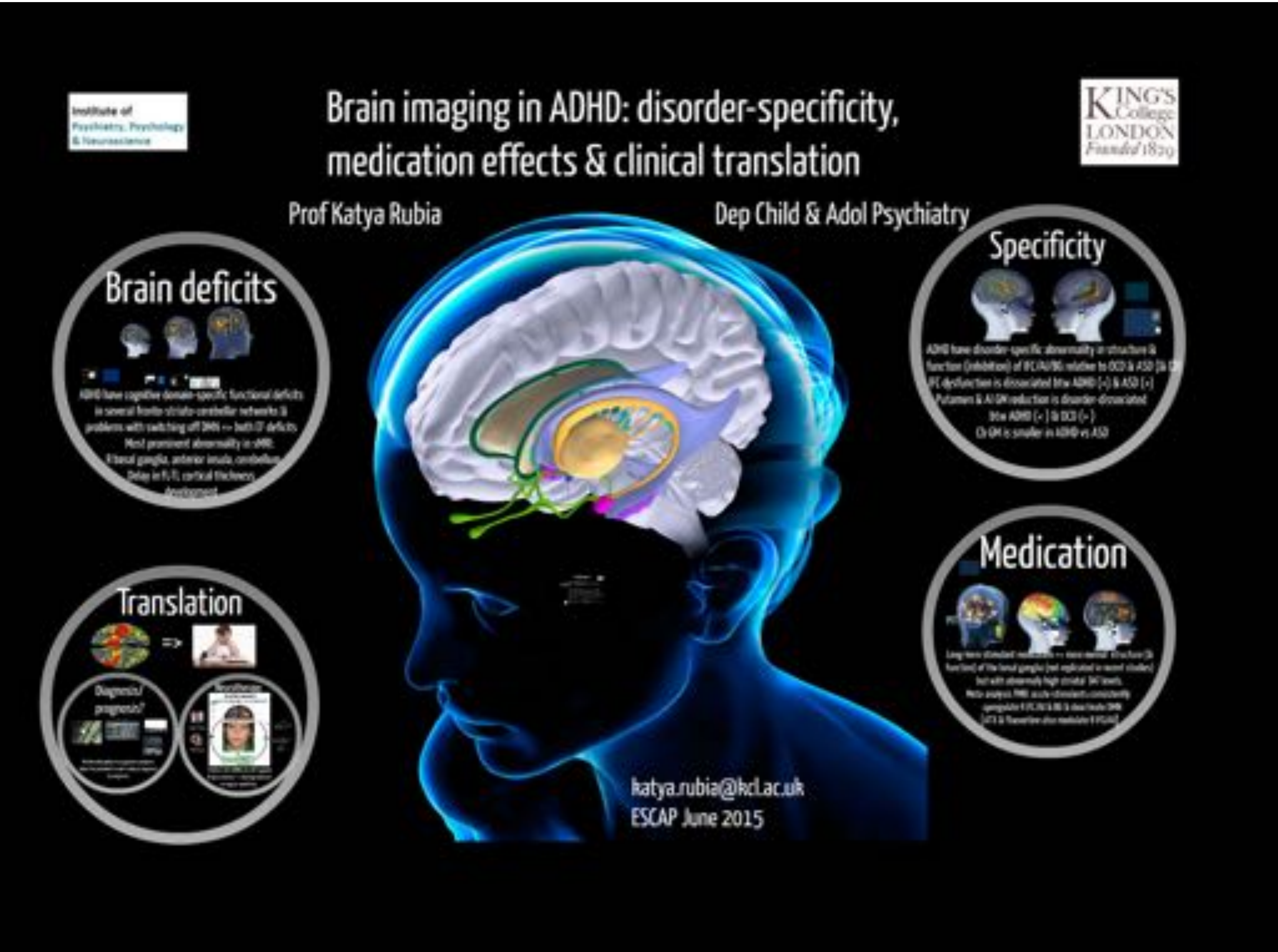
Brain imaging in ADHD: disorder-specificity, medication effects & clinical translation
Prof Katya Rubia
Dep Child & Adol Psychiatry
Institute of Psychiatry, Psychology & Neuroscience
KING'S College LONDON Founded 1829
Brain deficits
Specificity
Medication
Translation
katya.rubia@kcl.ac.uk
ESCAP June 2015

Institute of Psychiatry, Psychology & Neuroscience

Brain imaging in ADHD: disorder-specificity, medication effects & clinical translation

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Brain deficits

ADHD have cognitive domain-specific functional deficits in several fronto-striato-cerebellar networks & problems with switching off DMN <-> both FF deficits

Most prominent abnormality in sMRI

R basal ganglia, anterior insula, cerebellum

Delay in R-FL cortical thickness

Amalgamant

Specificity

ADHD have disorder-specific abnormality in structure & function (inhibition) of RFC/R/L/RG relative to OCD & ASD (& CD)

AFC dysfunction is dissociated btw ADHD (-) & ASD (-)

Putamen & Al GM reduction is disorder-dissociated btw ADHD (-) & OCD (-)

Cb GM is smaller in ADHD vs ASD

Translation

Diagnosis/ prognosis?

Medication

Long term stimulant medication <-> more normal structure (& function) of the basal ganglia (not replicated in recent studies) but with abnormally high striatal DAT levels.

Meta-analysis fMRI: acute stimulants consistently upregulate R FC/N & BG & deactivate DMN

[ATX & Fluoxetine also modulate R IFG/sFC

katya.rubia@kcl.ac.uk

ESCAP June 2015

Disclosures

Grant by Lilly for another project.
Speaker's honoraria from Lilly, Shire & Medice

Brain deficits

ADHD have cognitive domain-specific functional deficits in several fronto-striato-cerebellar networks & problems with switching off DMN => both EF deficits

Most prominent abnormality in sMRI:
R basal ganglia, anterior insula, cerebellum

Delay in FL-TL cortical thickness development

Attention Deficit Hyperactivity Disorder

Clinical manifestation

Age-inappropriate:

- Inattention
- Motor hyperactivity
- Impulsivity

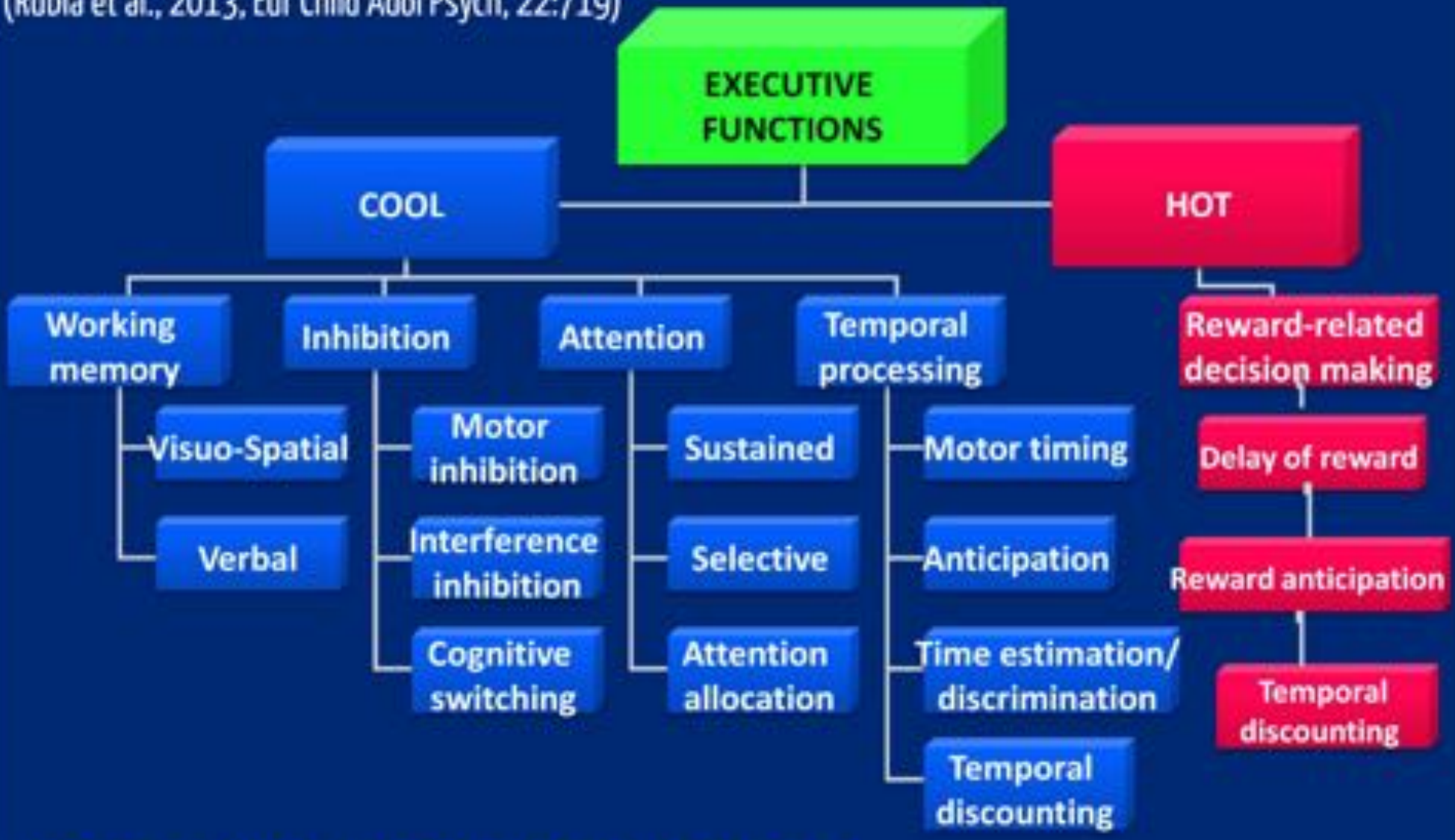
Prevalence: 5% worldwide (Polanczik et al. 2007)
Persistence into adulthood: 15-65%

