickness of a cerebral point is given. (**A**) The pathological trajectory has the same form as the typical trajectory but is displaced rightward along the age axis and so key characteristics such as the age of peak thickness, shown in the bold arrows, is attained later. (**B**) The pathological trajectory has the same form, but changes at a higher velocity. (**C**) The pathological trajectory loses the form or shape of a typical trajectory.

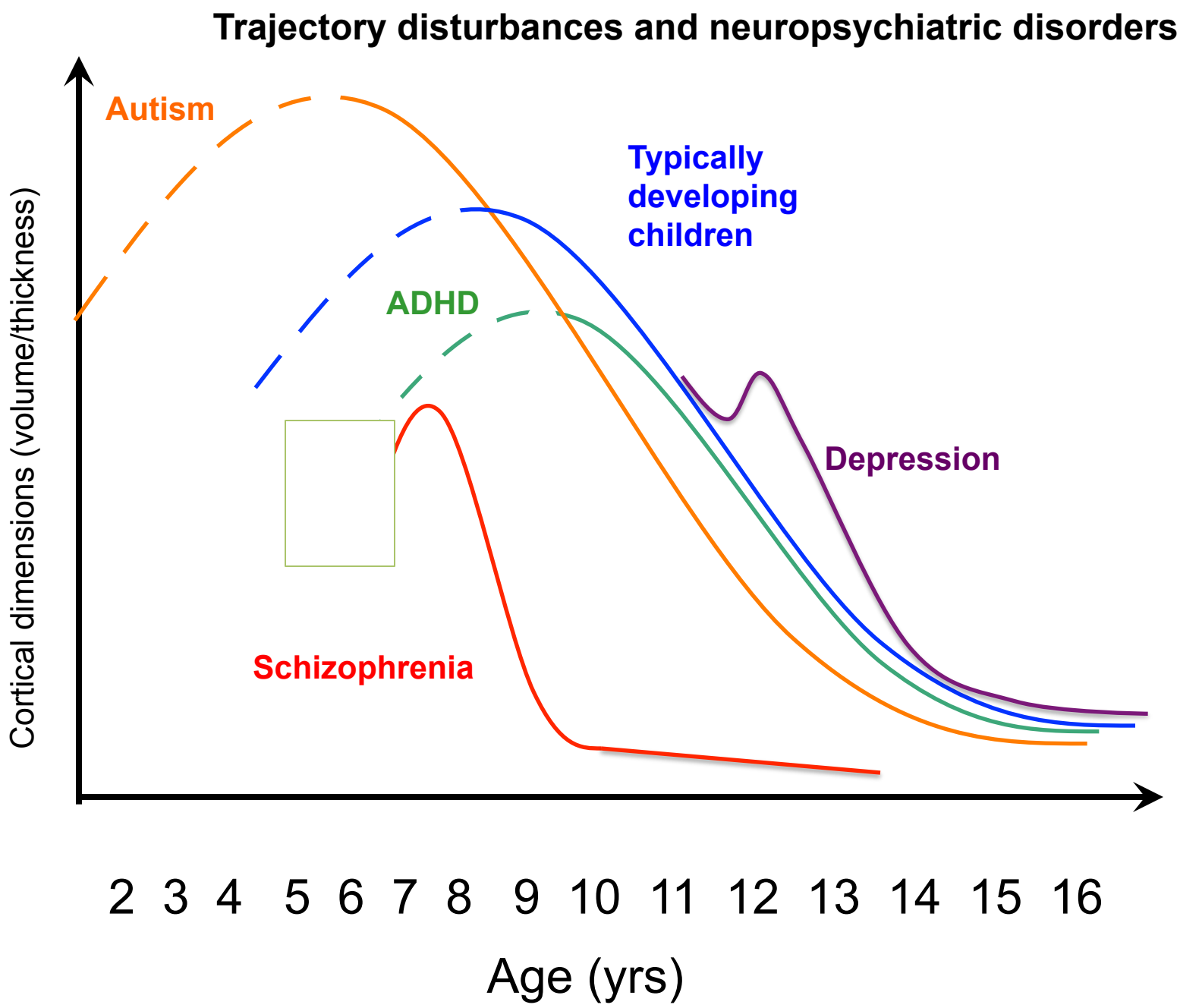
ADHD

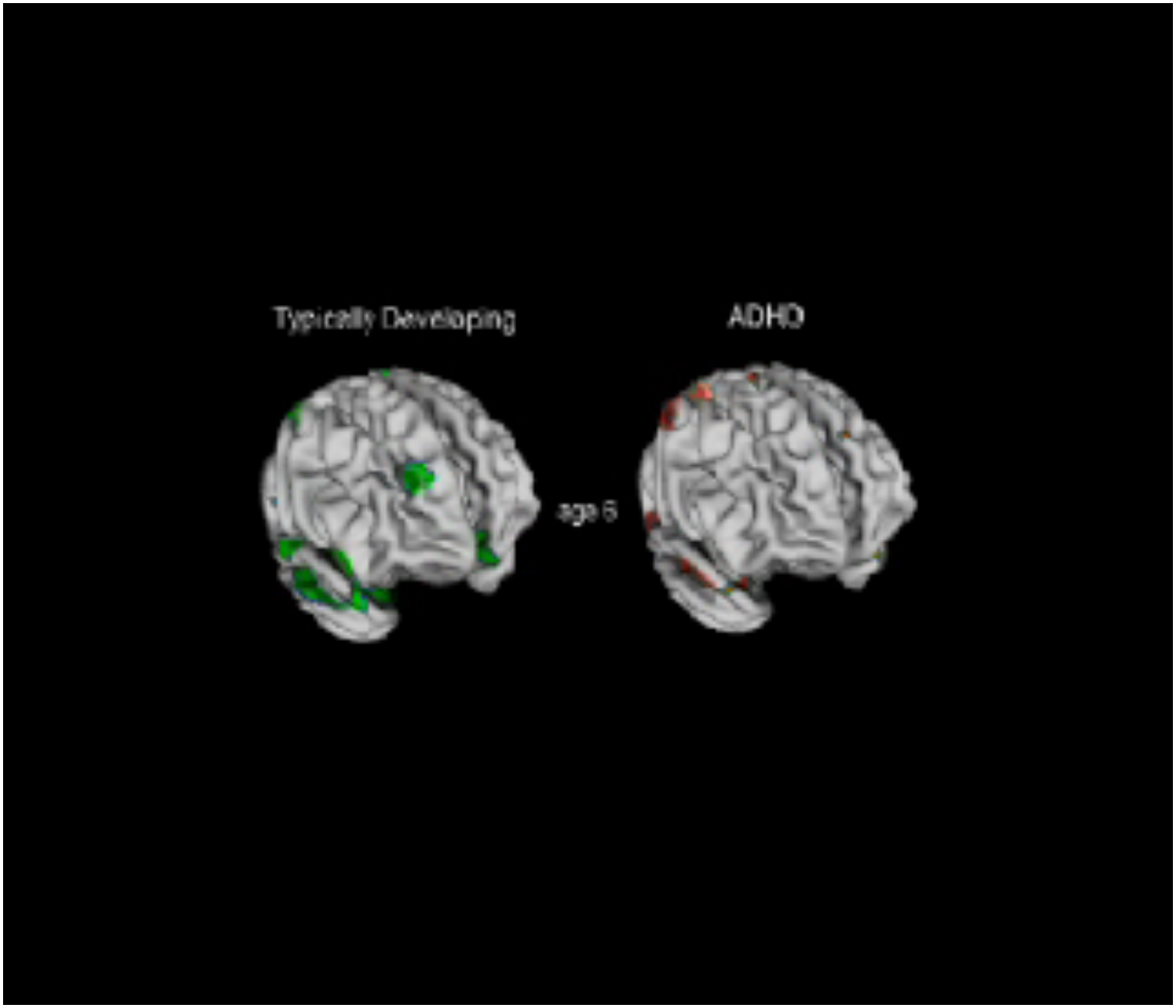

Trajectory disturbances and neuropsychiatric disorders
Typically developing children
Cortical dimensions (volume/thickness)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Age (yrs)

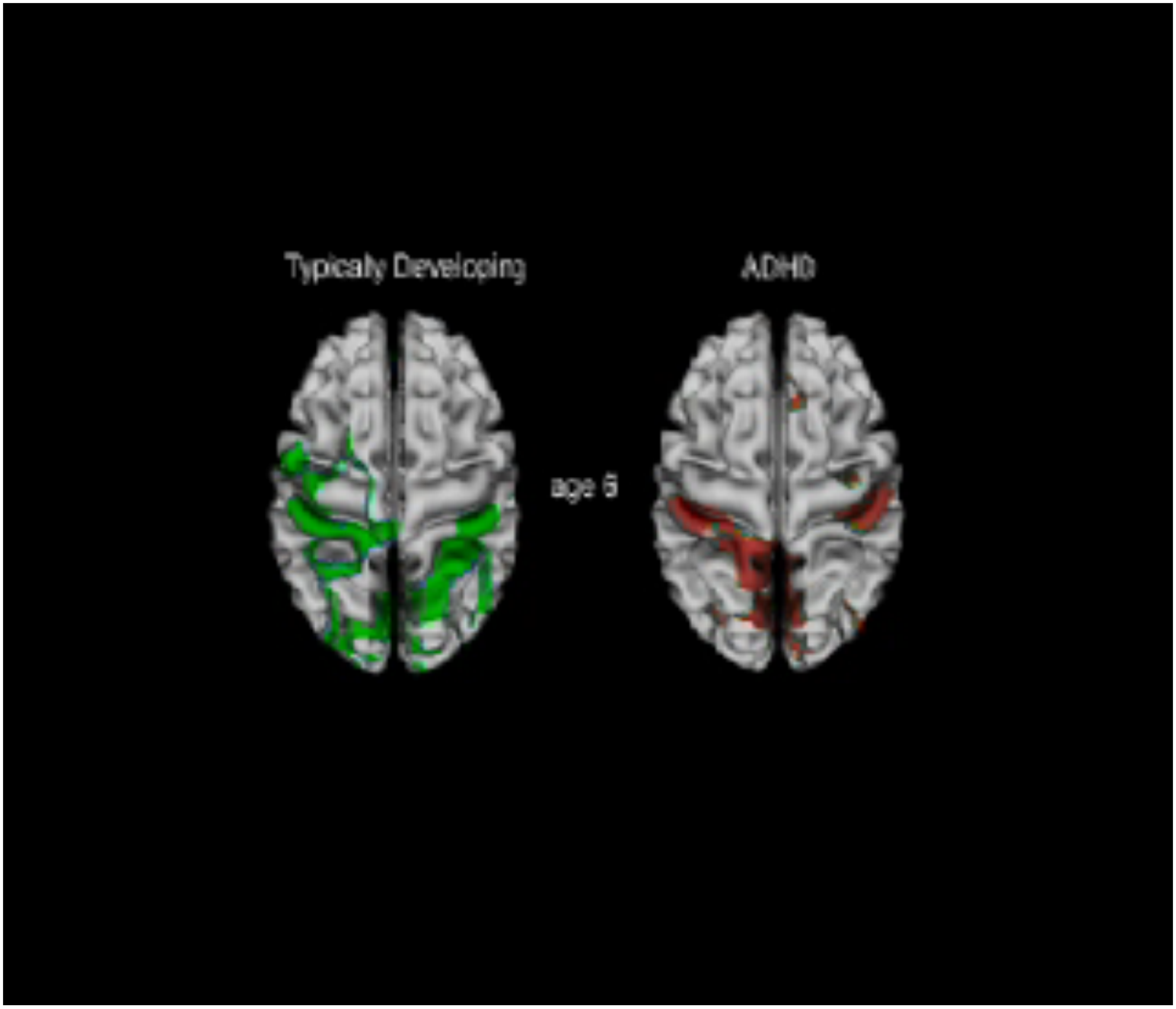

Trajectory disturbances and neuropsychiatric disorders
Typically developing children
ADHD
Cortical dimensions (volume/thickness)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Age (yrs)

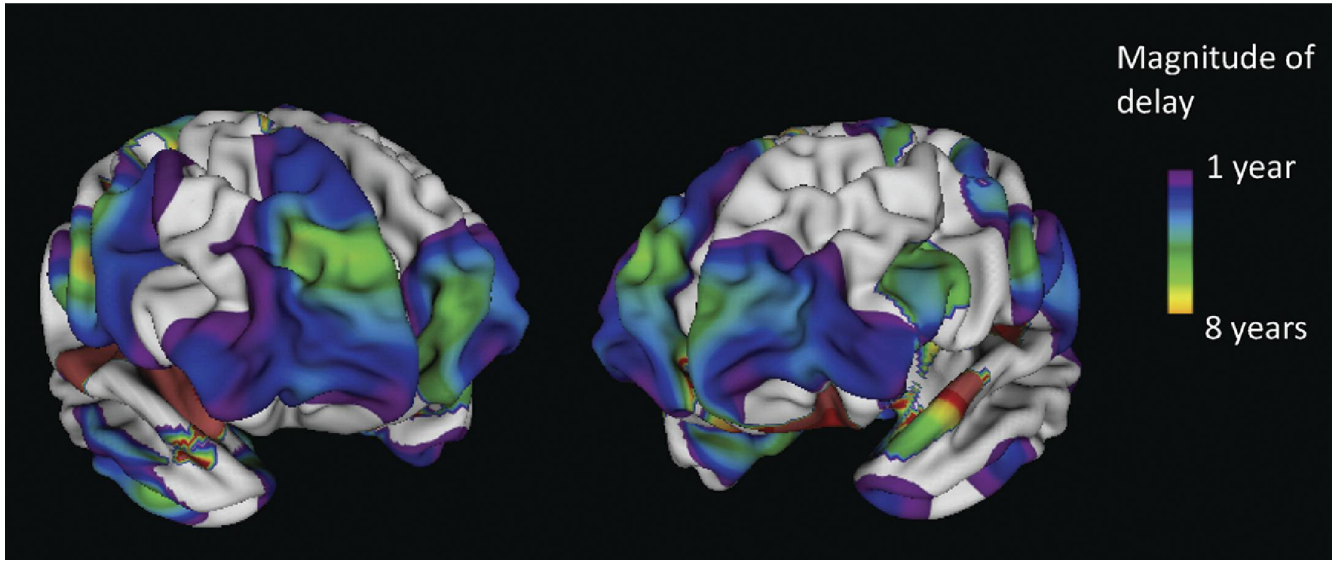

Trajectory disturbances and neuropsychiatric disorders
Autism
Typically developing children
ADHD
Cortical dimensions (volume/thickness)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Age (yrs)


Trajectory disturbances and neuropsychiatric disorders
Autism
Typically developing children
ADHD
Schizophrenia
Cortical dimensions (volume/thickness)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Age (yrs)


Trajectory disturbances and neuropsychiatric disorders
Autism
Typically developing children
ADHD
Depression
Schizophrenia
Cortical dimensions (volume/thickness)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Age (yrs)


Typically Developing
ADHD
age 6


Typically Developing
ADHD
age 6



In eta' evolutiva nell'ADHD si osserva un ritardo di sviluppo delle aree corticali prefrontali, parietali e temporali. Si stima che lo sviluppo di queste aree nell'ADHD, in termini di crescita di spessore corticale e successivo "pruning", avvenga con un **ritardo di 2-3 anni rispetto al neuro-sviluppo tipico**.

Shaw et al. *Biol Psychiatry*. 2012 72:191-197.