Ratio: Male/Female: 6:1

Treatment: once diagnosed – 70% of severe cases treated with psychostimulants (Methylphenidate)

Neuropsychological deficits in ADHD

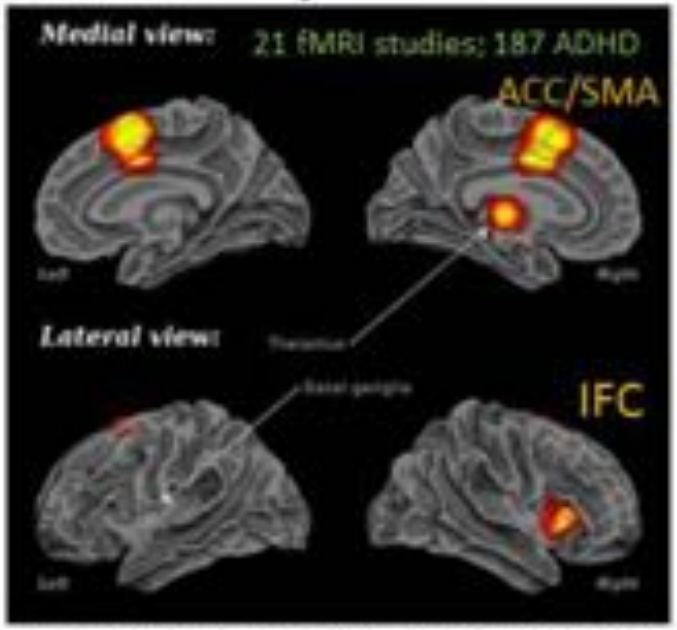
Mediated by late developing fronto-striatal networks that develop progressively btw childhood & adulthood (Rubia et al., 2013, Eur Child Adol Psych, 22:719)



Rubia et al., 2011, Biol Psych 15 69 (12): e69-87

Meta-analyses of whole brain fMRI studies in ADHD

A. Meta-analysis of inhibition



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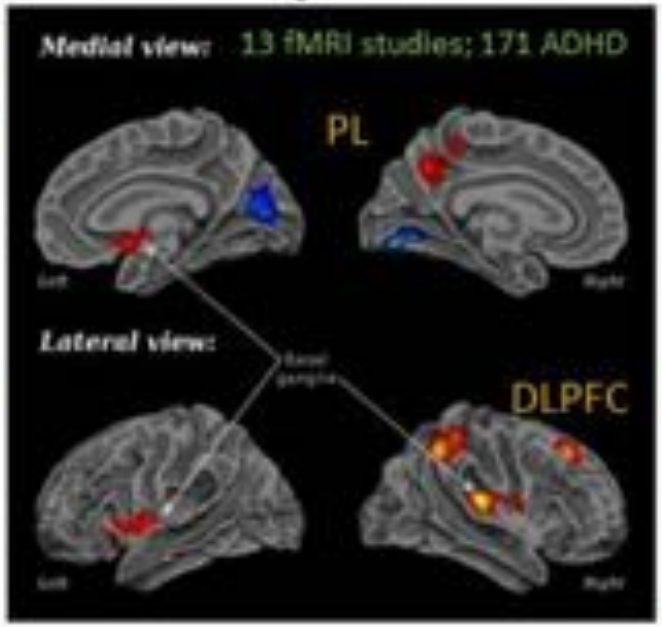
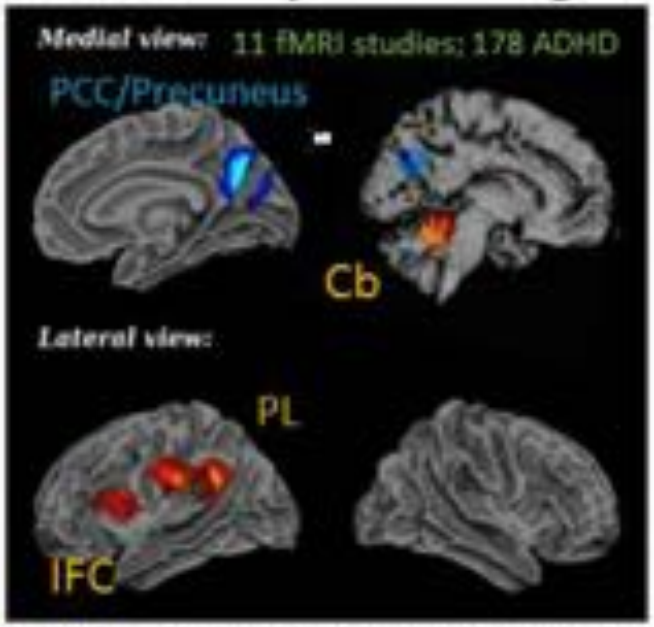
JAMA Psychiatry 70: 185.

B. Meta-analysis of attention



C. Meta-analysis of timing

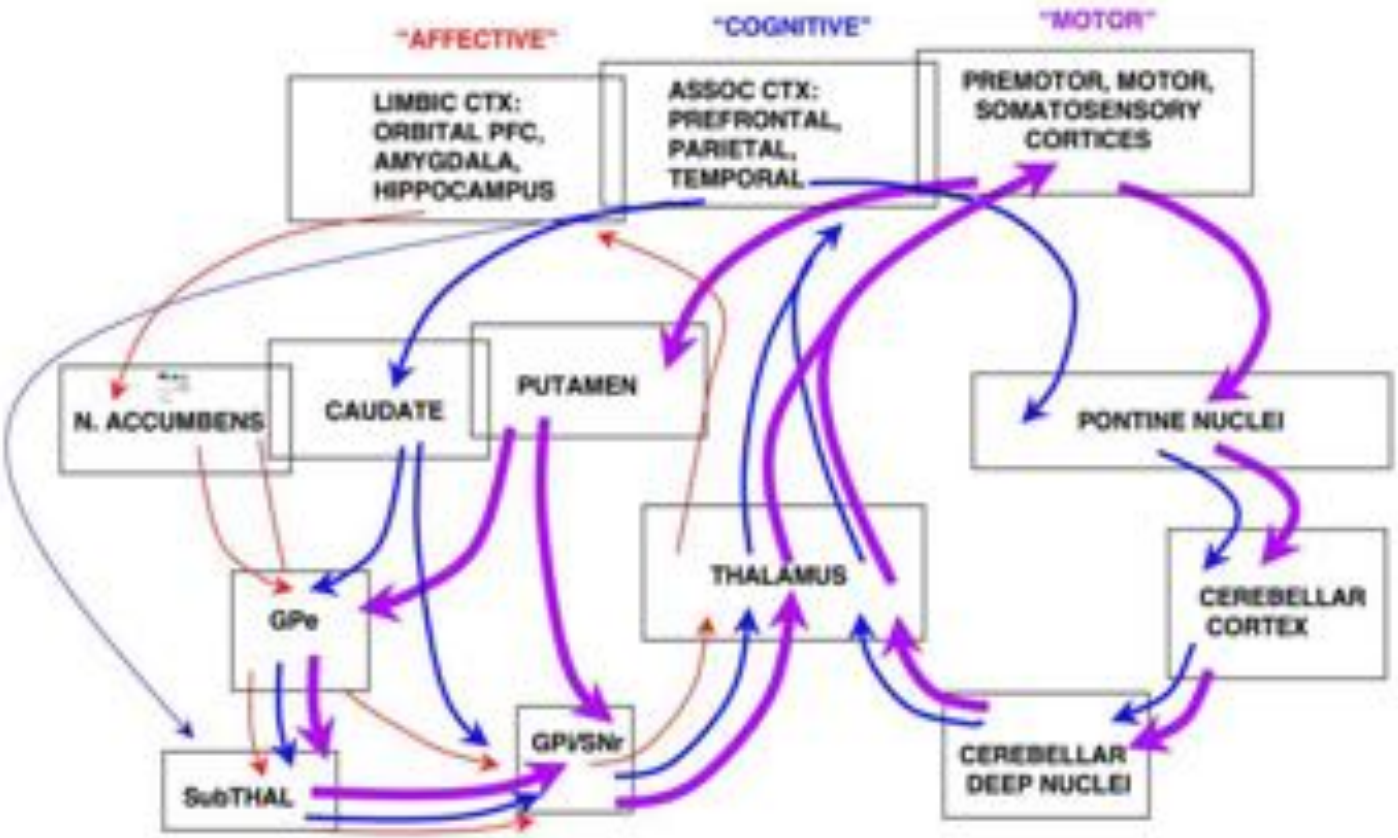


Hart et al., Neurosci Behavi Brain Res 36:2248.