Shaw et al. 2006, Nature 440: 676-679

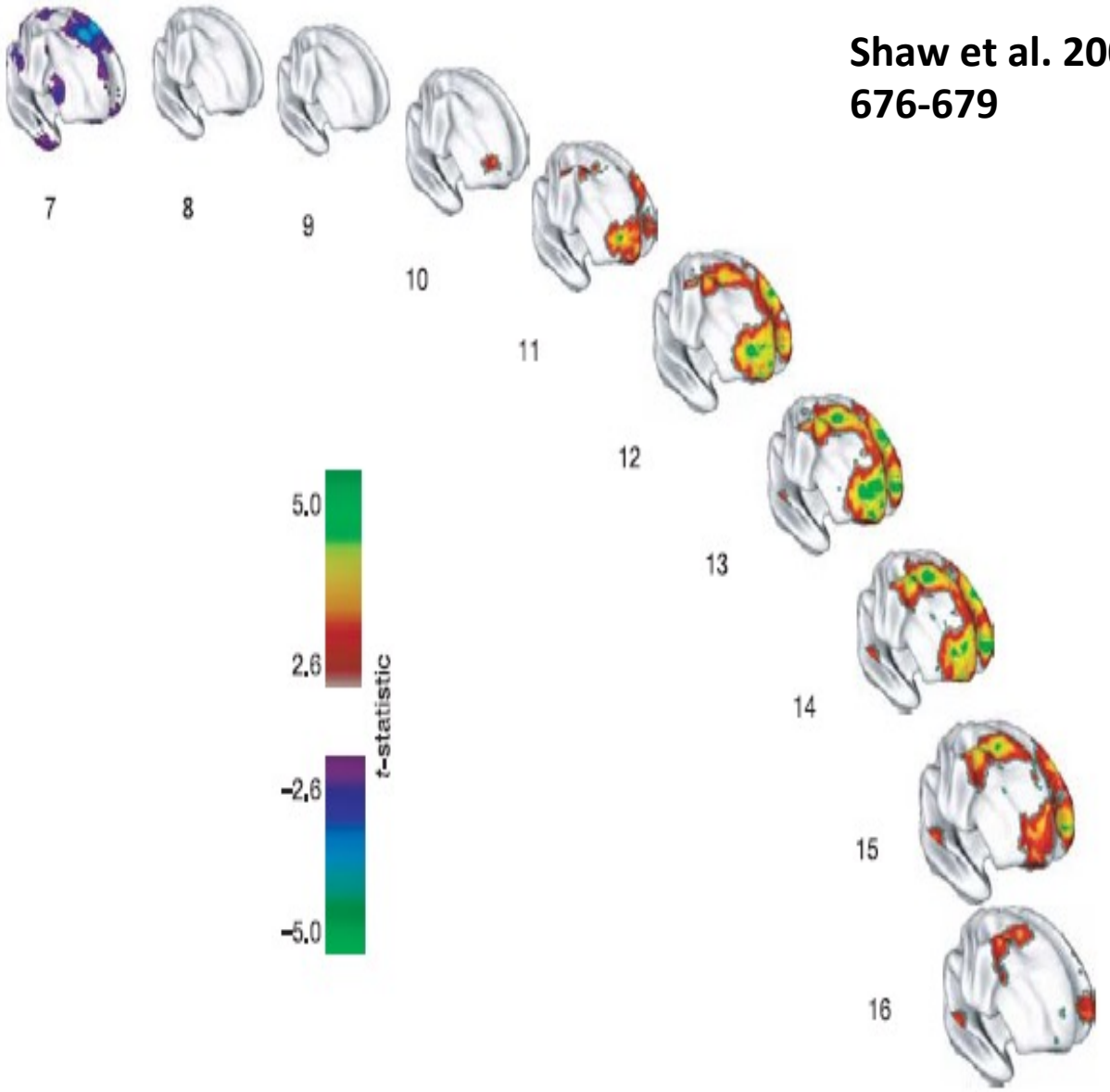
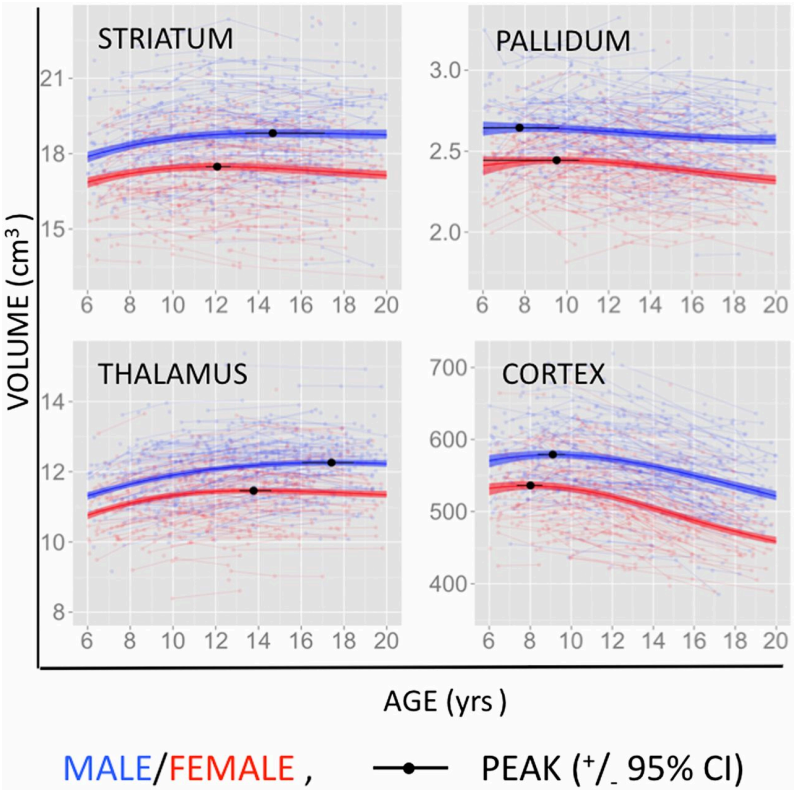
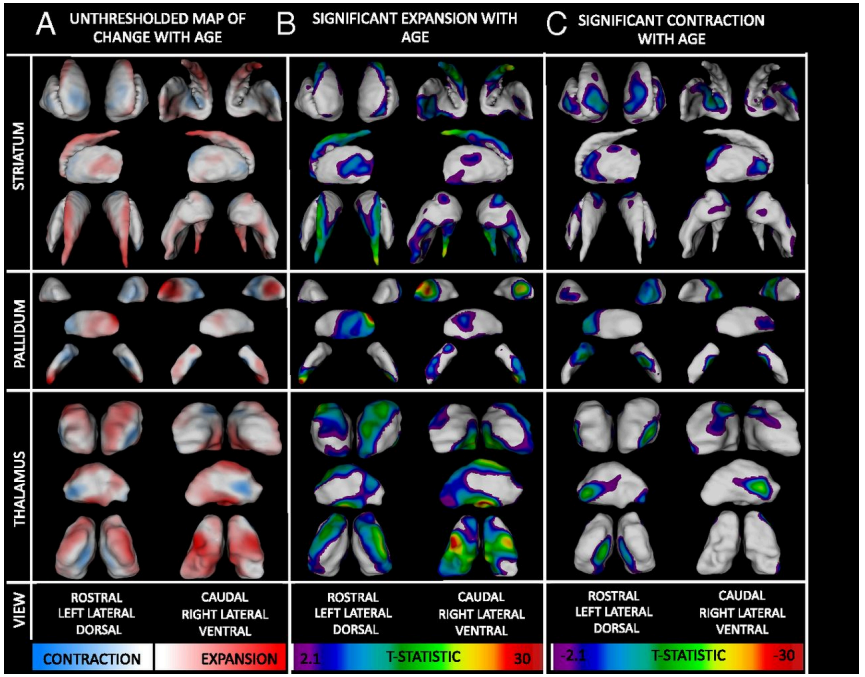


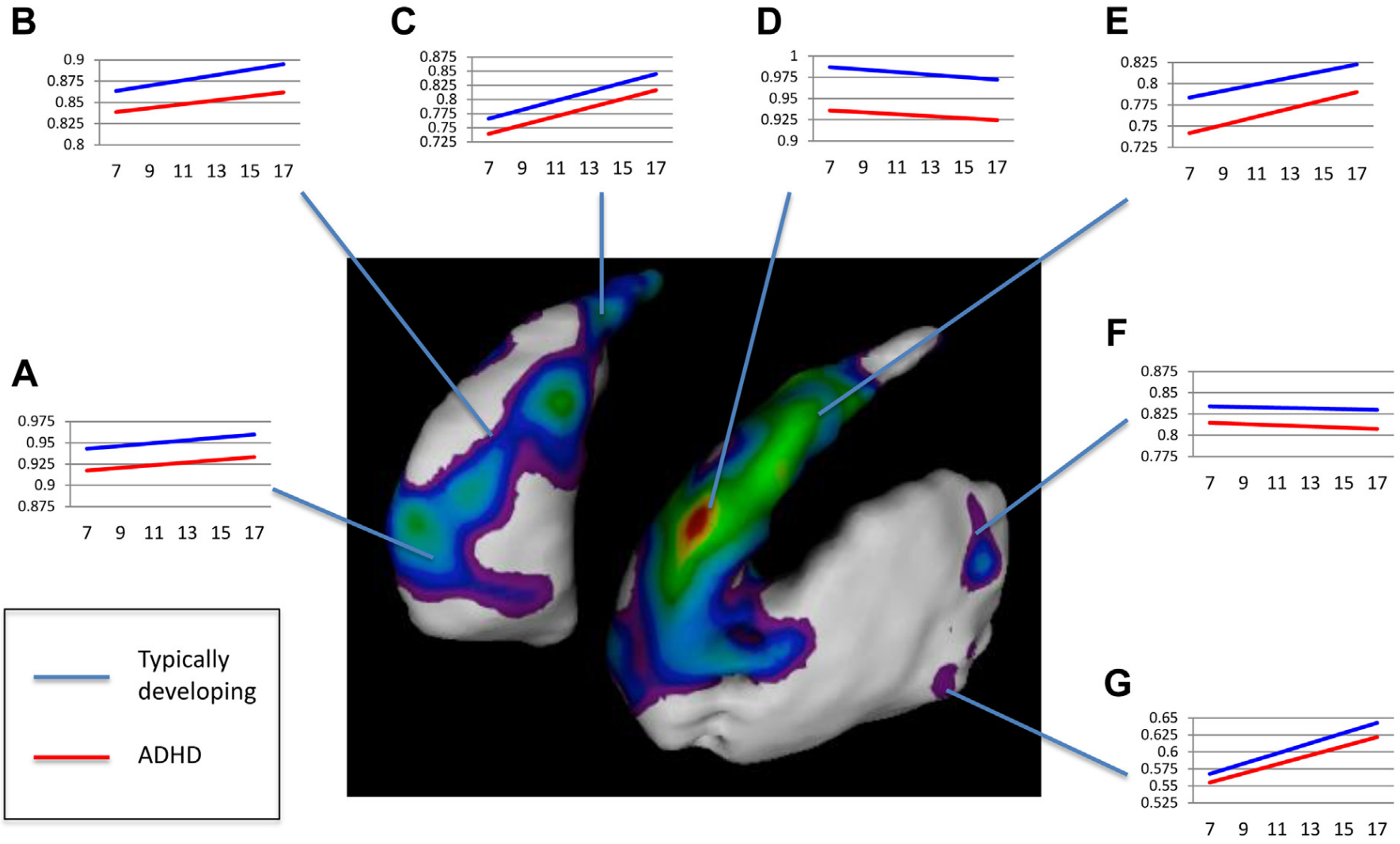
Figure 4 | Developing differences in cortical thickness between the superior and average intelligence groups. Group differences are represented by *t*-statistics ($t > 2.6$), and show that the superior intelligence group has a thinner superior prefrontal cortex at the earliest age (purple regions). There is then a rapid increase in cortical thickness (red, green and yellow regions) in the superior intelligence group, peaking at age 13 and waning in late adolescence.