Domain-specific functional deficits in different fronto-striatal & fronto-cerebellar circuits

Rubia et al., 2014, Exp Rev Neurother, 14:519-38

Fronto-striato-cerebellar circuits



Arnsten & Rubia 2012; JAACAP, 51(4):356-67

Meta-analysis of ROI studies of reward anticipation

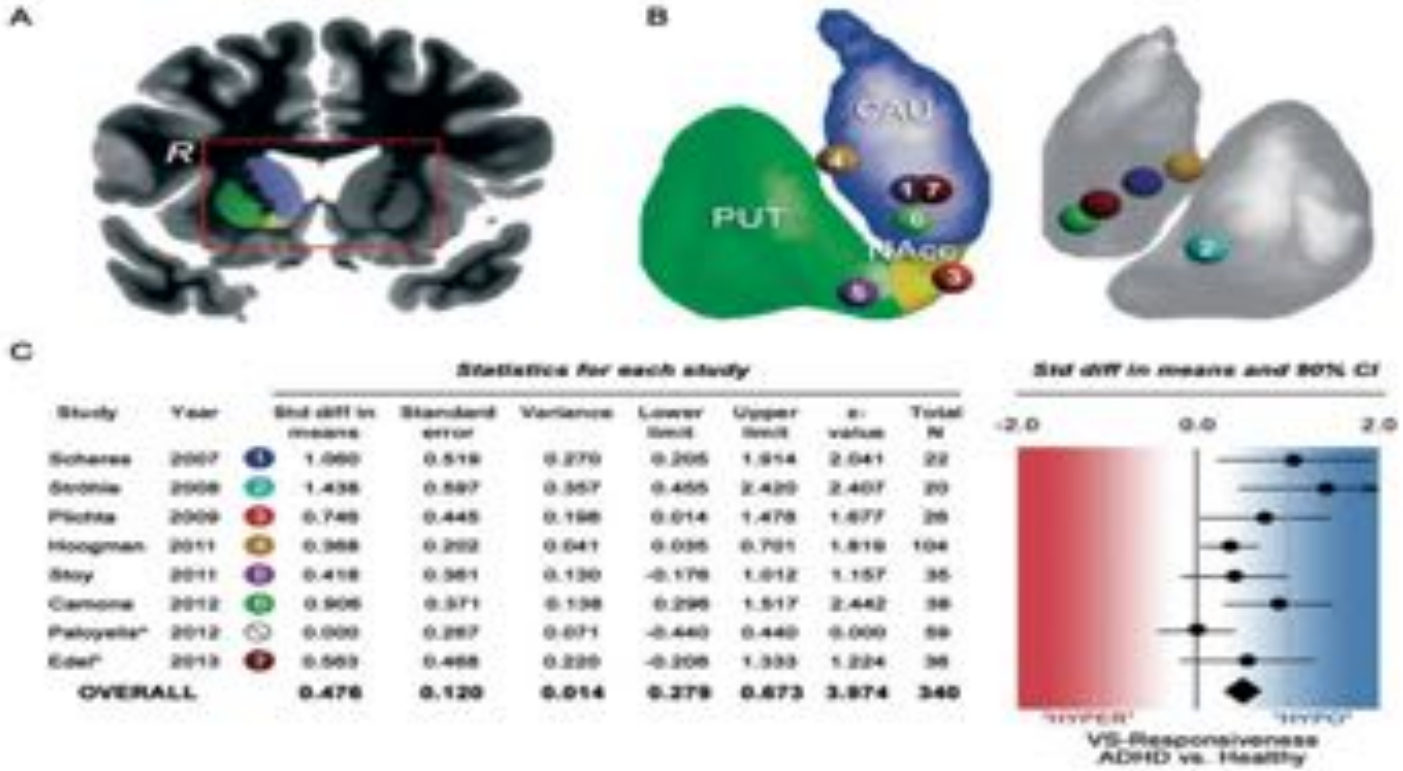


Fig. 1 Panel A shows the anatomical area of interest, i.e. the ventral-striatum (VS) including nucleus caudate (CAU), putamen (PUT) and the nucleus accumbens (NAcc). The right hemisphere is indicated by an "R". Panel B is a 3-D representation of the striat...

Michael M. Plichta , Anouk Scheres

Ventral–striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: A meta-analytic review of the fMRI literature

Neuroscience & Biobehavioral Reviews null 2013 null

http://dx.doi.org/10.1016/j.neubiorev.2013.07.012

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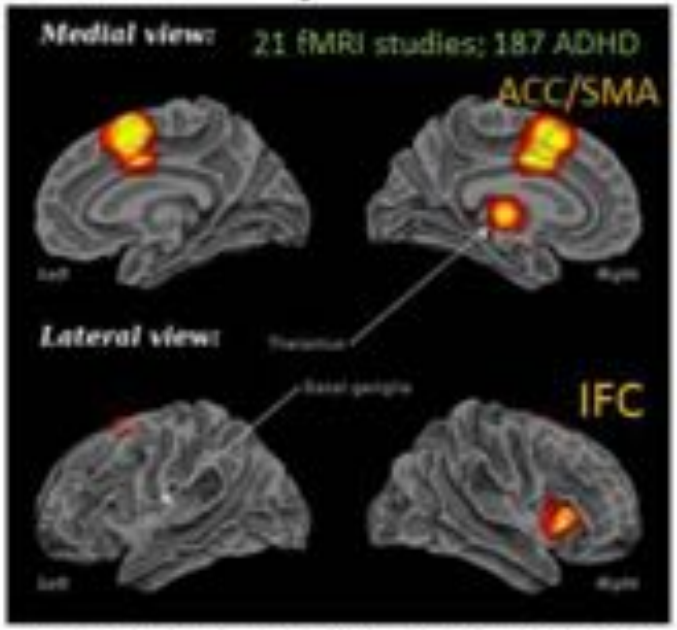

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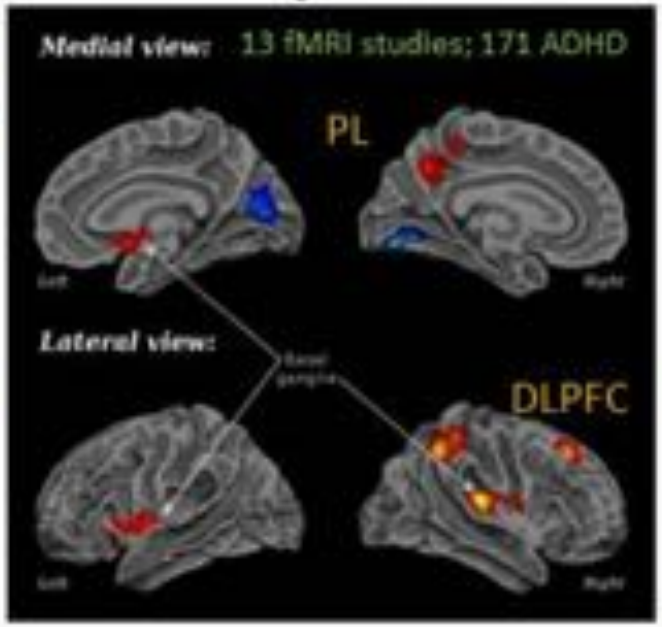

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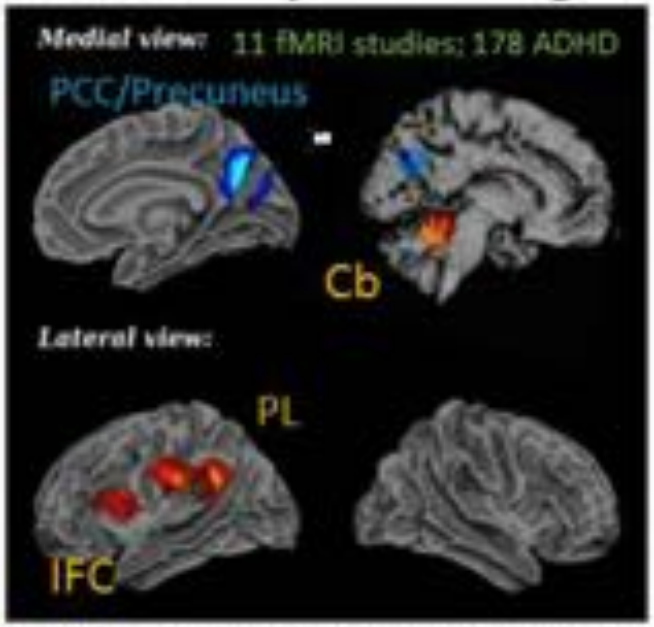

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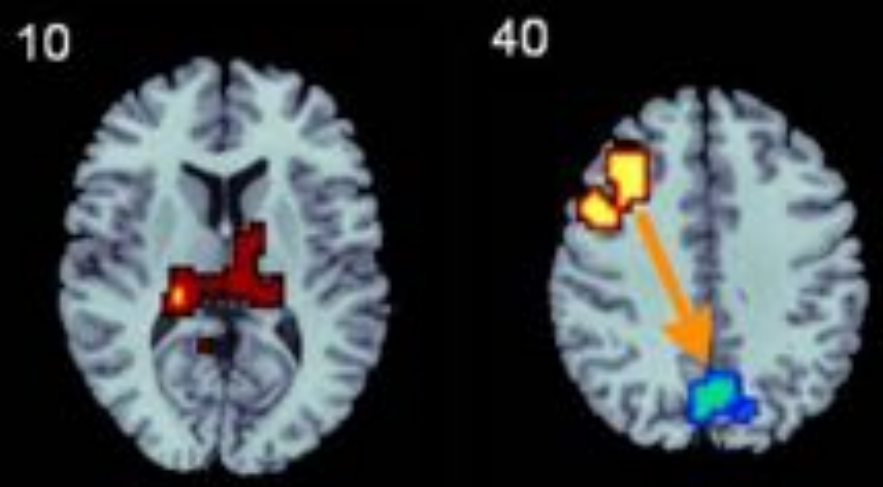
Domain-specific functional deficits in different fronto-striatal & fronto-cerebellar circuits

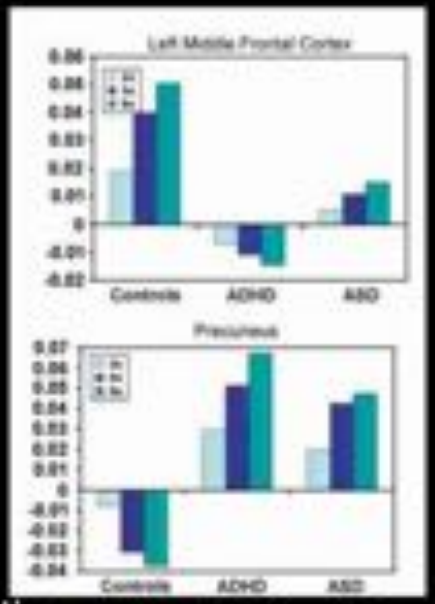
Rubia et al., 2014, Exp Rev Neurother, 14:519-38

Reduced deactivation of the default mode network

Parametric sustained attention task:
3 difficult levels

C > ADHD





- Performance: ADHD impaired in response variability => poor concentration
- With progressive attention load, PFC > activated in controls, not ADHD
- With progressive attention load, DMN > deactivated in controls not ADHD
- DMN anti-correlated with PFC activation