Neurosviluppo sotto-corticale

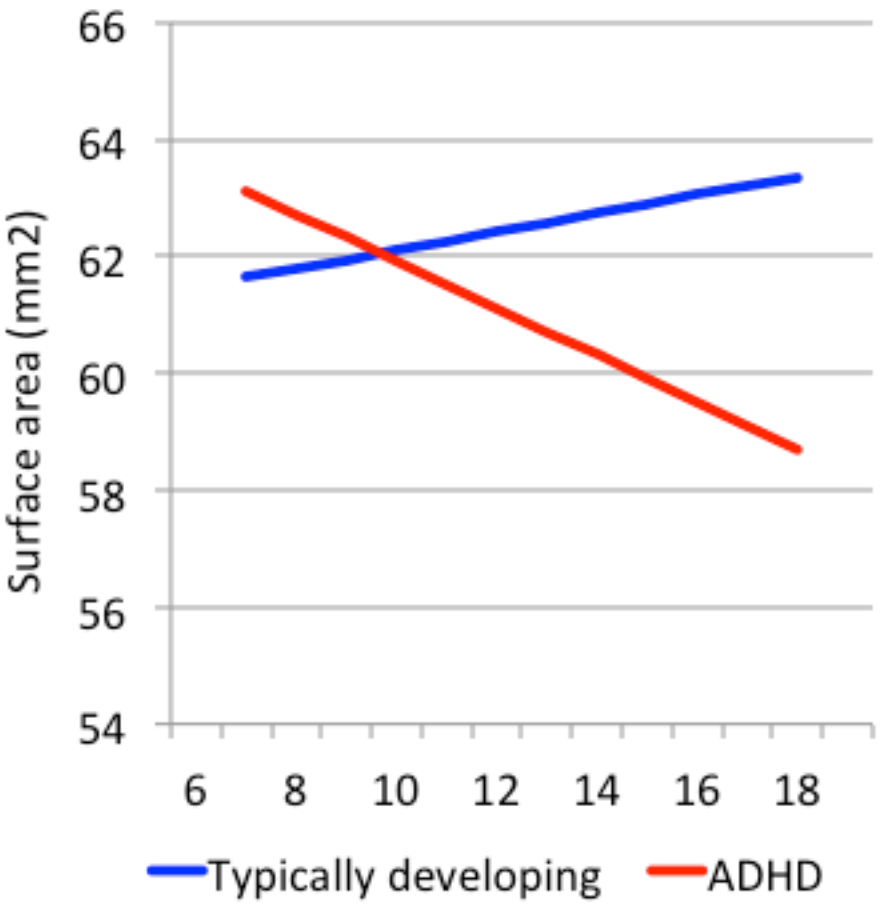


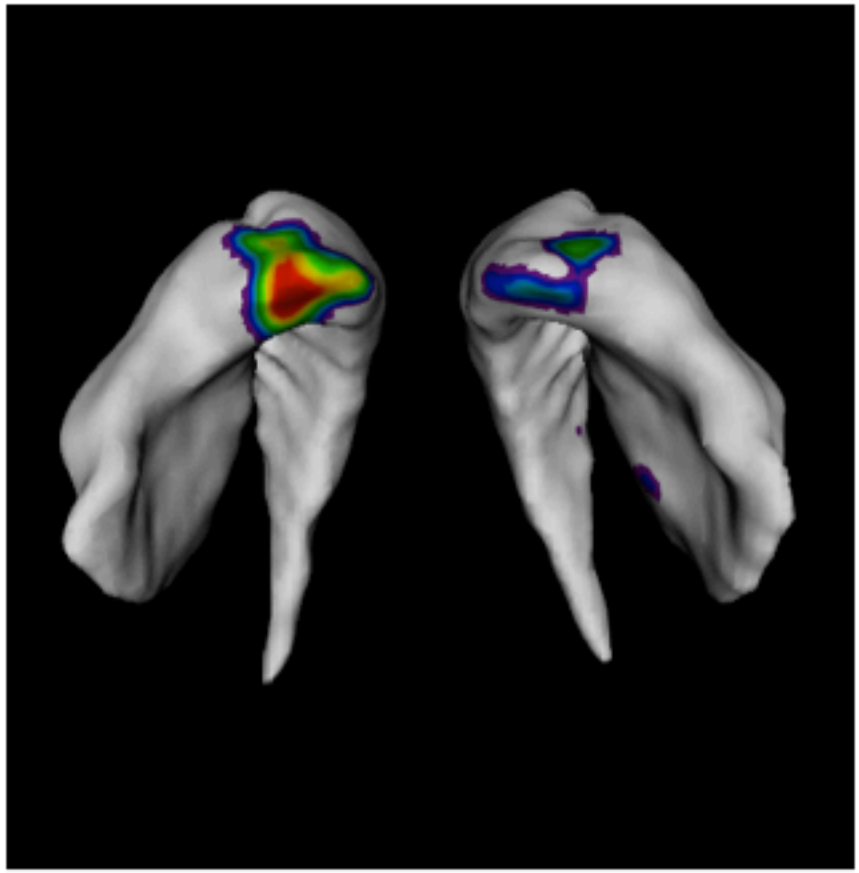


Raznahan et al. 2014



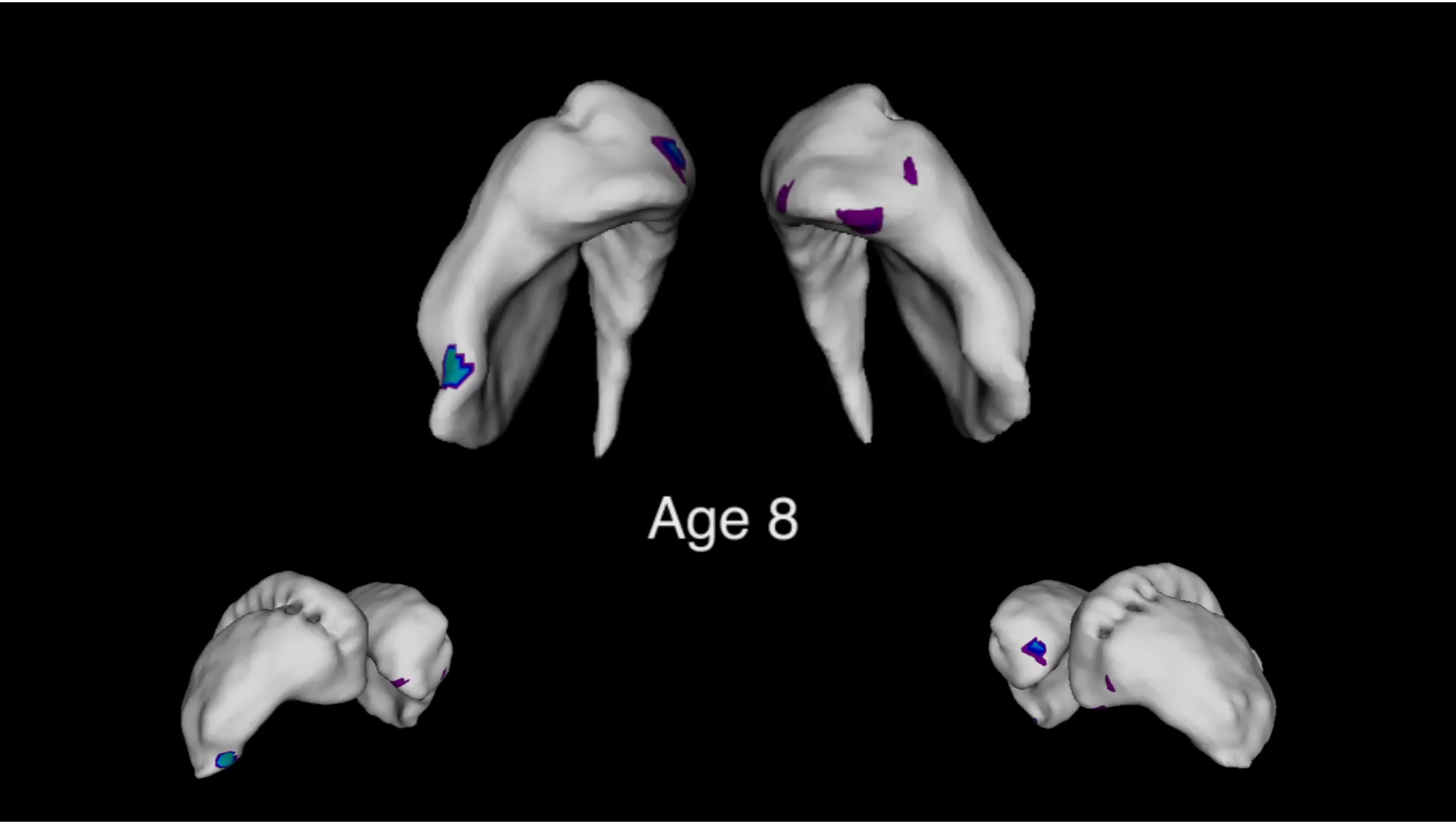
Shaw et al. 2014

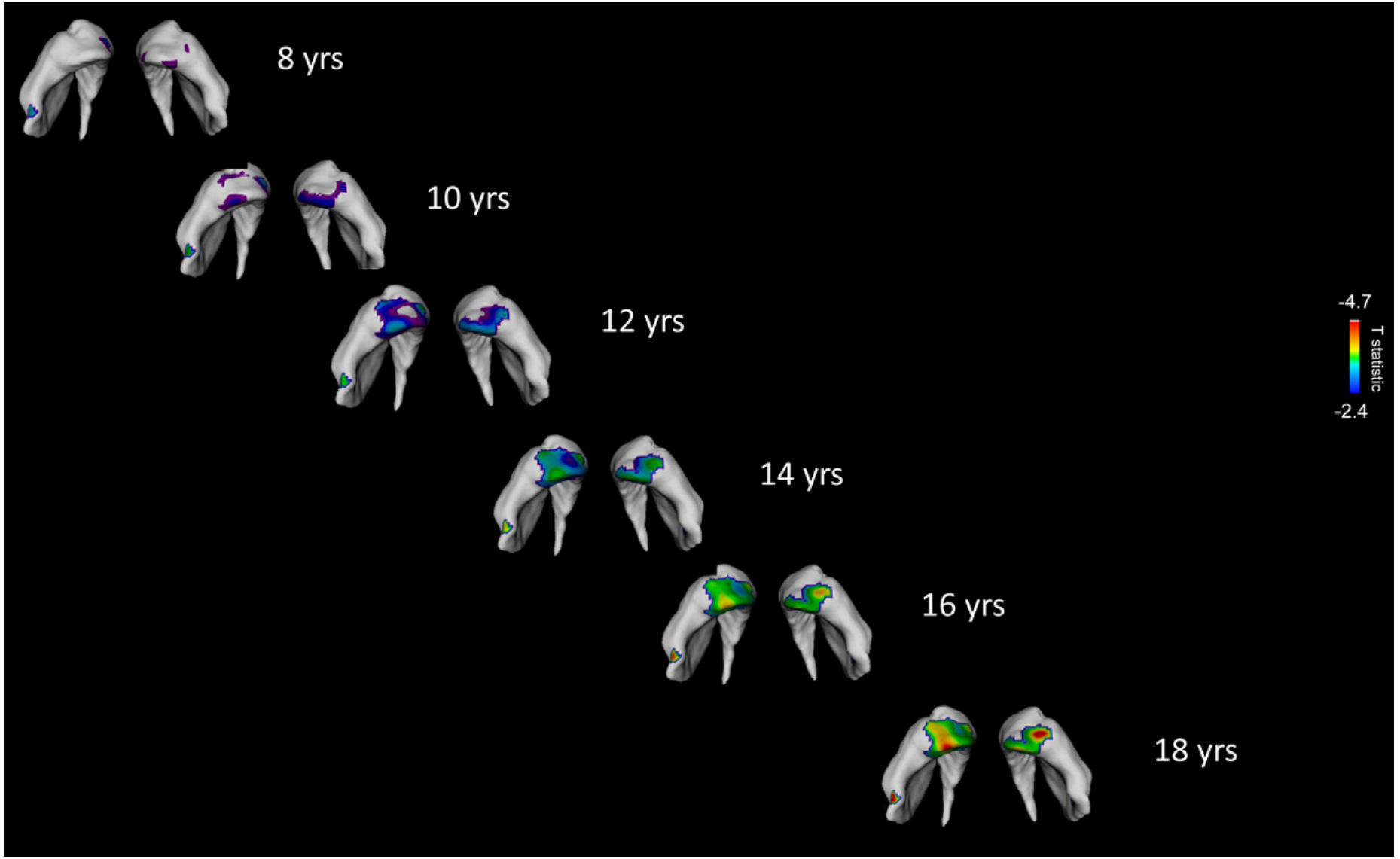


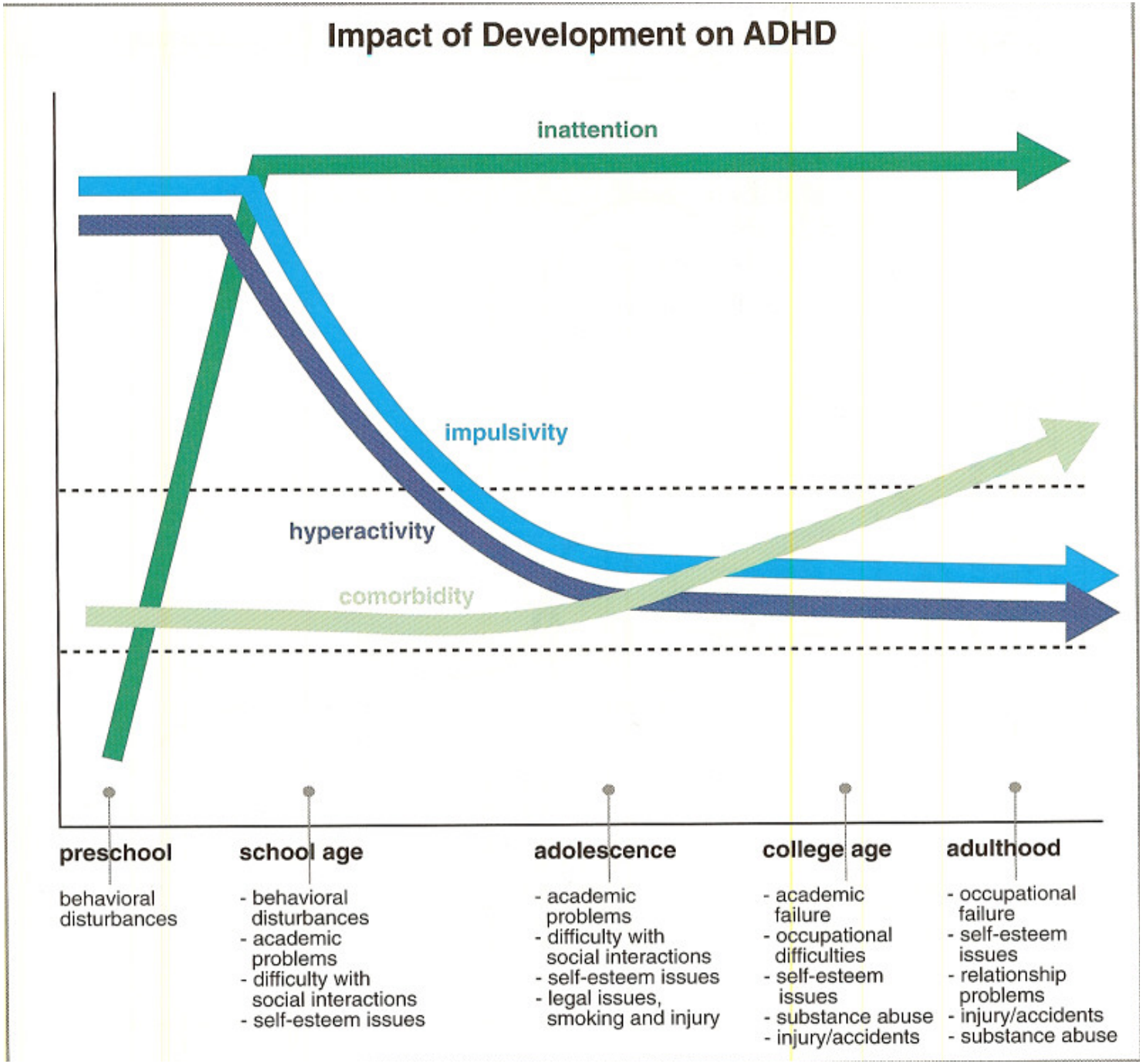


t= 5.6, $p < .0001$

Shaw et al. 2014

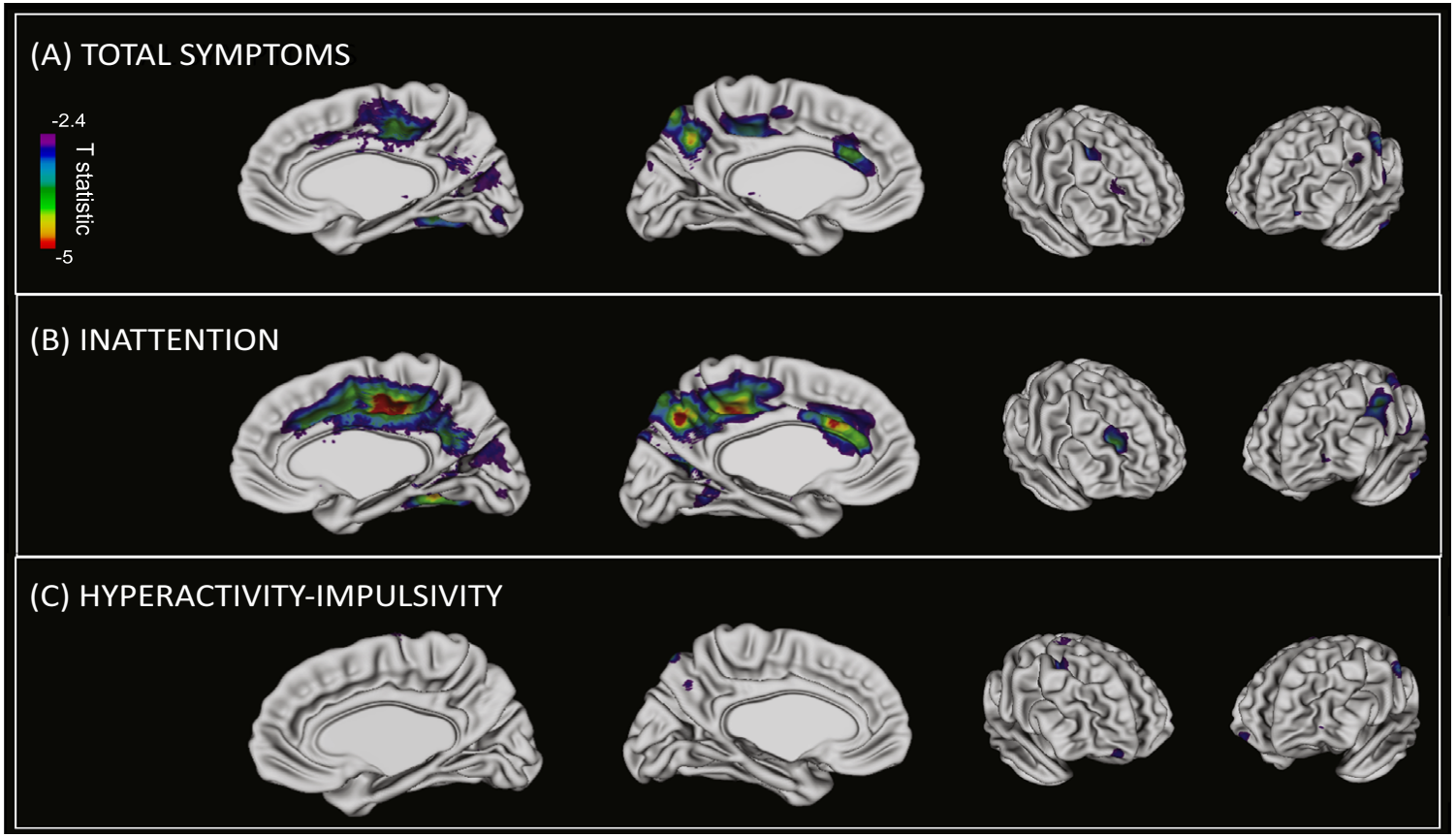

Age 8


8 yrs
10 yrs
12 yrs
14 yrs
16 yrs
18 yrs
-4.7
T statistic
-2.4



Stahl III Edition.
Chapter 17

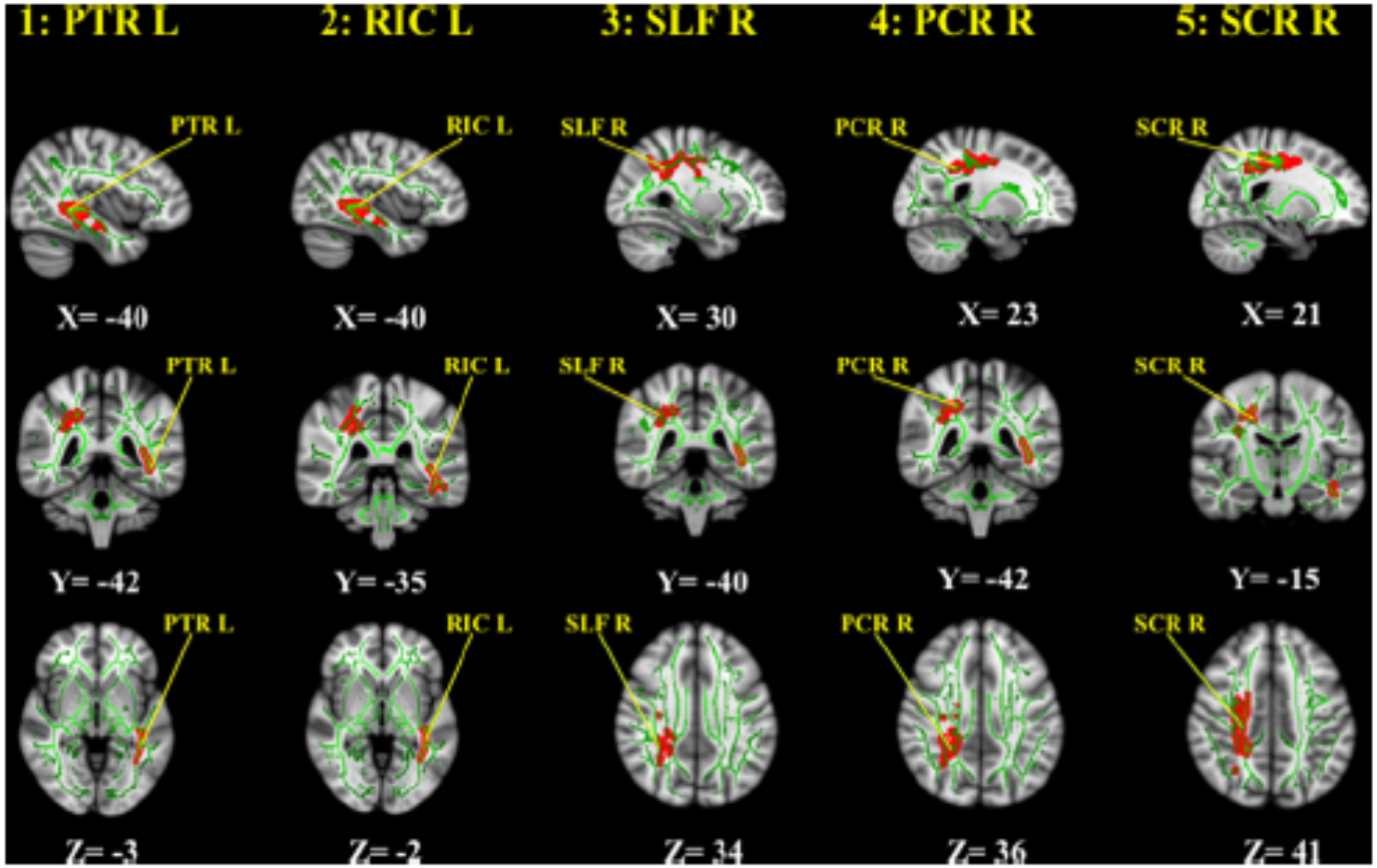
La centralita' dei sintomi "inattentivi"



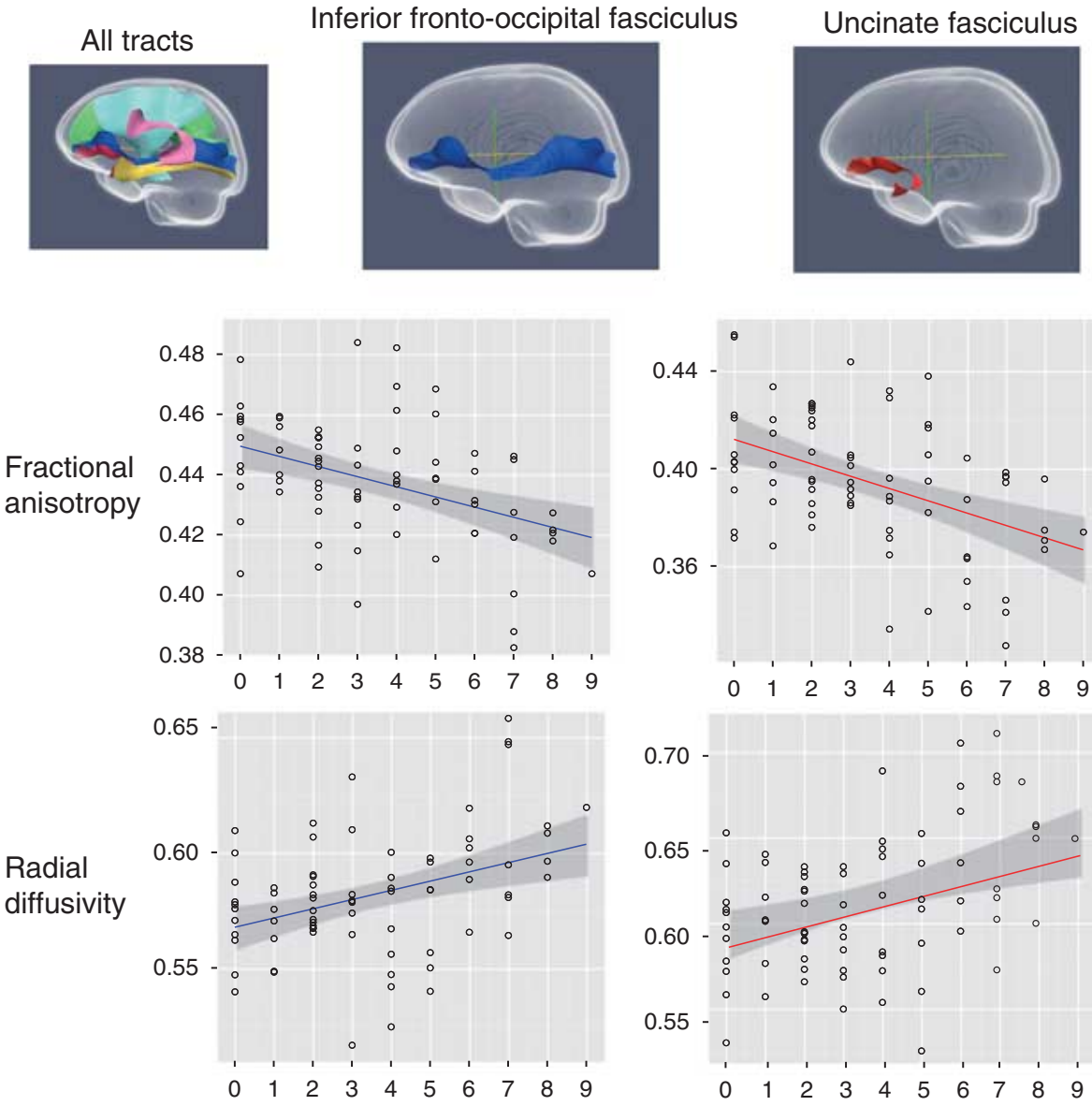
Shaw et al. 2013

White Matter Alterations at 33-Year Follow-Up in Adults with Childhood Attention-Deficit/ Hyperactivity Disorder