Christakou, Murphy, Chantiluke, Rubia, Molecular Psychiatry, 2013: 18(2):236-44

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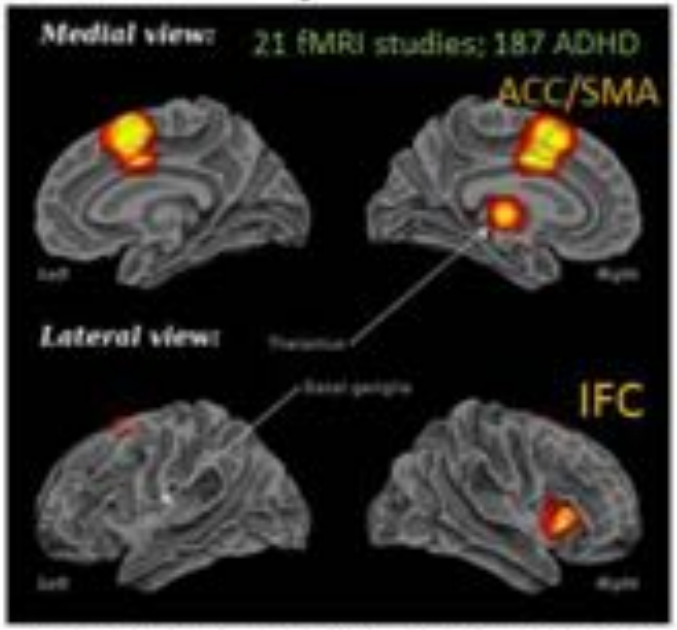

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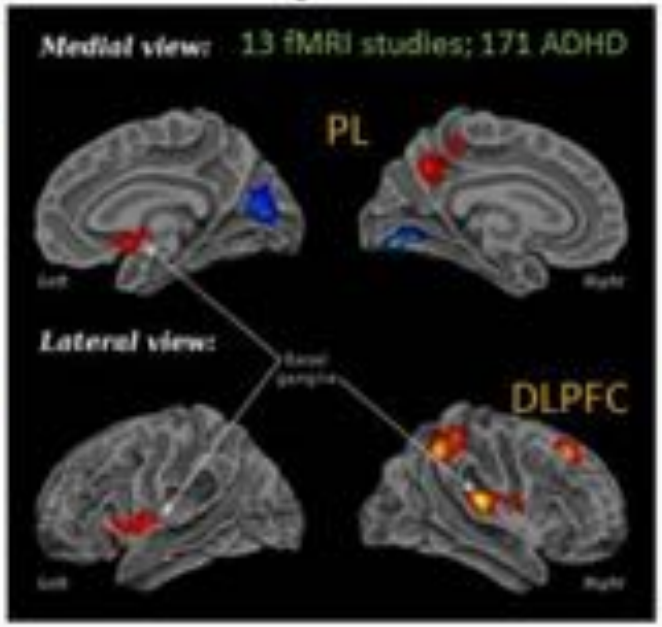

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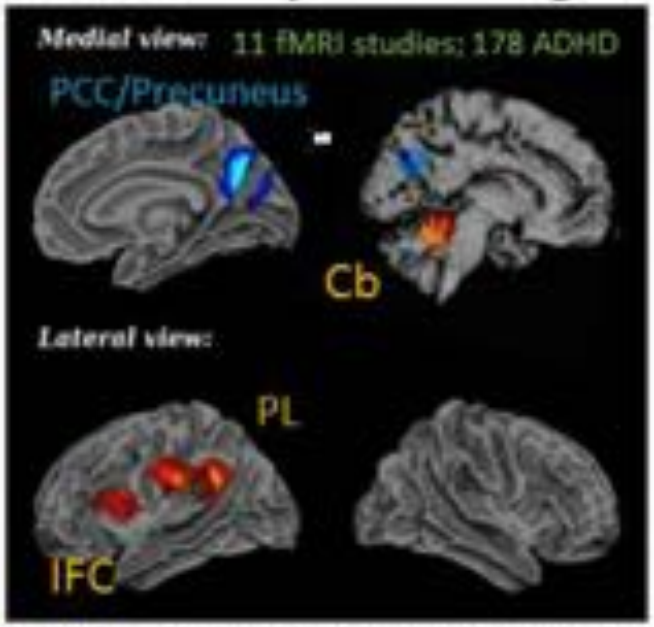

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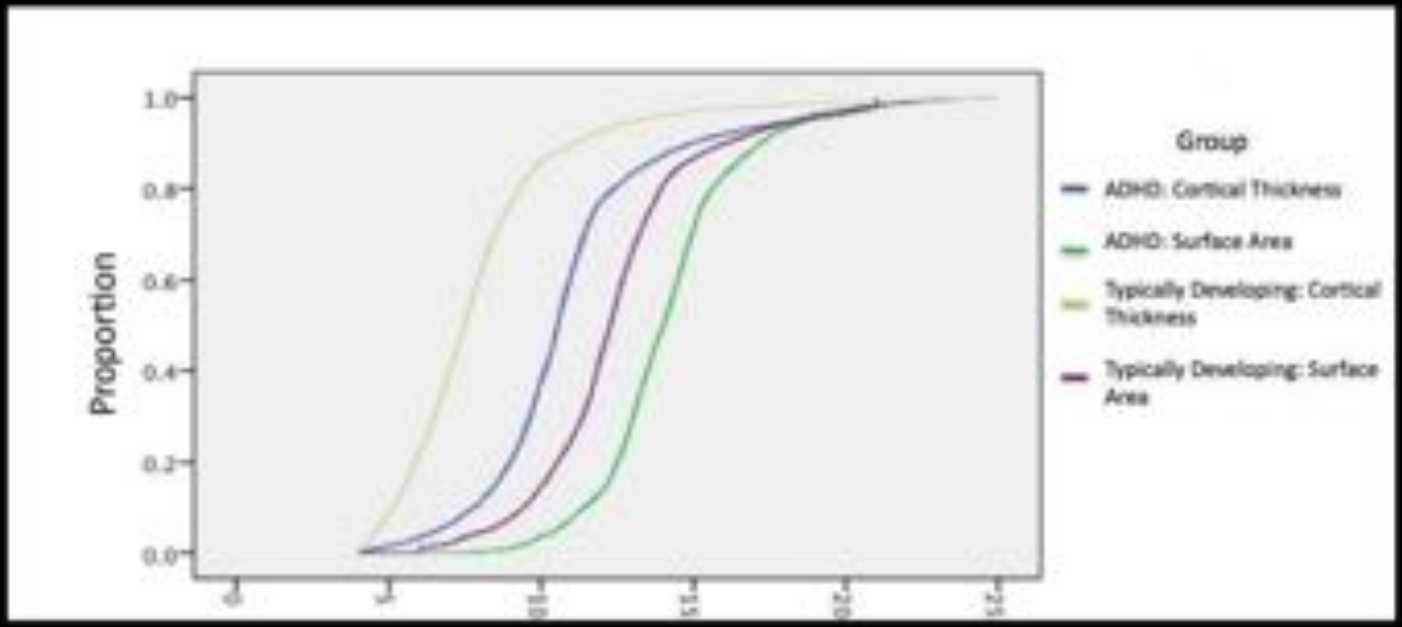
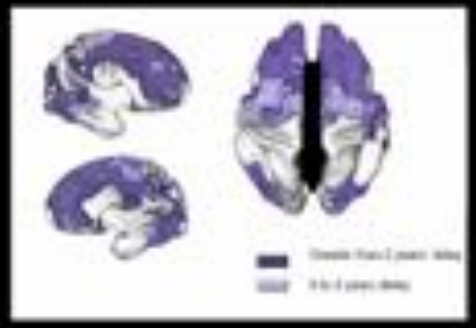
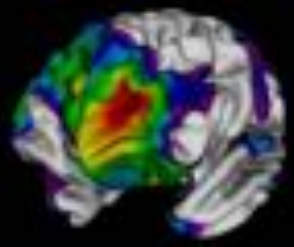
Delay of structural development





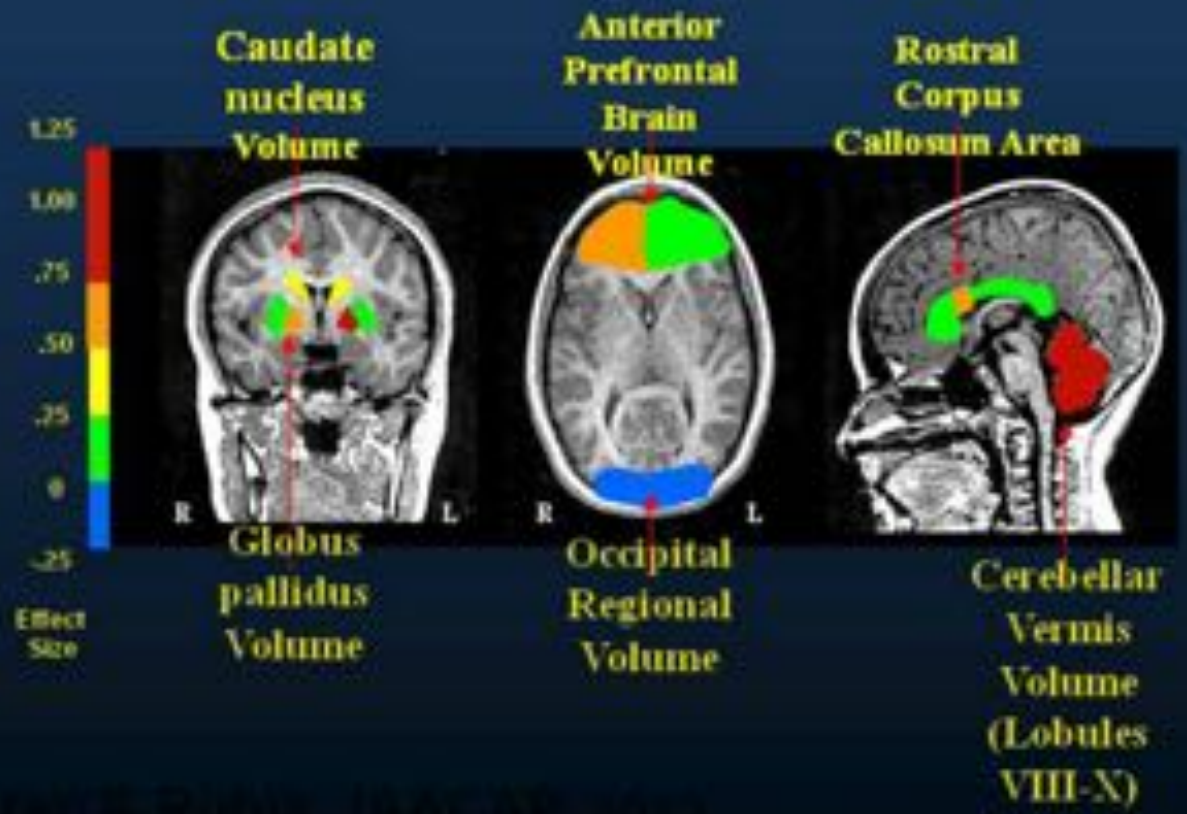


Peak of cortical thickness delayed
in FL up to 5 yrs
in TL (sup & middle) by 4 yrs
N = 223
Peak of surface area delayed by up to 2 years
in FL, up to 1 year in PL, TL

Shaw et al., 2007, PNAS
Shaw et al., 2012, Biol Psych

Meta-analysis of structural MRI

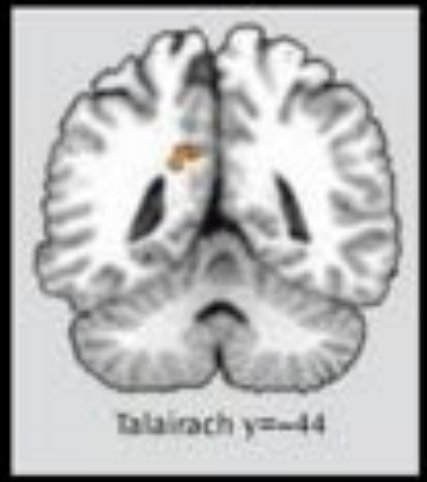
Regions of interest meta-analysis



Effect sizes of MRI studies of ADHD Brain Morphometry (Swanson et al., 2004, in Posner , Cogn Neurosci of attention, NY, Guilford Press, p 430-445)
(Region of interest meta-analysis: Valera et al., Biol Psych 2007; 61: 1361-1369)

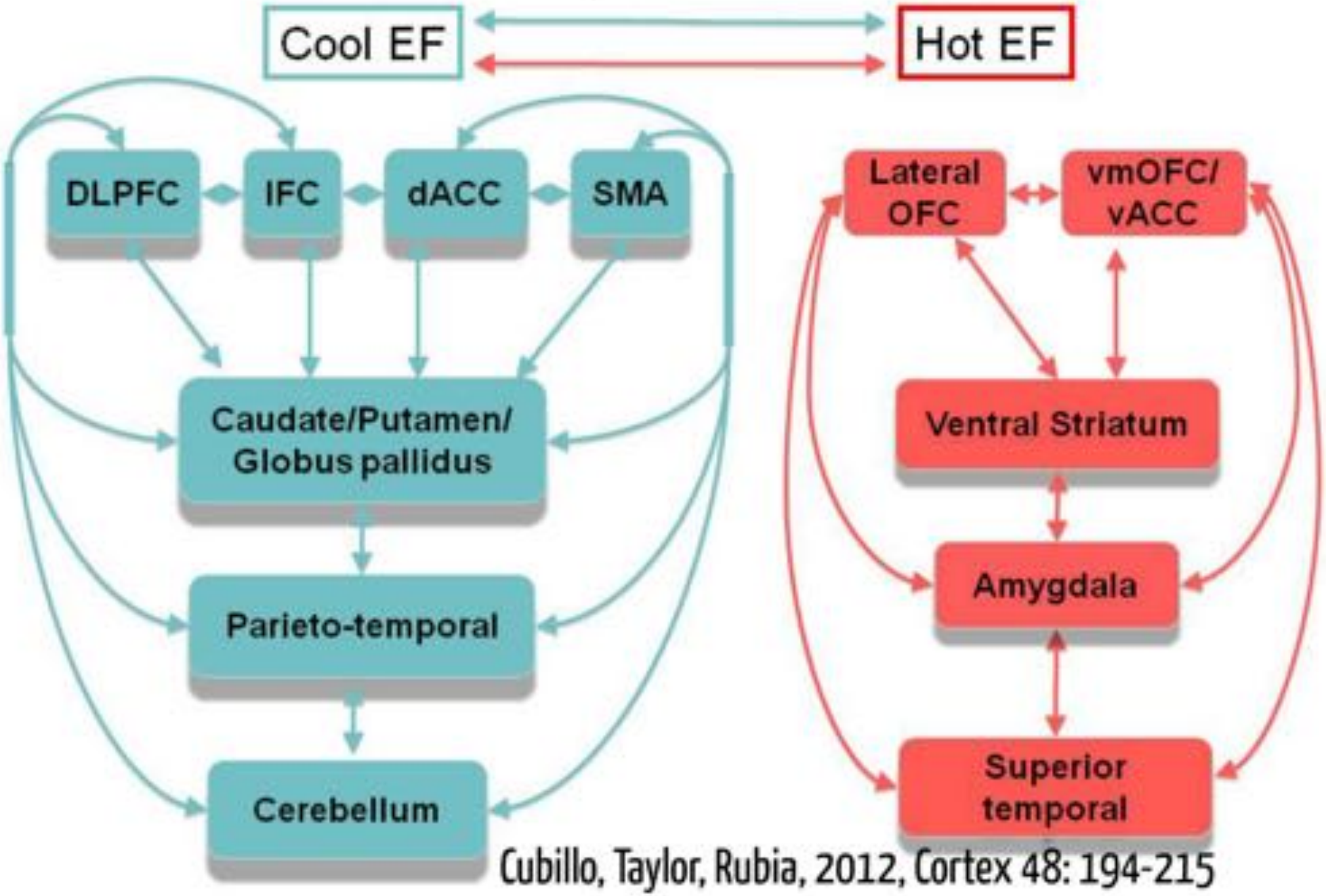
Meta-analysis of 14 whole-brain MRI studies

- 14 studies (5 adults; 9 children)
- N combined: 347 ADHD, 313 Controls
- Reduction of global volume
- Reduction of GM in right
  - caudate, putamen, globus pallidus
- Enhanced GM in left posterior cingulate/precuneus

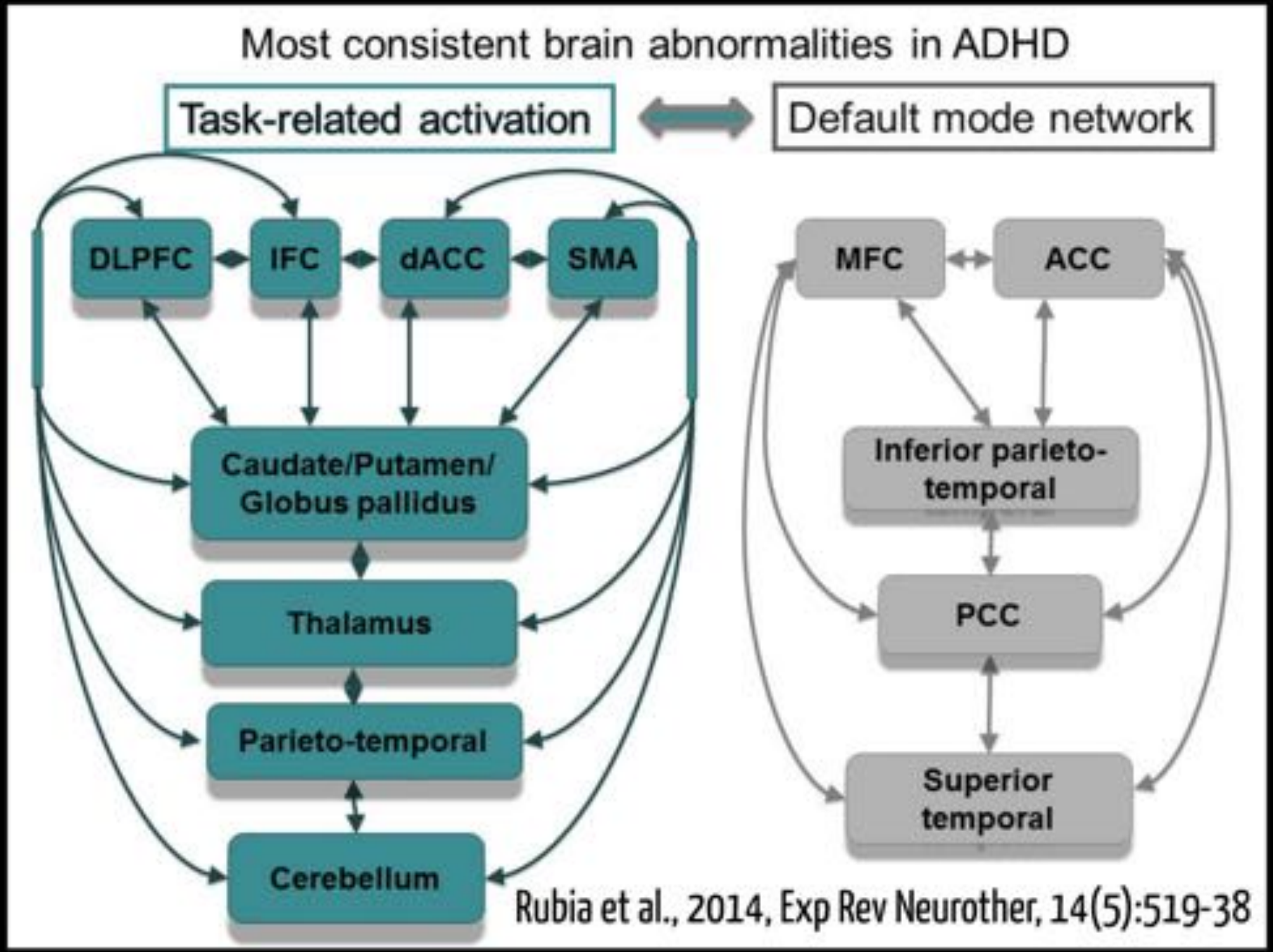


Nakao,Radua, Rubia, Mataix 2011, American J Psychiatry 8:1154-1163

Brain abnormalities in ADHD patients in cool & hot EF networks



Cubillo, Taylor, Rubia, 2012, Cortex 48: 194-215


Most consistent brain abnormalities in ADHD
Task-related activation
Default mode network
DLPFC
IFC
dACC
SMA
Caudate/Putamen/
Globus pallidus
Thalamus
Parieto-temporal
Cerebellum
MFC
ACC
Inferior parieto-
temporal
PCC
Superior
temporal
Rubia et al., 2014, Exp Rev Neurother, 14(5):519-38