Cortese at al. *BP 2013*

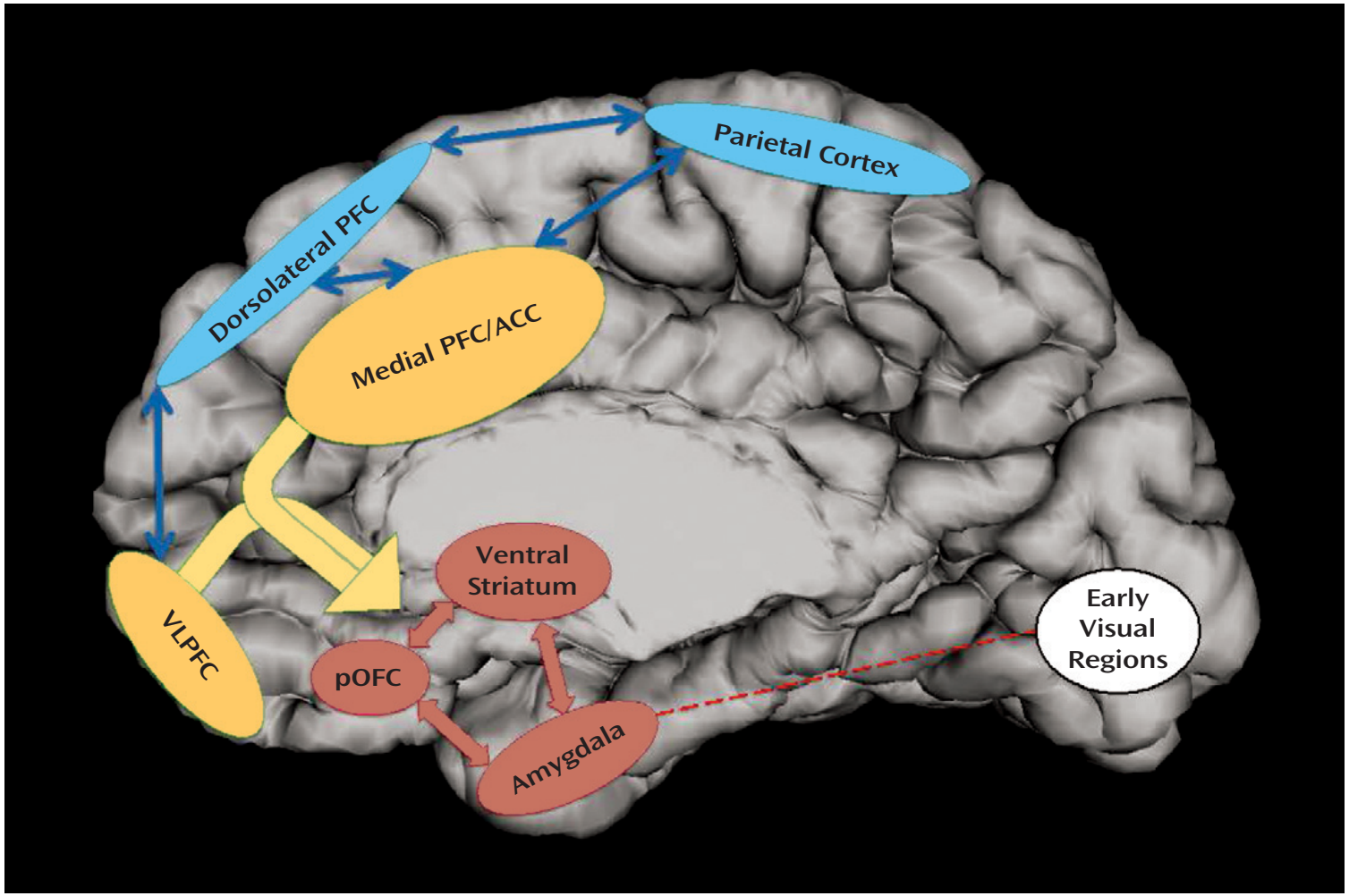


ADHD vs Controls



Shaw et al. 2015

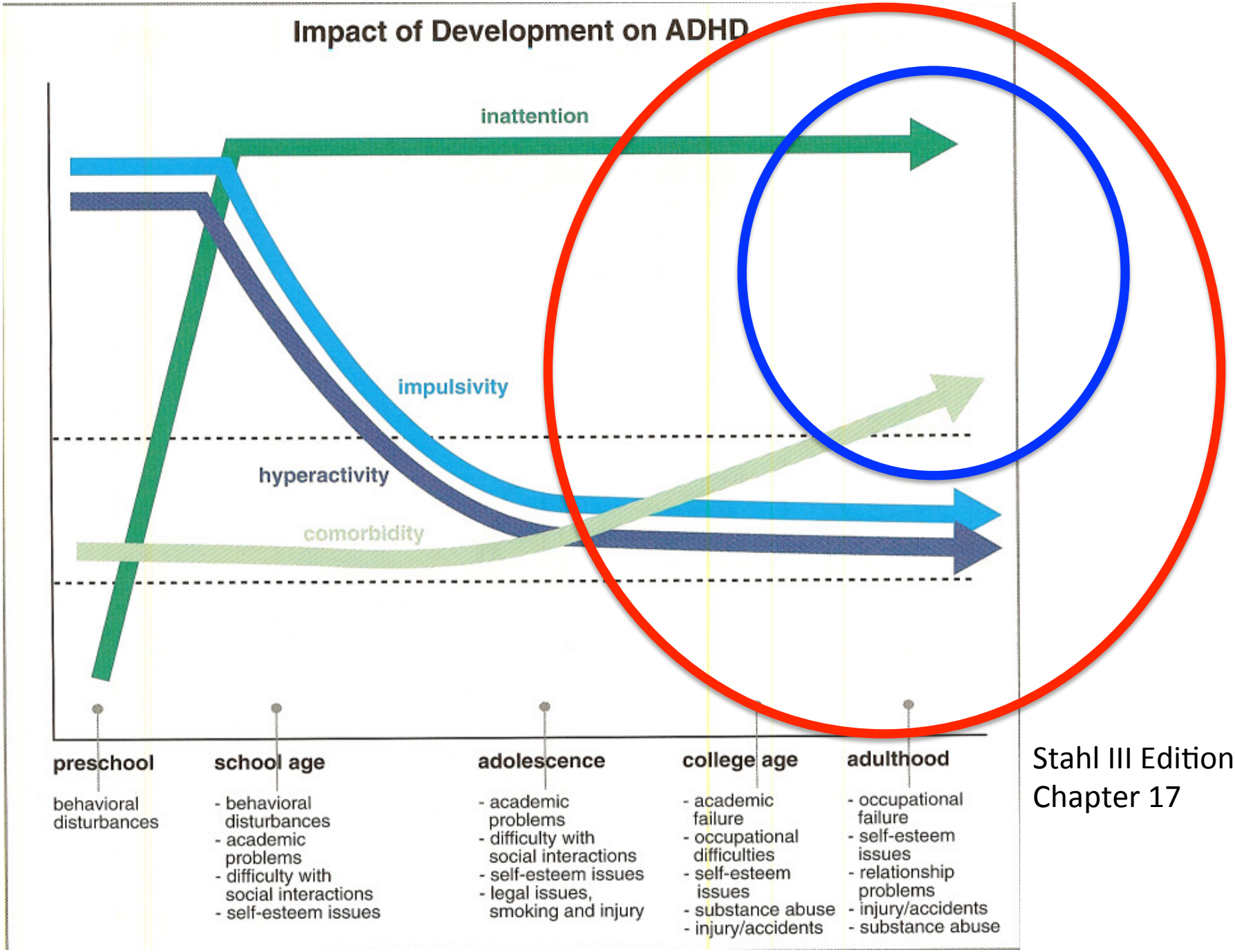
ADHD e regolazione emotiva



Shaw et al. 2014

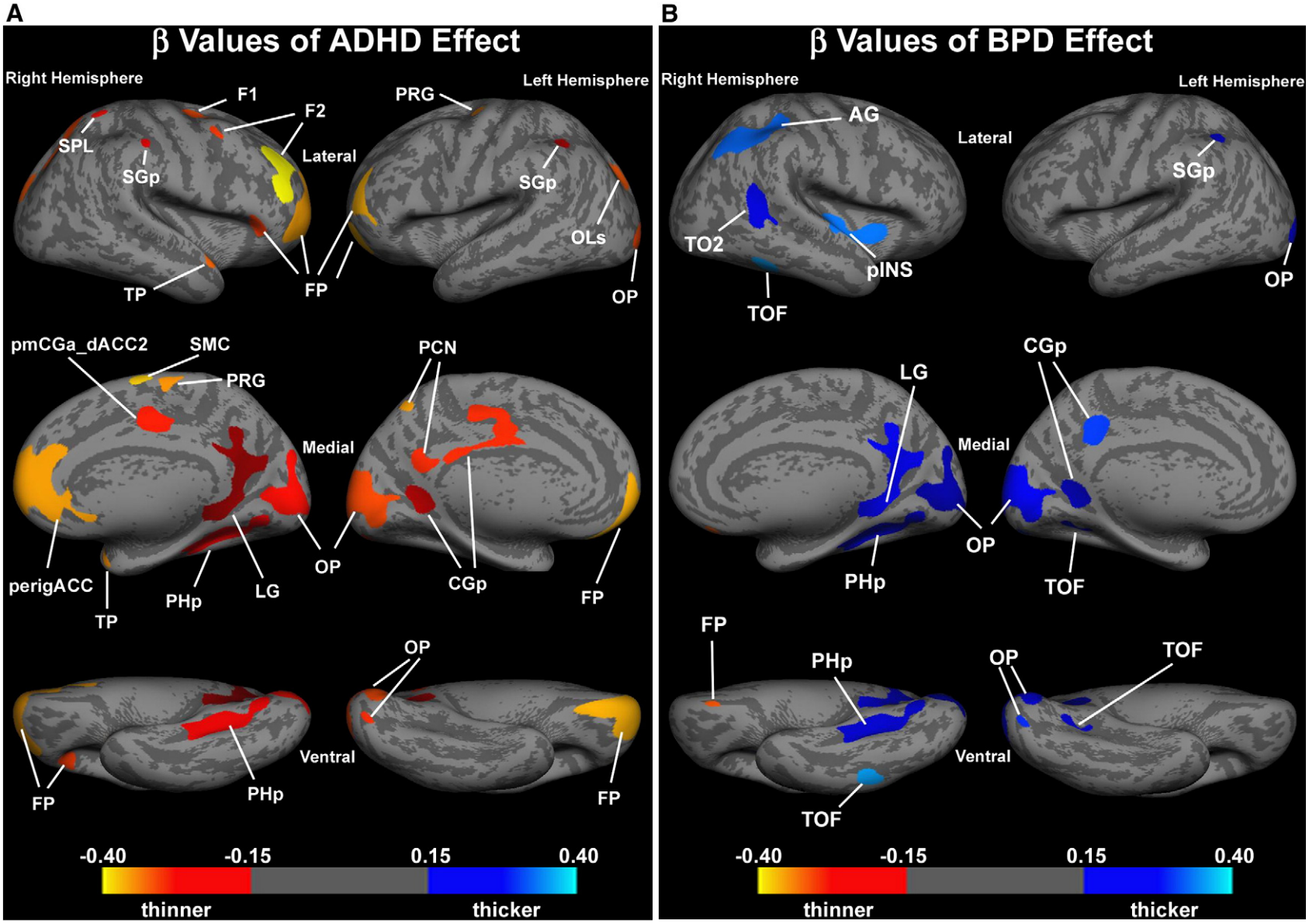
TABLE 4. Three Models to Explain the Overlap Between ADHD and Emotion Dysregulation

	Phenomenology		Pathophysiology			
Model	Correlations Between ADHD and Emotion Dysregulation	Clinical Course	Psychological Basis	Neural Basis	Genetic	Treatment
Emotion dysregulation is integral to ADHD	Extremely high	Yoked clinical courses for symptoms of ADHD and emotion dysregulation	Deficits in behavioral inhibition and working memory mediate both core ADHD symptoms and emotion dysregulation	Anomalies confined to fronto-striatal-cerebellar circuits	Same genetic basis for ADHD with emotion dysregulation and ADHD alone	Treatments that improve ADHD will improve emotion dysregulation
Combined ADHD and emotion dysregulation defines a distinct entity	ADHD subgroup exists that is high on both symptom domains	Distinct clinical course for ADHD with emotion dysregulation and ADHD alone	Distinct cognitive deficits in ADHD with emotion dysregulation and ADHD alone	Distinct neural bases for ADHD with emotion dysregulation and ADHD alone	Distinct genetic bases for ADHD with emotion dysregulation and ADHD alone	Existing treatments for ADHD may be less effective for ADHD with emotion dysregulation
Symptoms of ADHD and emotion dysregulation are correlated but distinct dimensions	Modest	Similar but dissociable clinical courses for symptoms of ADHD and emotion dysregulation	Deficits in emotion processing mediate dysregulation and correlate with deficits mediating core ADHD symptoms	Anomalies extend beyond fronto-striato-cerebellar circuits to (para)limbic regions	Some genes shared between ADHD alone and ADHD with emotion dysregulation	Treating “core” ADHD symptoms benefits emotion dysregulation, but separate treatment may also be needed

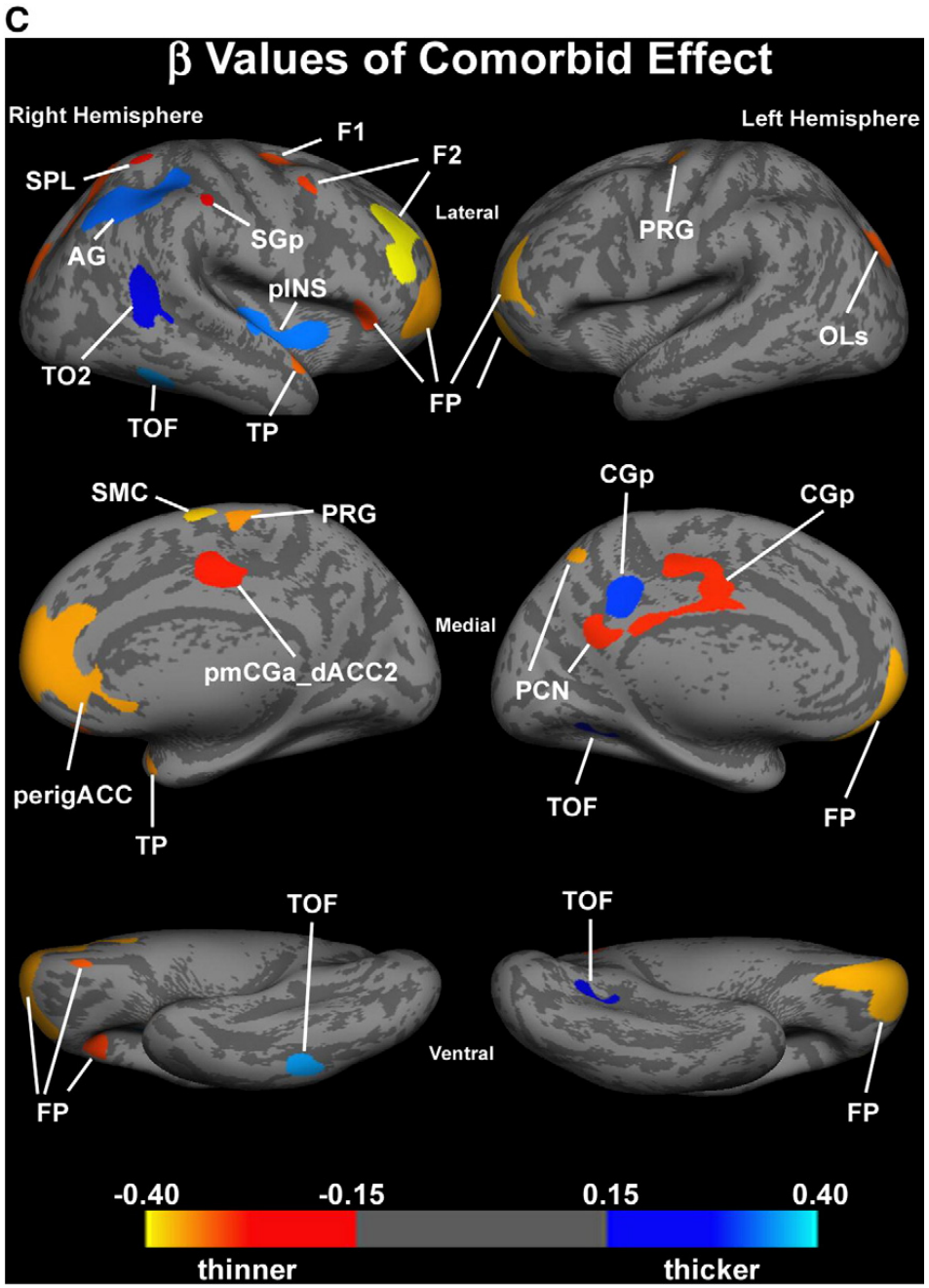


Stahl III Edition.
Chapter 17

Rispetto alle sue comorbidità l'ADHD è qualcosa che corre parallelamente rispetto all'evoluzione del disturbo o dei disturbi diagnosticabili insieme a esso

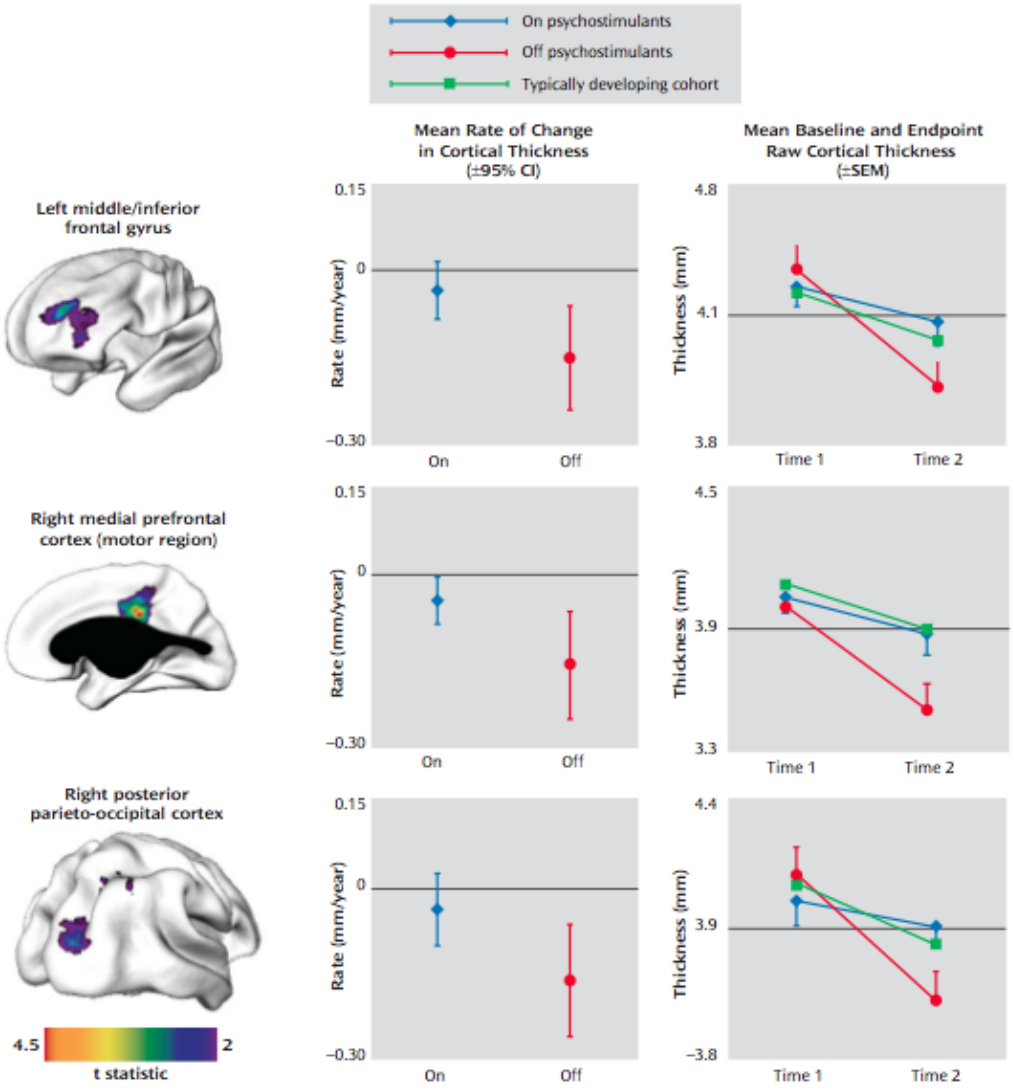


Makris et al. 2012



Makris et al. 2012

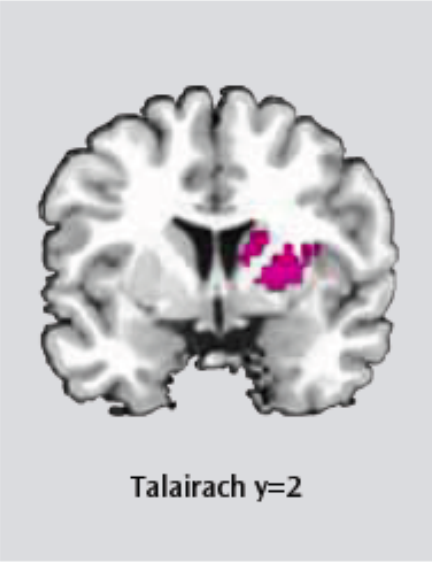
FIGURE 1. Differences in Rate of Cortical Growth in Adolescents With ADHD Taking or Not Taking Psychostimulant Medication[a]