Brain deficits

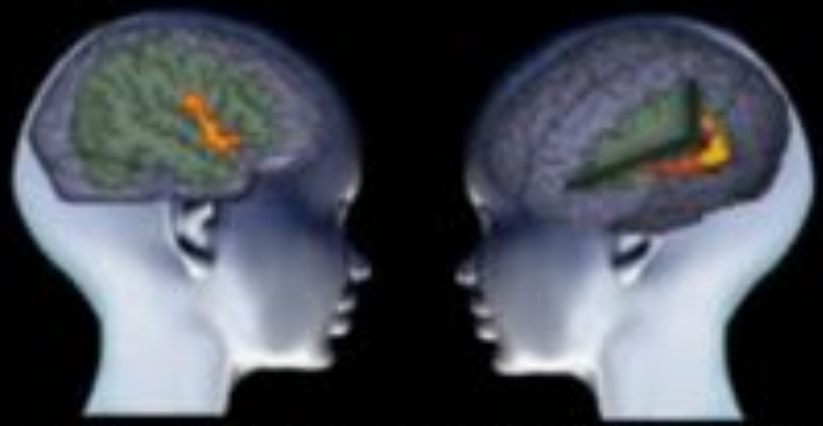
ADHD have cognitive domain-specific functional deficits in several fronto-striato-cerebellar networks & problems with switching off DMN => both EF deficits

Most prominent abnormality in sMRI:
R basal ganglia, anterior insula, cerebellum

Delay in FL-TL cortical thickness development

l Psychiatry

Specificity



ADHD have disorder-specific abnormality in structure & function (inhibition) of IFC/AI/BG relative to OCD & ASD (& CD)

IFC dysfunction is dissociated btw ADHD (<) & ASD (>)

Putamen & AI GM reduction is disorder-dissociated btw ADHD (<) & OCD (>)

Cb GM is smaller in ADHD vs ASD

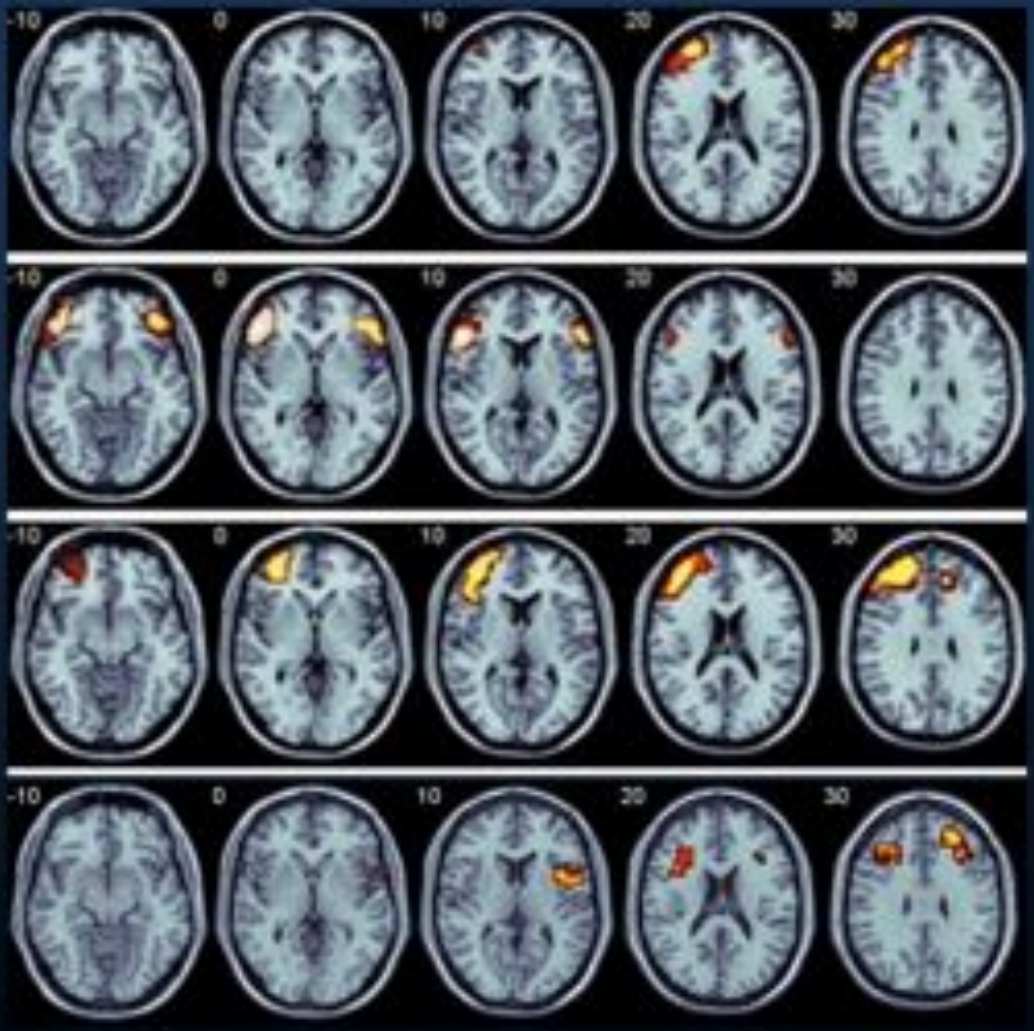
Comparisons with related disorders

- CD (Conduct disorder) (comorbidity 50-80%)
  - Shared deficits in EF, attention, motivation control
  - Deficits in paralimbic system (different from ADHD)

- OCD (Obsessive-compulsive disorder) (~30% comorbidity)
  - Shared deficits in tasks of inhibitory control
  - Deficits in inhibitory fronto-striatal networks

- ASD (Autism spectrum disorder) (~30% comorbidity)
  - Shared deficits in EF (inhibition); attention
  - Deficits in fronto-striatal, parietal, temporal, & cerebellar areas

Dysfunctions specific to ADHD (CD; C)



Stop

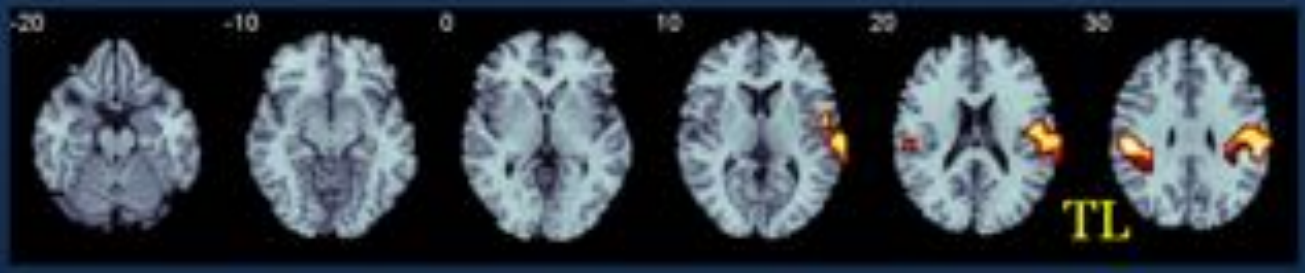
Sustained attention

Oddball

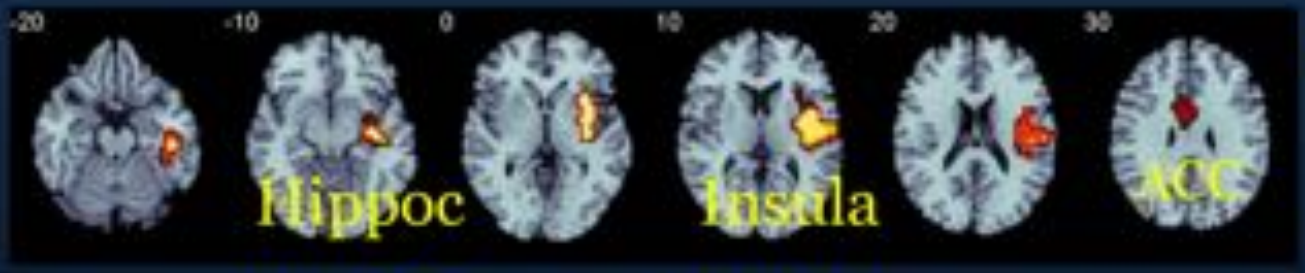
Switching

Rubia et al., AJP, 2008, AJP, 2009, JCPP 2009, HBM, 2010, for review: Rubia, Biol Psych, 2011

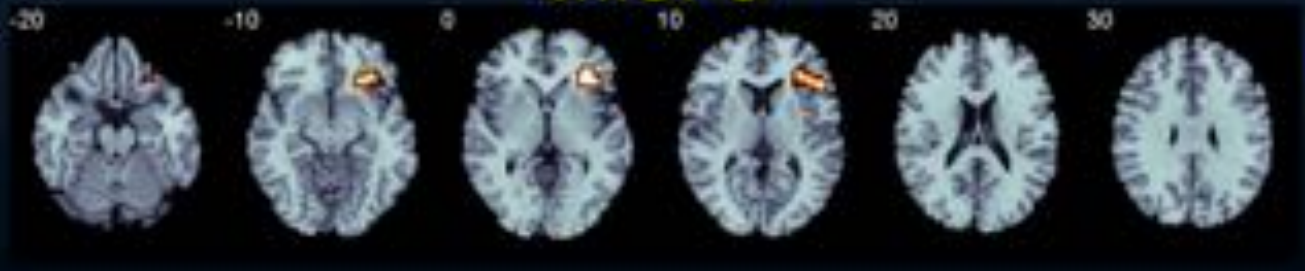
Dysfunctions specific to CD (ADHD; C)



Inhibition failure

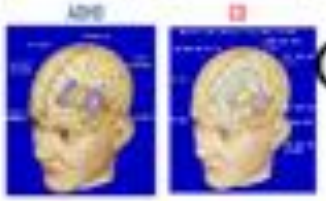


Sustained attention



Reward

Rubia et al., AJP, 2008, AJP, 2009, for review: Rubia, Biol Psych, 2011

ADHD pathophysiology  CD pathophysiology

Inferior/dorsolateral PFC
Top-down cognitive control

Basal ganglia
Fine-tuning/selection:
motor, cognitive, emotional

Parieto-temporal
Attention

Cerebellum
Calibration:
motor, cognitive

Lateral orbital & ventromedial PFC
Top-down affect & motivation control

Amygdala
Emotion processing

Temporal lobe
Aggression/performance
monitoring

Rubia, 2011, Biol Psych, 69:e69-e87

Comparisons with related disorders

- CD (Conduct disorder) (comorbidity 50-80%)
  - Shared deficits in EF, attention, motivation control
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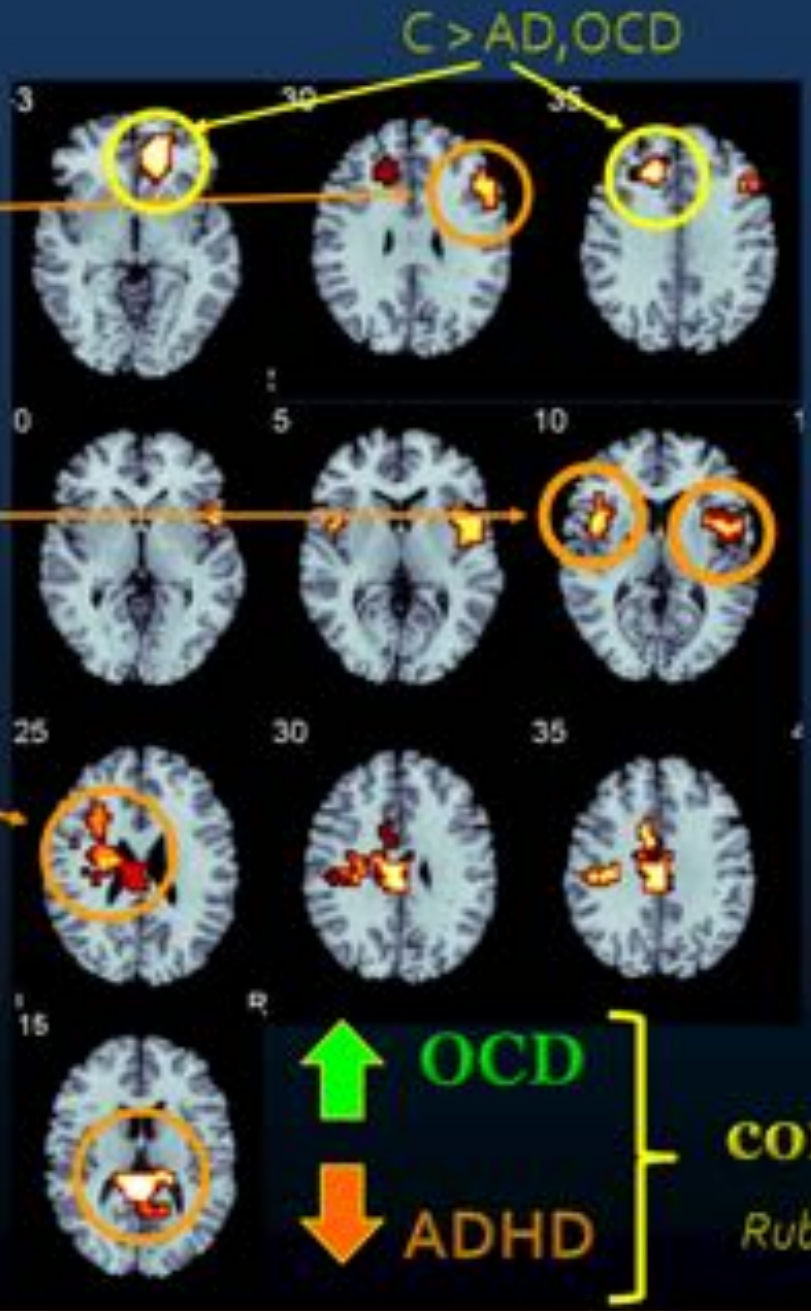
ADHD vs OCD & C
OCD
ADHD
corr with severity

ADHD vs OCD & C


C > AD,OCD
Stop
C, OCD > AD
Switch
C > AD (OCD)
C, OCD > AD
Oddball
OCD
ADHD
corr with severity
Rubia et al., HBM, 2010, HBM 2011

Comparisons with related disorders

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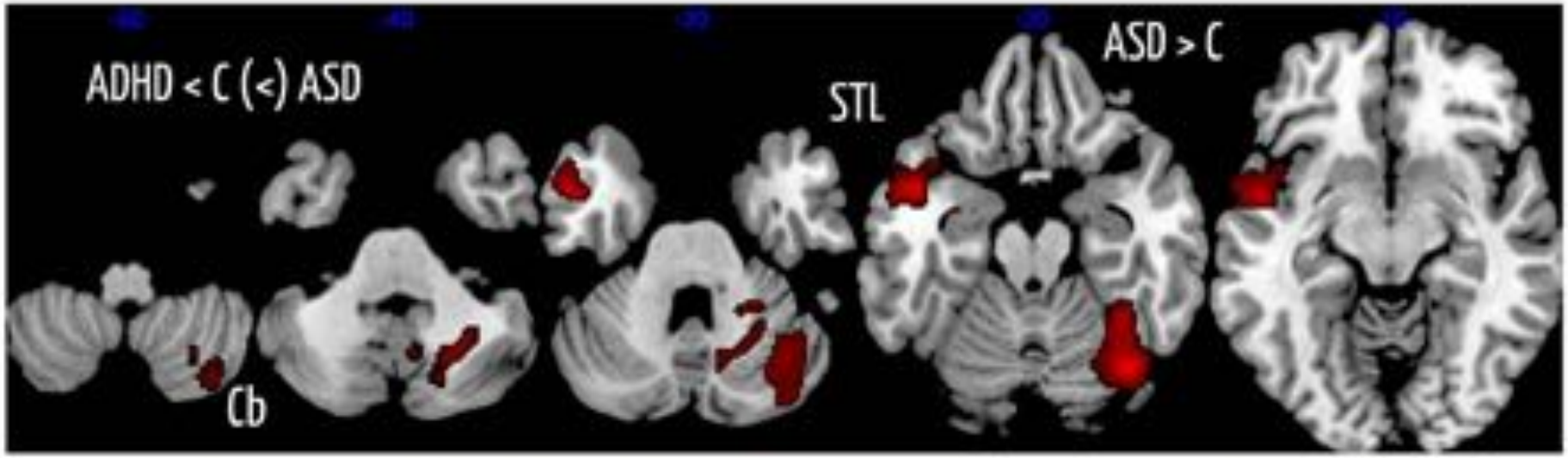
a u t i s m

Specificity of brain structure: ADHD & ASD

N: ADHD: 44, Controls: 33, ASD: 19

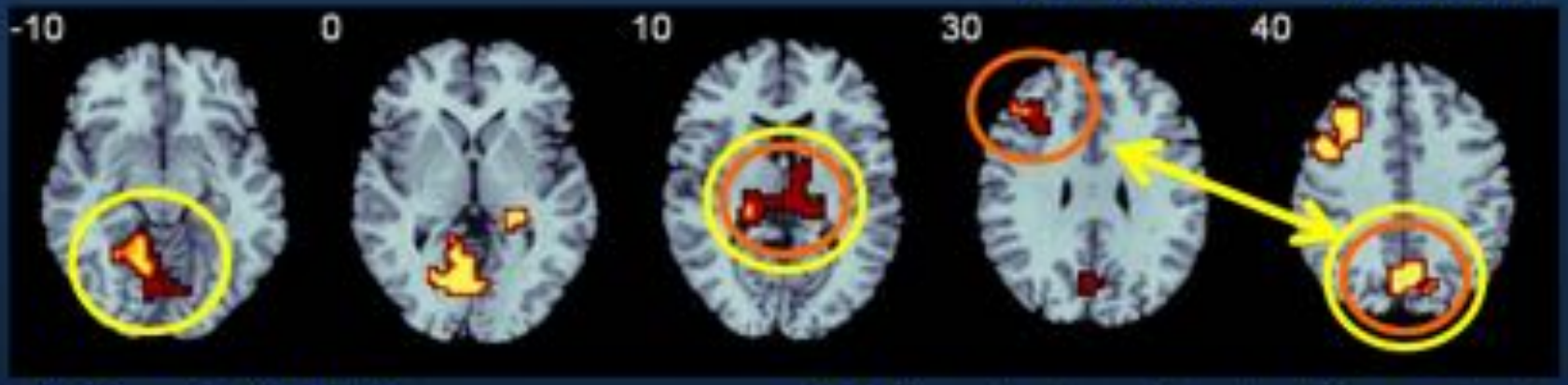


Lim, Chantiluke, Cubillo, Smith, Mehta, Rubia, Psychol Medicine 45(5):965-76.