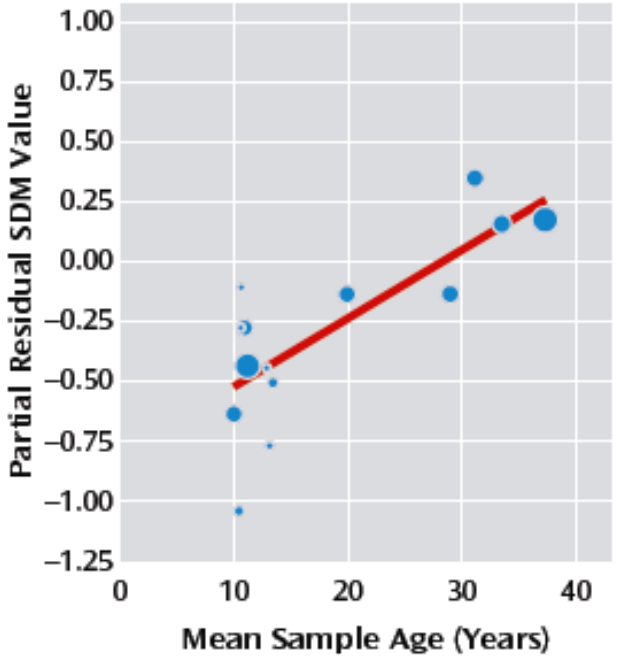


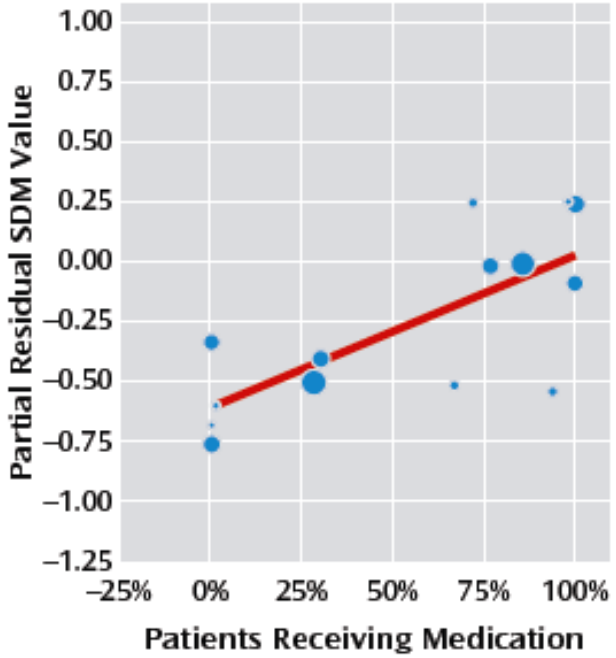
Shaw et al. *Am J Psychiatry*. 2009 166:58-63.

Gray Matter Volume Abnormalities in ADHD: Voxel-Based Meta-Analysis Exploring the Effects of Age and Stimulant Medication

FIGURE 2. Results of the Metaregression Analysis Showing Independent Associations of Mean Age and Percentage of Patients Receiving Stimulant Medication With More Normal Gray Matter Volumes in the Right Basal Ganglia[a]

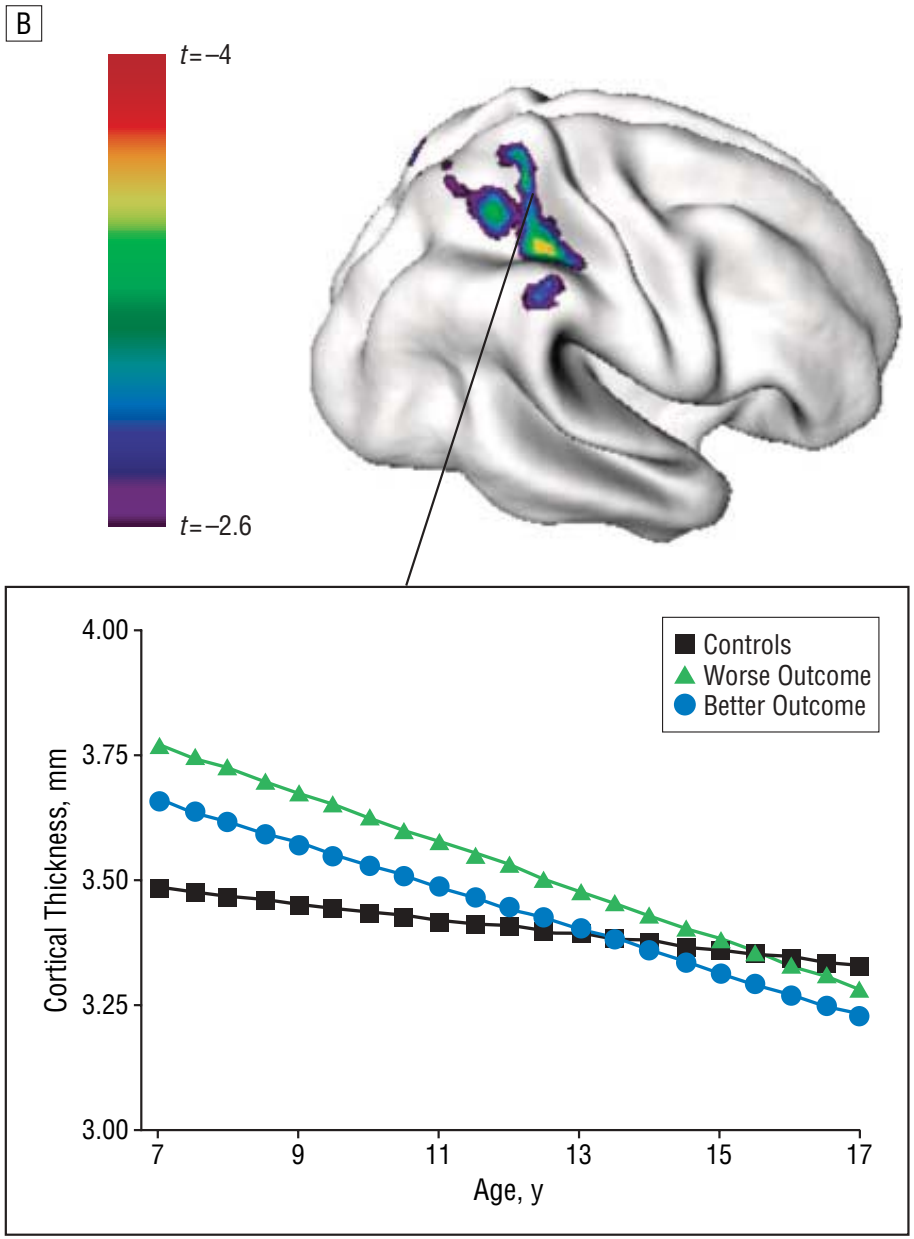






[a] In the graphs, each study is represented as a dot, with dot size reflecting sample size: large dots indicate samples with over 40 patients; medium dots, samples with 20–40 patients; and small dots, samples with under 20 patients. The regression line (metaregression signed differential mapping slope) is presented as a straight line. SDM refers to the signed differential mapping meta-analytic method (www.sdmproject.com).

Nakao et al. *AJP* 2011



Shaw et al. *Arch Gen Psychiatry*. 2006 63:540-549.

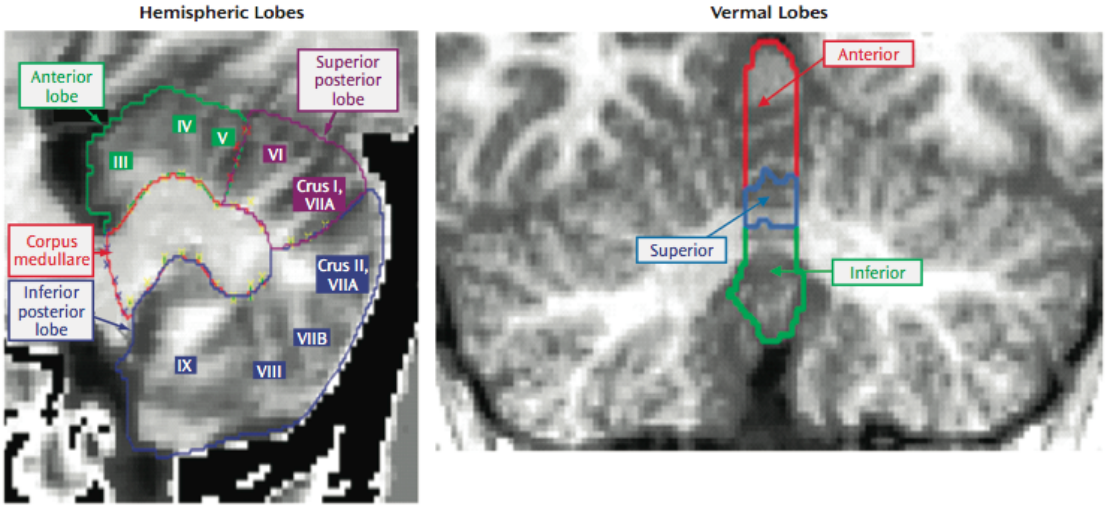


FIGURE 3. Developmental Trajectory of Whole Cerebellum in ADHD Patients With Better and Worse Outcomes and Healthy Comparison Subjects[a]

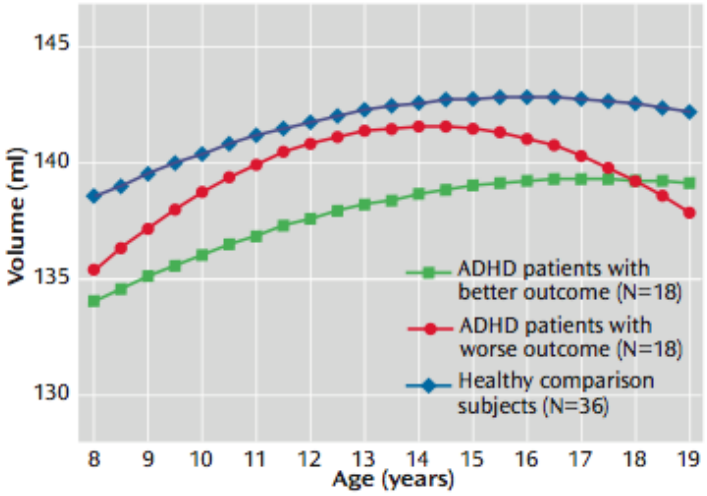


FIGURE 2. Developmental Trajectory of Left Anterior Hemisphere in ADHD Patients and Healthy Comparison Subjects

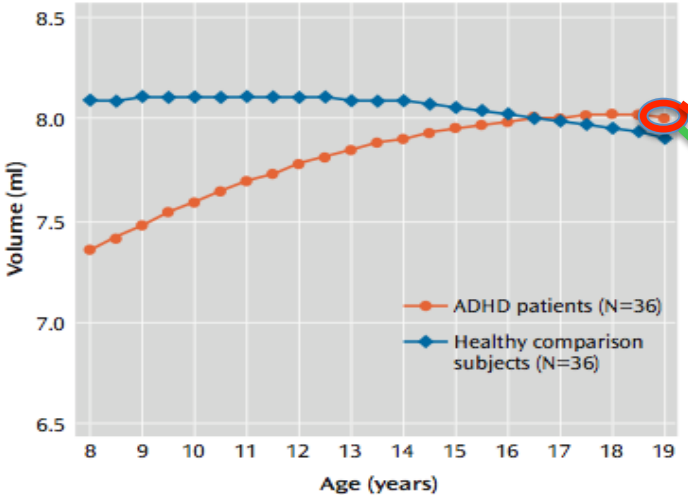
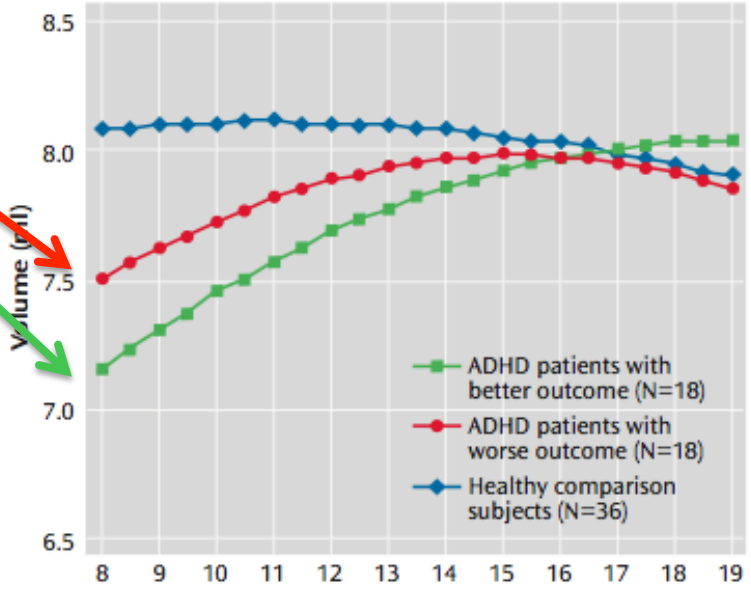
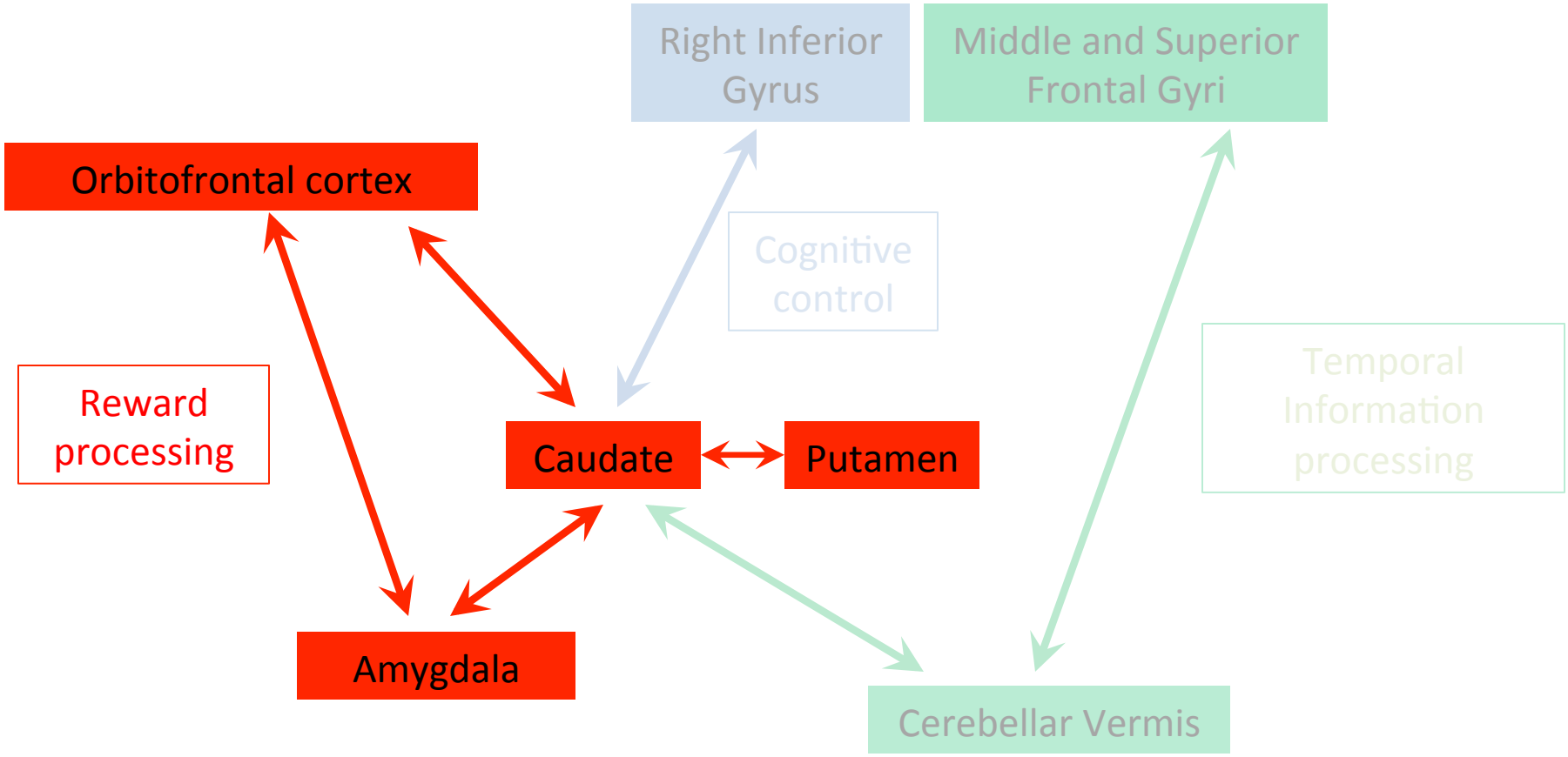


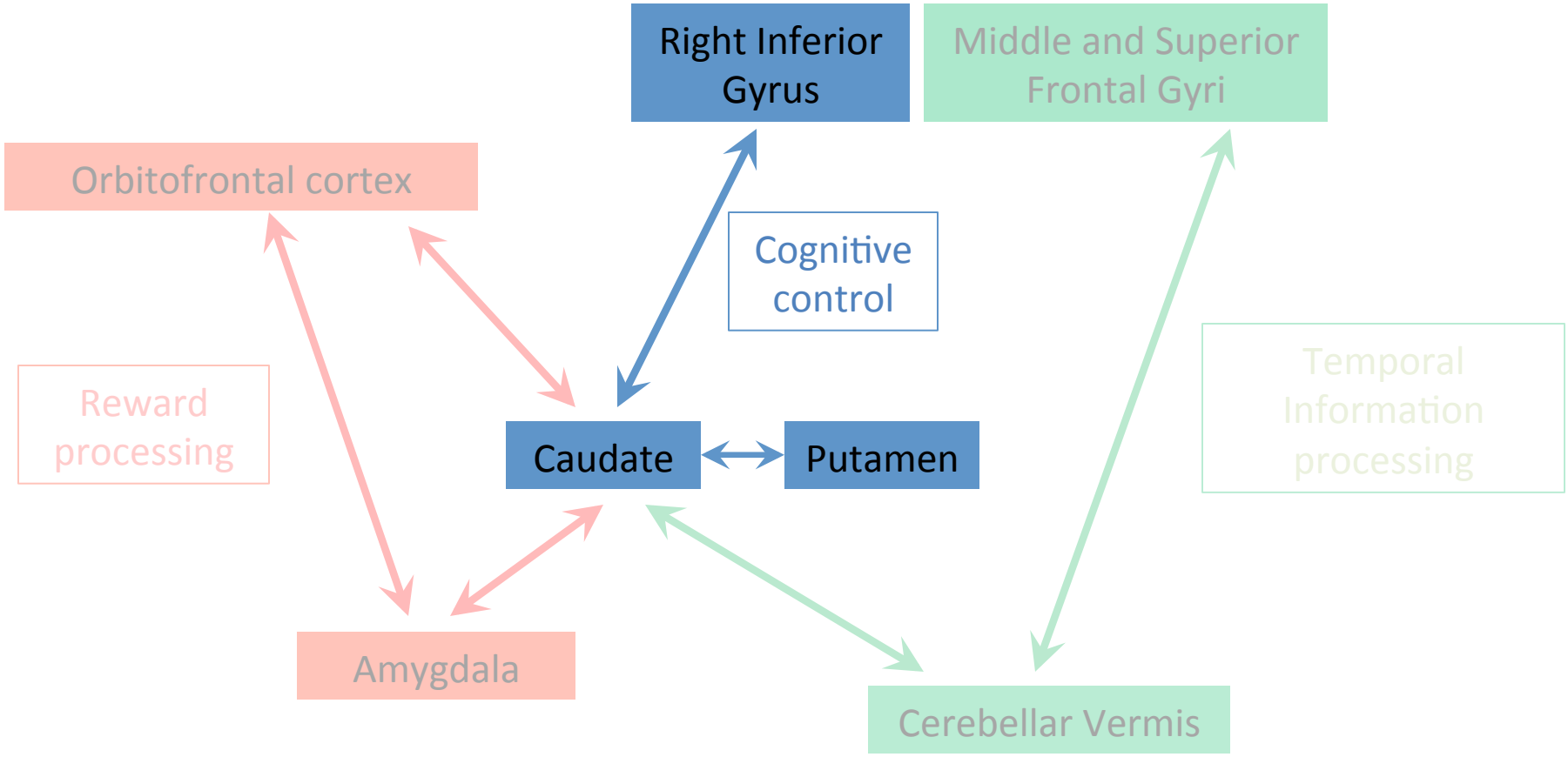
FIGURE 5. Developmental Trajectory of Left Anterior Hemisphere in ADHD Patients With Better and Worse Outcomes and Healthy Comparison Subjects[a]

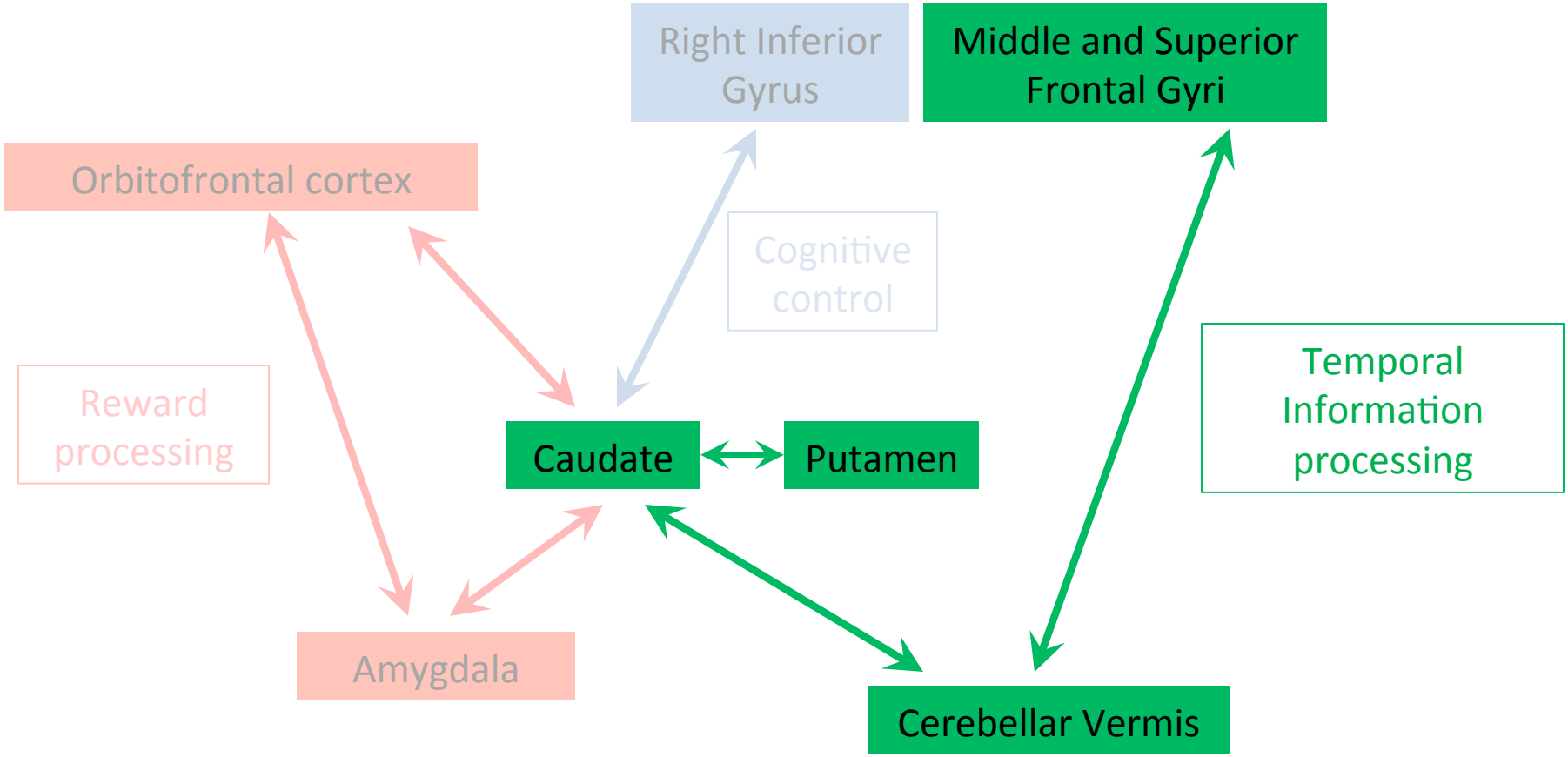


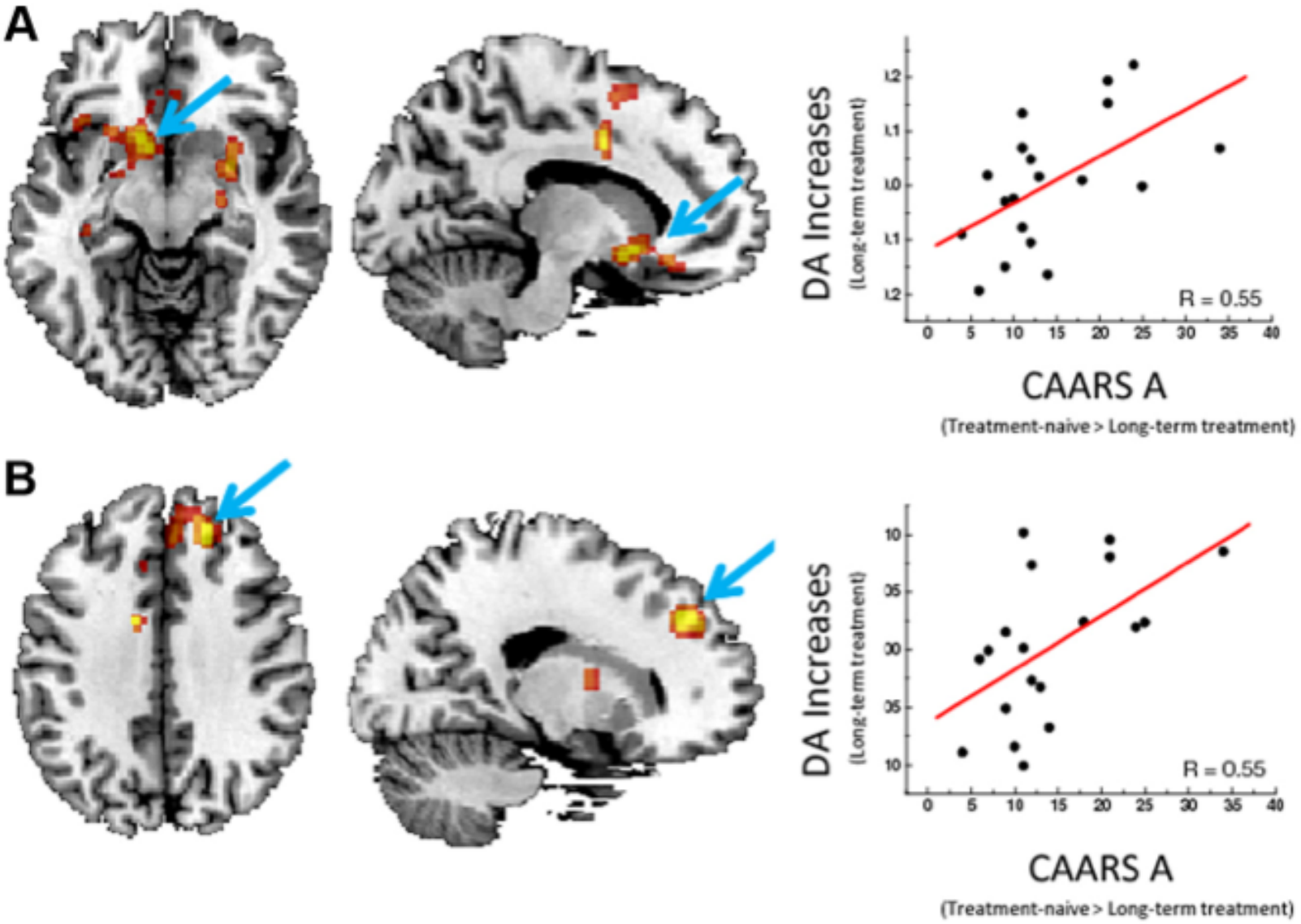
Mackie et al. *Am J Psychiatry*. 2007 164:647-655.

Neuro-anatomia funzionale dell'ADHD: focus sulle dimensioni di interesse clinico


Right Inferior Gyrus
Middle and Superior Frontal Gyri
Orbitofrontal cortex
Cognitive control
Reward processing
Caudate
Putamen
Temporal Information processing
Amygdala
Cerebellar Vermis

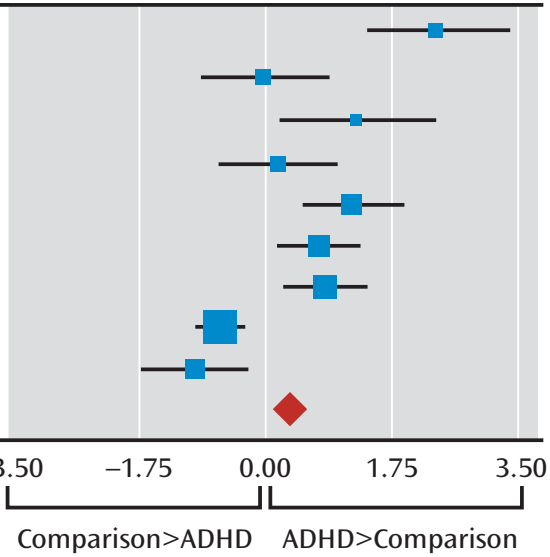

Right Inferior Gyrus
Middle and Superior Frontal Gyri
Orbitofrontal cortex
Cognitive control
Reward processing
Temporal Information processing
Caudate
Putamen
Amygdala
Cerebellar Vermis


Right Inferior Gyrus
Middle and Superior Frontal Gyri
Orbitofrontal cortex
Cognitive control
Reward processing
Temporal Information processing
Caudate
Putamen
Amygdala
Cerebellar Vermis



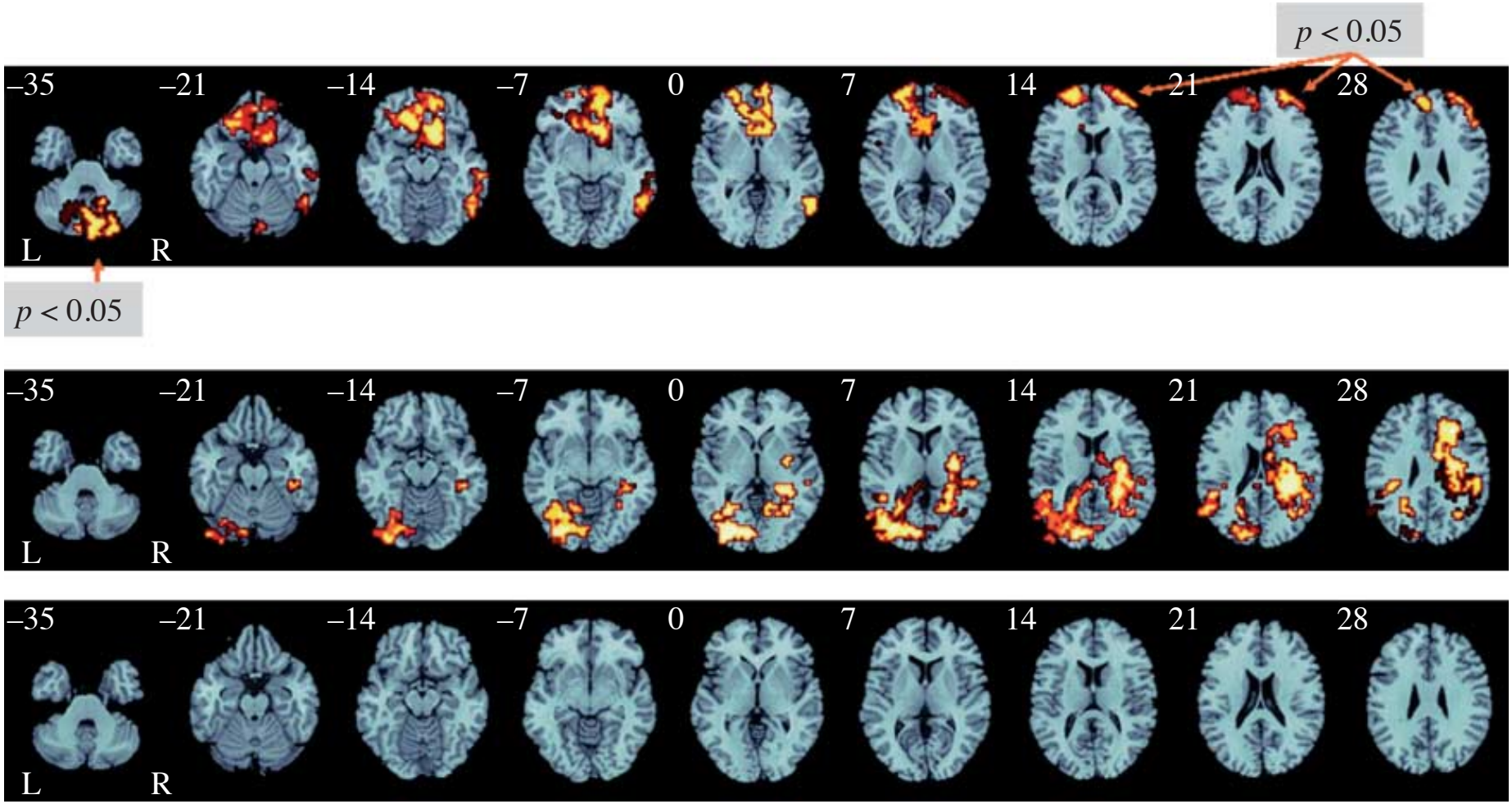
Volkow et al. *Journal of Neuroscience*. 2012 32:841-849.

Study	Hedges' g	SE	Variance	Lower Limit	Upper Limit	z	p
Dougherty et al., 1999 (16)	2.37	0.52	0.27	1.35	3.39	4.57	<0.01
van Dyck et al., 2002 (17)	–0.02	0.45	0.20	–0.90	0.86	–0.05	0.97
Cheon et al., 2004 (32)	1.26	0.55	0.30	0.19	2.33	2.30	0.03
Jucaite et al., 2005 (33)	0.16	0.41	0.17	–0.65	0.97	0.39	0.70
la Fougere et al., 2006 (34)	1.19	0.36	0.13	0.48	1.91	3.29	0.001
Larisch et al., 2006 (35)	0.75	0.32	0.10	0.12	1.38	2.34	0.02
Spencer et al., 2007 (36)	0.81	0.30	0.09	0.22	1.40	2.70	0.007
Volkow et al., 2009 (10)	–0.62	0.21	0.04	–1.02	–0.21	–2.98	0.003
Hesse et al., 2009 (37)	–0.99	0.37	0.14	–1.72	–0.26	–2.64	0.008
Overall	0.23	0.11	0.01	0.01	0.46	2.03	<0.05



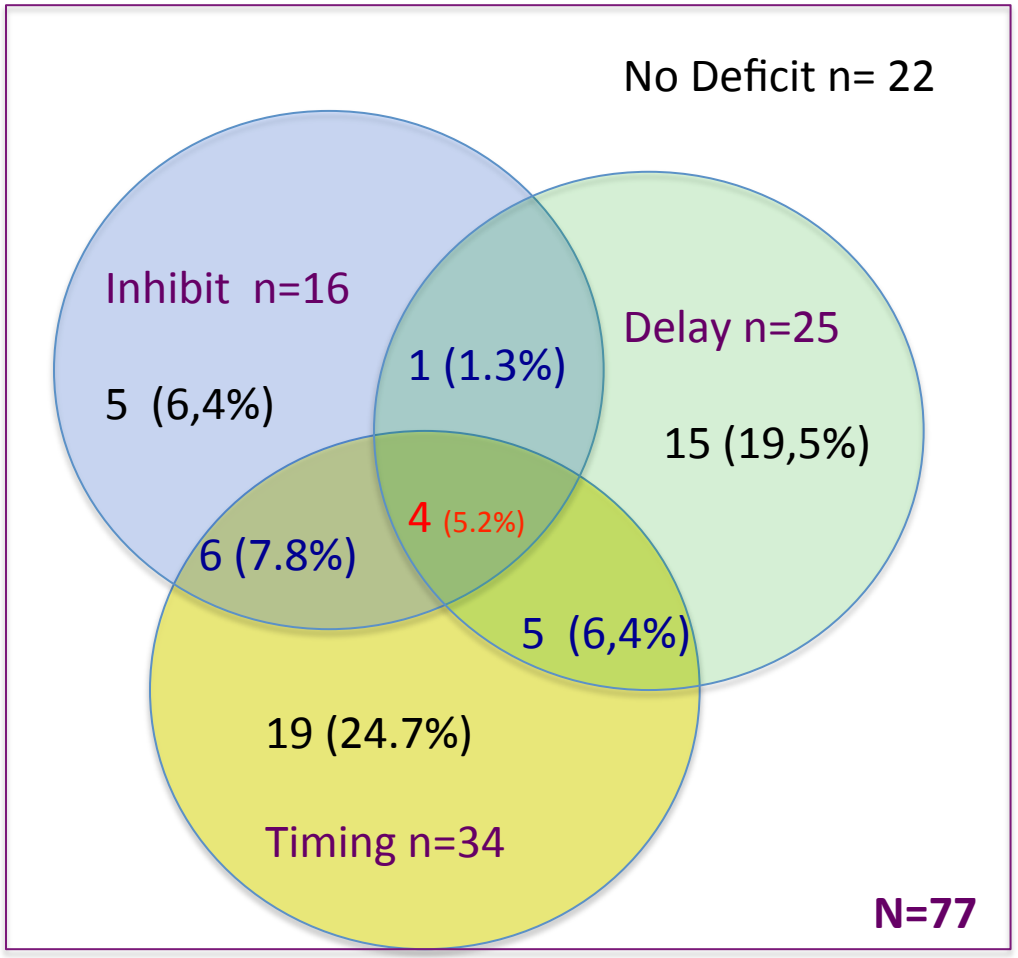
- The meta-analysis and meta-regression analysis show that striatal dopamine transporter levels in ADHD depend on chronic psychostimulant treatment;
- Medication-naive patients have low striatal dopamine transport- er levels, whereas patients receiving long-term medication have high levels;
- The previously reported high dopamine transporter density in ADHD patients may potentially represent up-regulation secondary to chronic administration of psychostimulants, rather than primary pathophysiology of ADHD.

Fusar-Poli et al. 2012



Rubia et al. *Phil Trans R Soc B*. 2009 364:1919-1931.

Beyond the Dual Pathway Model: Evidence for the Dissociation of Timing, Inhibitory, and Delay-Related Impairments in Attention-Deficit/Hyperactivity Disorder



Familial effect for inhibition and timing less for delay

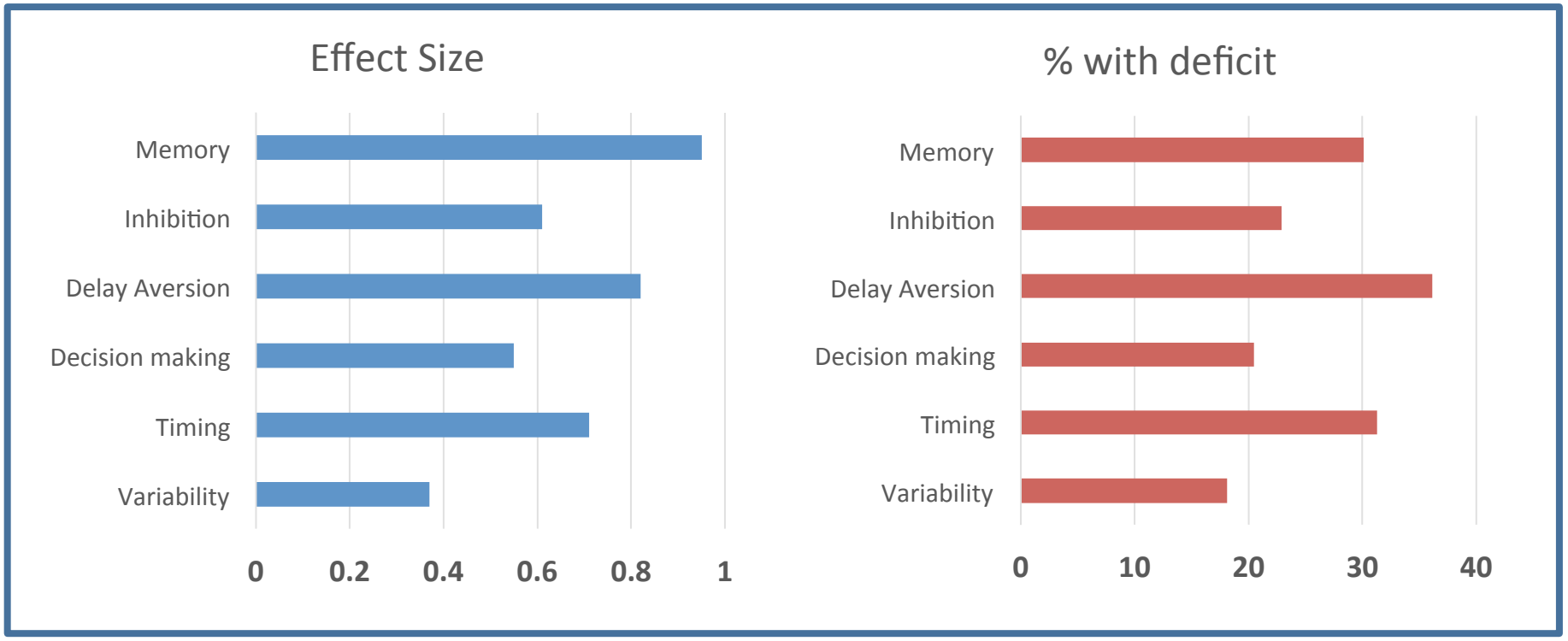
Sibling impairment intermediate between controls and probands
No evidence of cosegregation

Timing associated with reading problems
Delay associated with low IQ

Sonuga-Barke et al. *JAACAP 2010*

Neuropsychological Deficits in Treatment-Naïve Boys with ADHD

- 83 Drug naïve boys (6 – 12 years) with DSM IV ADHD
- 66 Healthy control boys matched for age
- All completed all tasks in one session with breaks
- Tasks were counterbalanced across two orders



Coghill, Seth, Matthews, 2013

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
Journal of Child Psychology and Psychiatry 54:6 (2013), pp 619–627

Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits

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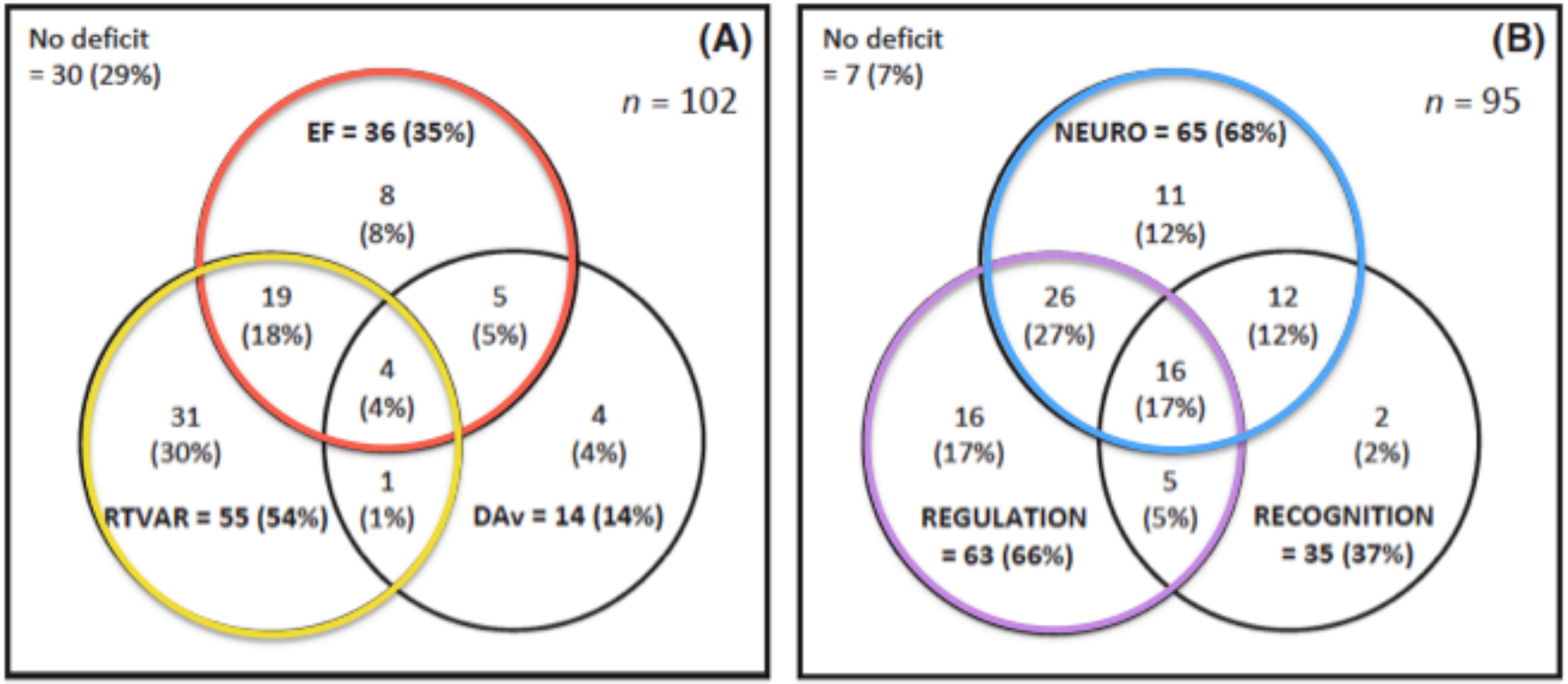
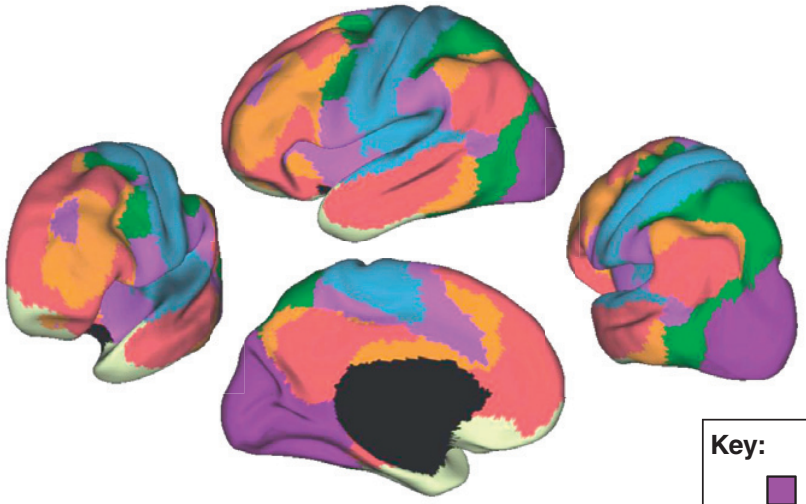
[1]Department of Clinical Neuroscience and Stockholm Brain Institute, Karolinska Institutet, Stockholm, Sweden;
[2]Department of Psychology, Uppsala University, Uppsala, Sweden



EF = Executive functioning (i.e., working memory, inhibition, shifting), RTVAR = Reaction time variability, DAv = Delay aversion, NEURO = Neuropsychological functioning, REGULATION = Emotion regulation, RECOGNITION = Emotion recognition

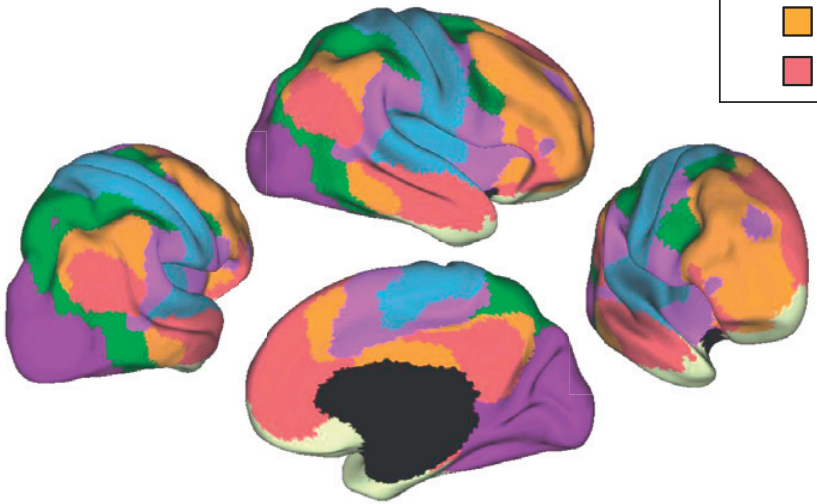
Proportion of ADHD cases with neuropsychological impairments (A) or impairments in neuropsychological and emotional functioning (B)



Left hemisphere

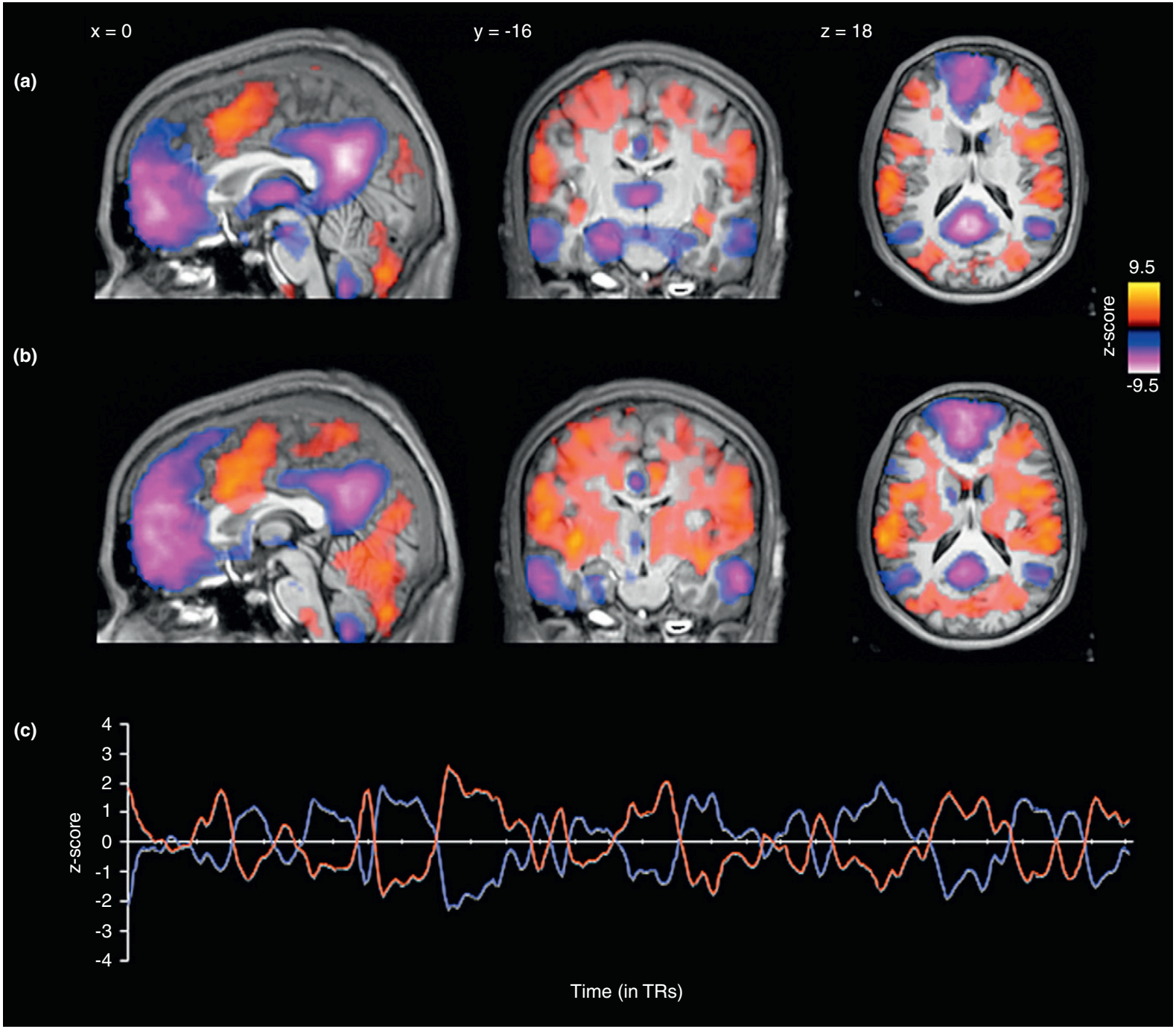
Key:

- Visual
- Somatomotor
- Dorsal attention
- Ventral attention
- Limbic
- Frontoparietal
- Default



Right hemisphere

Castellanos & Proal 2012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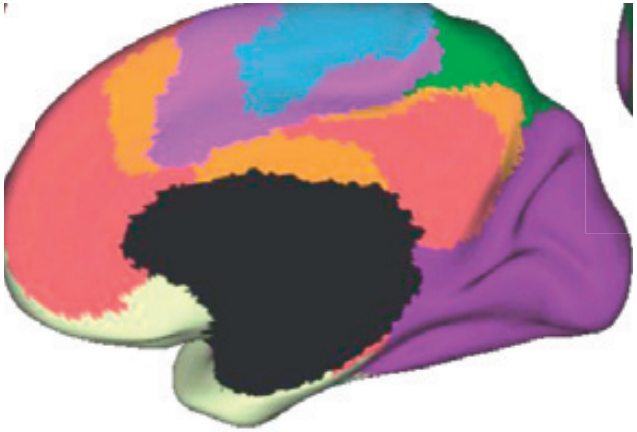
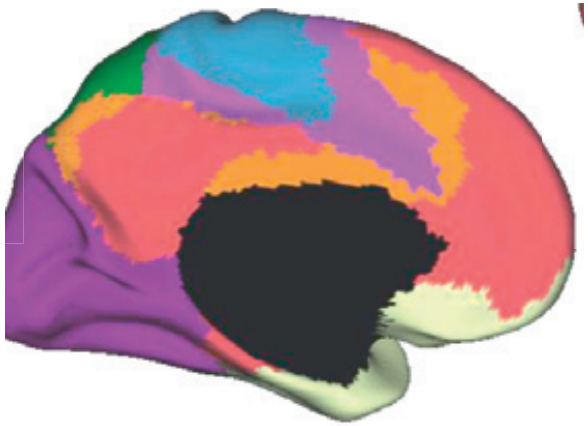
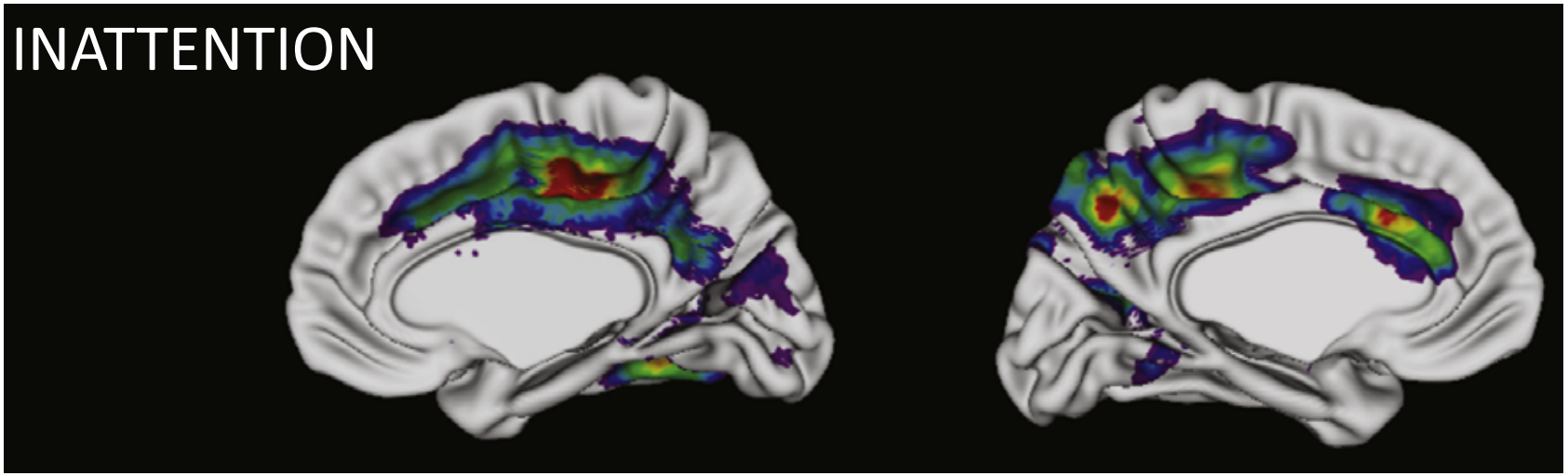
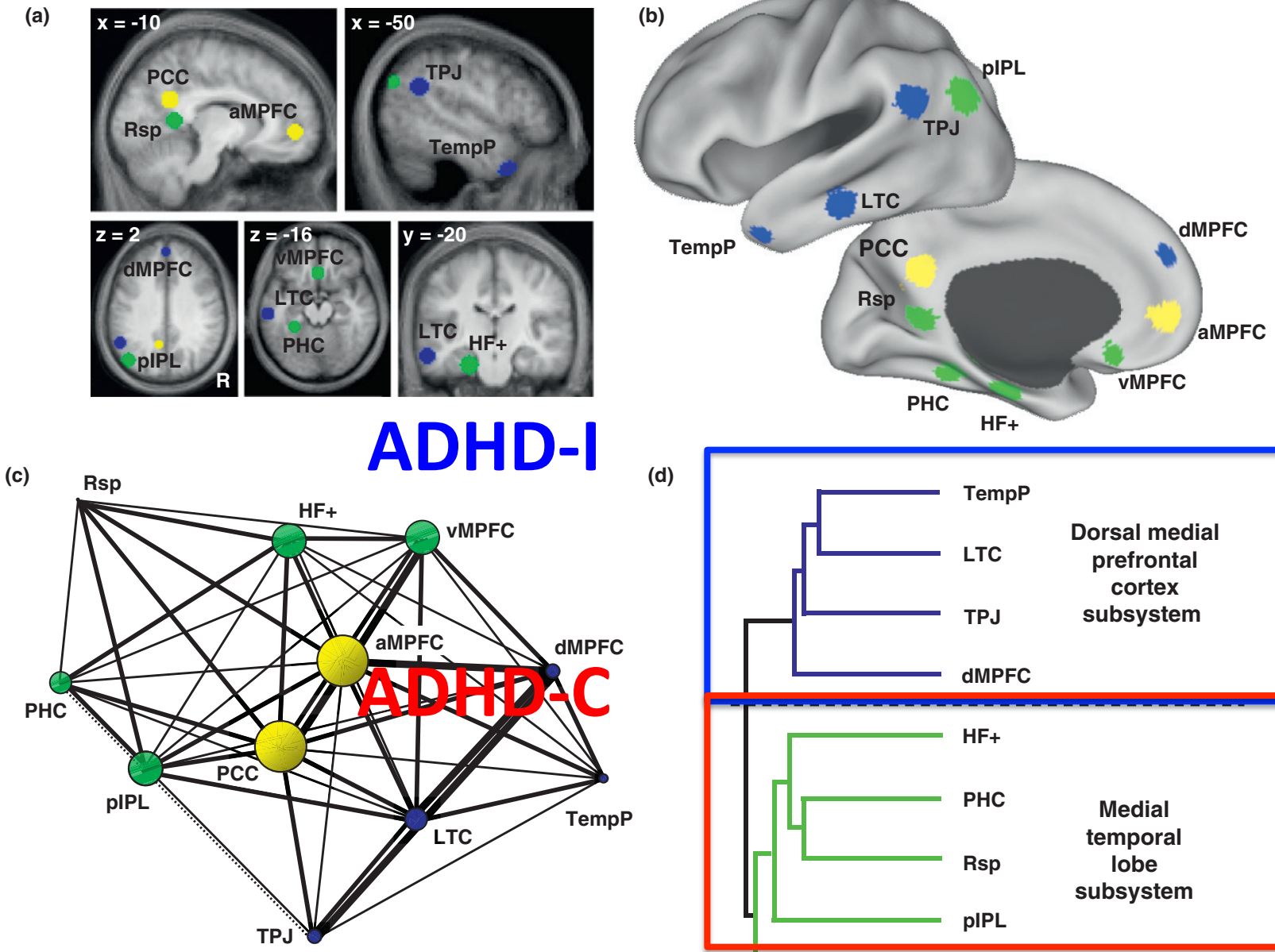
y = -16
z = 18
(a)
(b)
9.5
z-score
-9.5
(c)
4
3
2
1
0
-1
-2
-3
-4
z-score
Time (in TRs)






INATTENTION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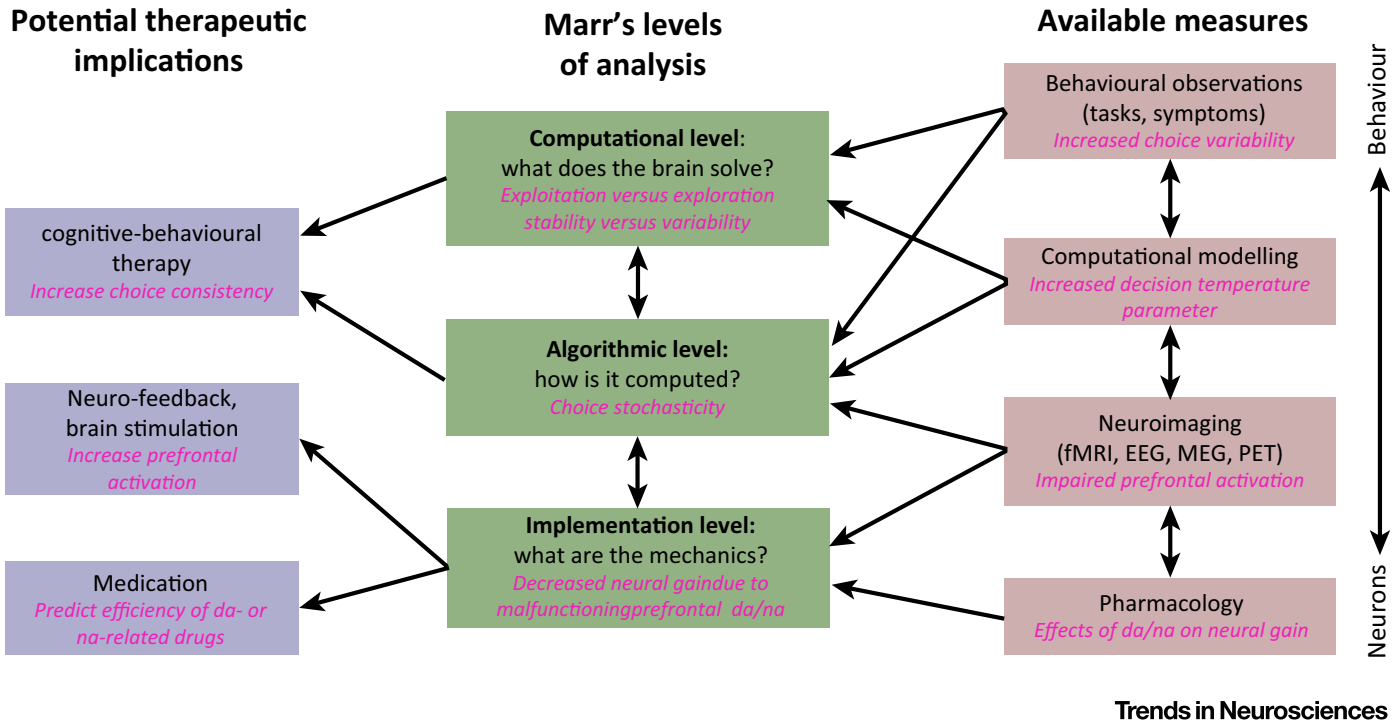
PCC
Rsp
aMPFC
x = -50
TPJ
TempP
z = 2
dMPFC
pIPL
R
z = -16
vMPFC
LTC
PHC
y = -20
LTC
HF+
(b)
pIPL
TPJ
LTC
TempP
dMPFC
PCC
Rsp
aMPFC
vMPFC
PHC
HF+
ADHD-I
(c)
Rsp
HF+
vMPFC
aMPFC
dMPFC
PHC
ADHD-C
PCC
pIPL
LTC
TempP
TPJ
Key:
0.000 - 0.249
0.250 - 0.449
0.500 - 0.749
(d)
TempP
LTC
TPJ
dMPFC
Dorsal medial prefrontal cortex subsystem
HF+
PHC
Rsp
pIPL
Medial temporal lobe subsystem
vMPFC

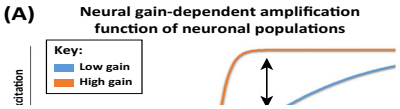
Approccio computazionale: una nuova maniera di superare i modelli classici?



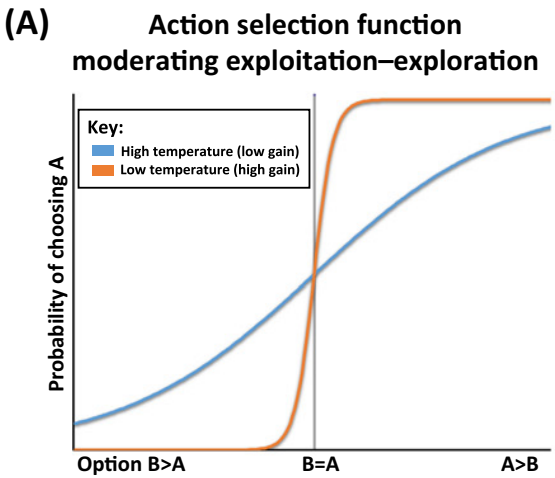
Hauser et al. 2016

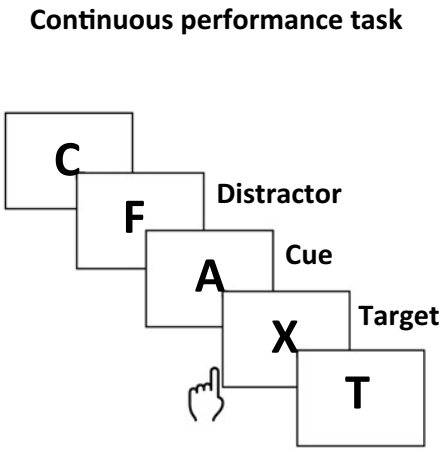
DATI COMPORTAMENTALI ⟷ **MODELLO MATEMATICO** ⟷ **CIRCUITISTICA**

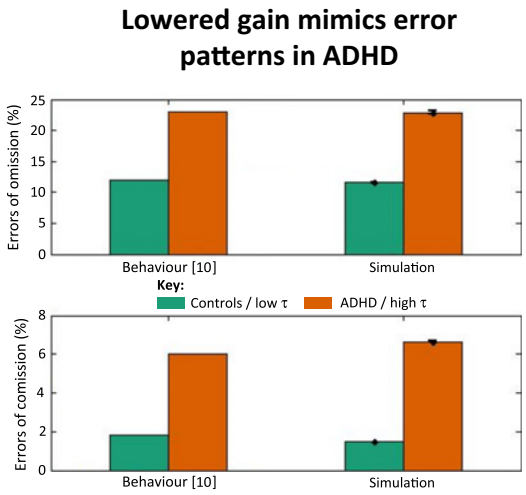
Aproccio Computazionale



Generare ipotesi di ricerca

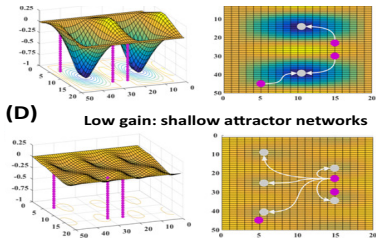






Trends in Neurosciences

con caratteristiche neurobiologiche definite

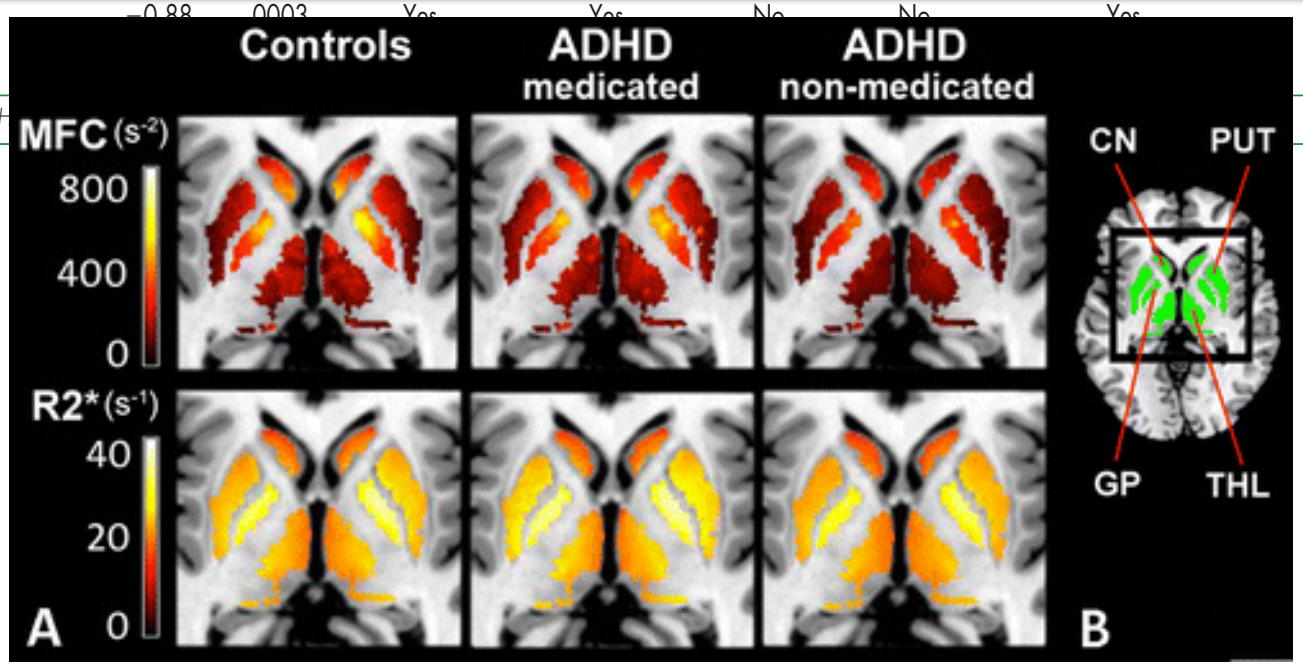


“Nuovi” markers

TABLE 1 Summary of Significant Standard Mean Difference Meta-analyses Findings

Source	Biomarkers Symbol	d	p	Significant after Bonferroni correction?	Significant Heterogeneity?	Publication Bias?	Associated with Drug Response?	Associated with Symptoms Severity?	Associated with Neurophysiological/ Cognitive functioning?
Urine	NE	0.41	.003	Yes	No	No	Yes: ↓	Yes	No
Urine	MHPG	−0.43	.002	Yes	Yes	No	Yes: ↓	Yes	No
Platelet	MAO	−1.05	<.0001	Yes	Yes	No	Yes: ↑	Yes	No
Urine	NM	0.51	.05	No	Yes	No	No	No	No
Urine	M	0.45	.009	No	No	No	No	No	No
Serum	ferritin (iron stores)	−0.86	.01	No	Yes	No	No	Yes	Yes
Serum/plasma/urine	Zn	−0.88	.0003	Yes	Yes	No	No	Yes	Yes
Saliva	Cortisol								No

Note: MAO = Monoamine oxidase; MH



Adisetiyo et al. 2014

Considerazioni conclusive e di utilita' nella pratica clinica a partire dai dati di ricerca

- Al momento non esistono affidabili parametri neuro-biologici in grado di aumentare l'accuratezza diagnostica ne' di imporsi come indici prognostico-terapeutici nell'ADHD in eta' evolutiva o nell'adulto;
- Tuttavia, recenti conoscenze neurobiologiche fanno ipotizzare che la modulazione dell'outcome nell'ADHD, anche nell'adulto, e' principalmente funzione del rimodellamento corticale e dei rapporti della corteccia con le strutture sotto-corticali;
- Poiche' la scelta del trattamento farmacologico piu' adatto passa dal saper leggere in maniera dinamica l'interazione sindromica dimensionale e lo stadio della traiettoria evolutiva al quale ogni paziente viene intercettato, sono giustificati studi di imaging multi-modale e di biomarkers neuro-radiologici e non neuro-radiologici che riflettano aspetti dinamici-longitudinali-neuroevolutivi utili in senso diagnostico, prognostico e terapeutico.

Grazie per…l'Attenzione!