ADHD vs ASD & controls

Parametric sustained attention

C > ASD > ADHD



ASD > C, ADHD

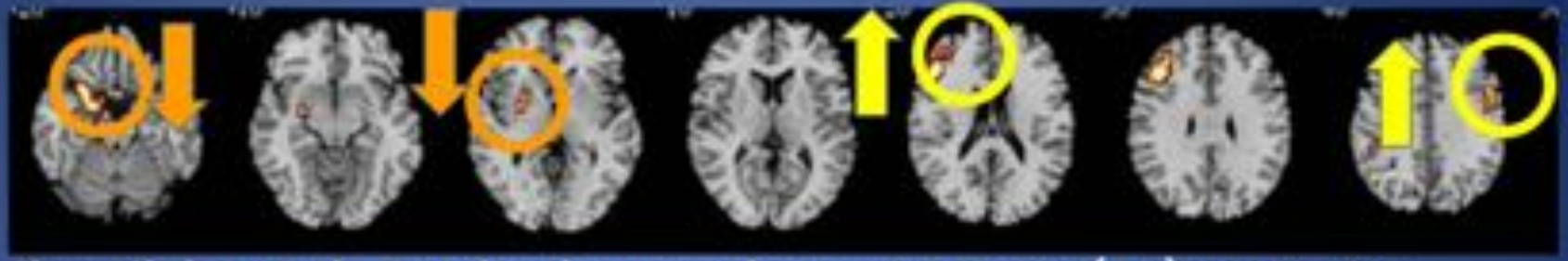
DMN not deactivated in patients

- Performance: Only ADHD impaired in response variability
- Left DLPFC deficit more pronounced in ADHD
- Disorder-specific fronto-cerebellar dysregulation in ASD

Christakou, Murphy, Chantiluke, Murphy, Rubia, Mol Psych, 8(2):236-44.

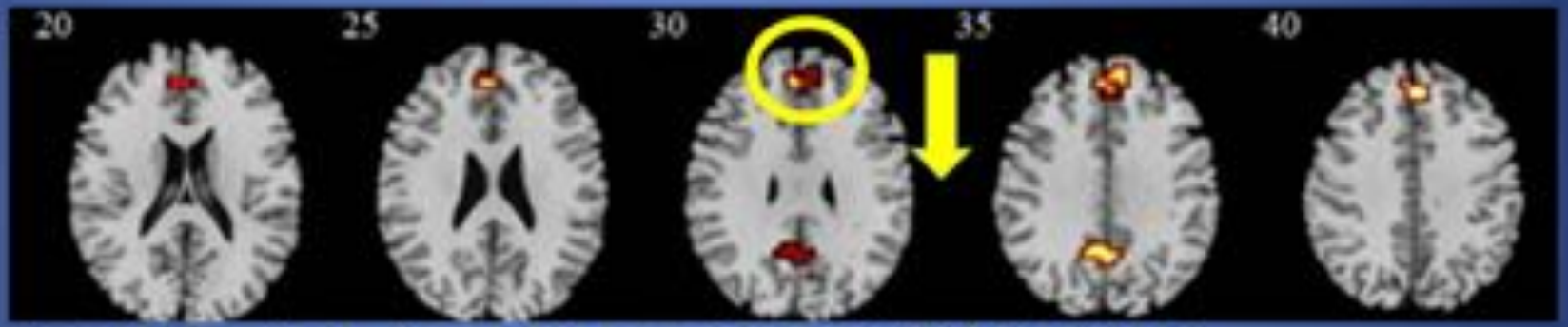
ADHD vs ASD

STOP task



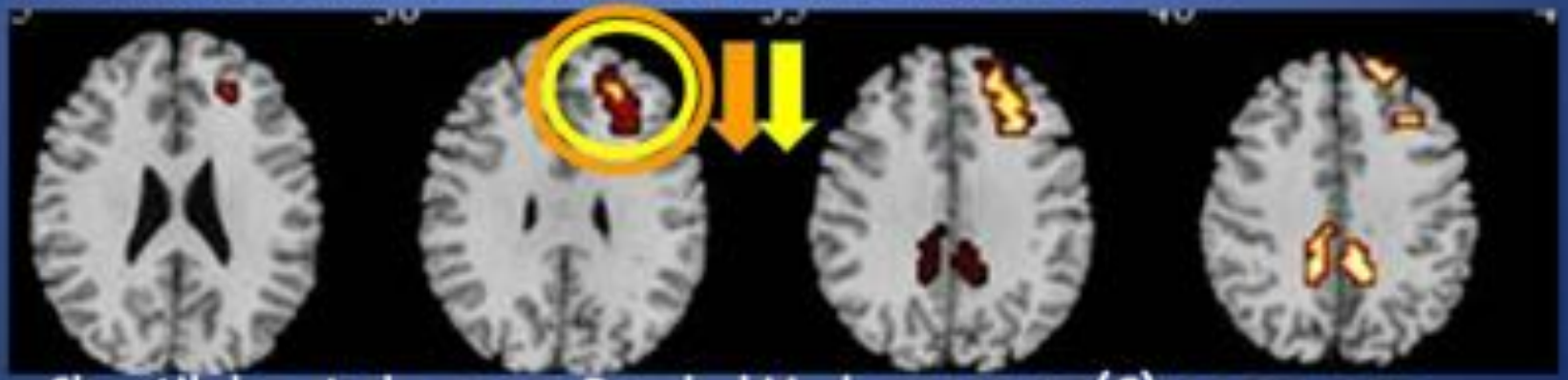
Chantiluke et al., Psychopharmacology 2015; 232(12):2071-82.

Reversal task



Chantiluke et al., Cereb Cortex. 2015; 25(7):1757-70.

WM task

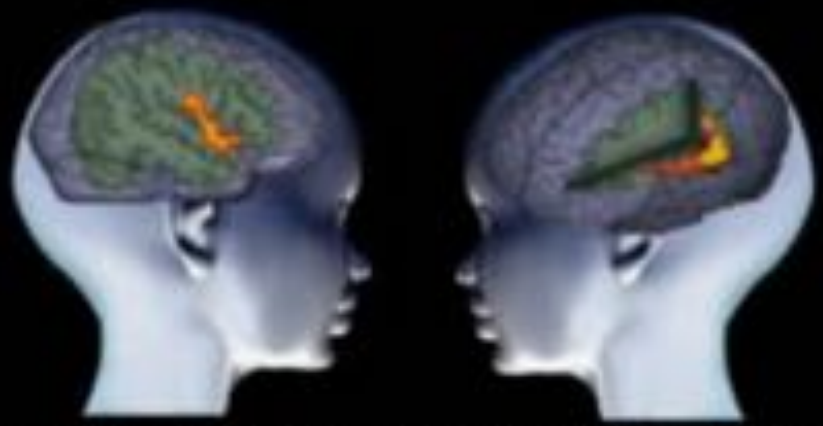


Chantiluke et al., 2015, Psychol Med. 2015; 45(6):1195-205.

Chantiluke et al., 2014, Cerebral Cortex, in press; Chantiluke et al., in submission

l Psychiatry

Specificity



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Medication

Long-term stimulant medication => more normal structure (& function) of the basal ganglia (not replicated in recent studies) but with abnormally high striatal DAT levels.

Meta-analysis fMRI: acute stimulants consistently upregulate R IFC/AI & BG & deactivate DMN

[ATX & Fluoxetine also modulate R IFG/AI]

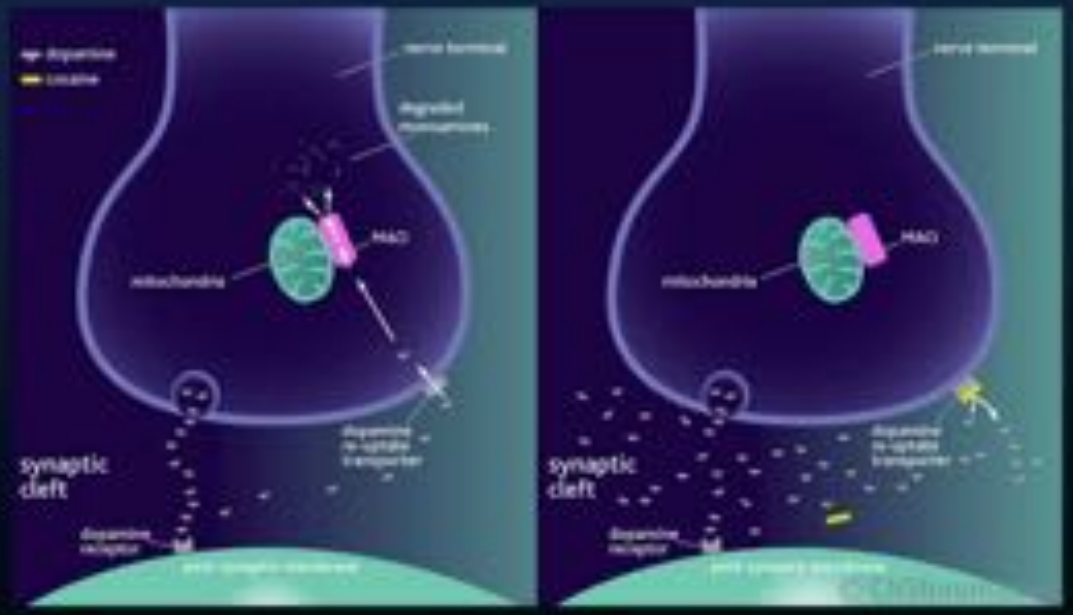
Methylphenidate

- Stimulant medication "gold-standard" ADHD
- Effective in 70-80% of patients
- In UK, once diagnosed 80% receive MPH

- Blocks DAT & NET inhibitor (50% DAT in BG):
- in BG mostly DAT => enhances DA availability (also PCC)
- in PFC mostly NET => enhances both DA & NE

Atomoxetine blocks NET

- Disadvantages
  - Heart rate & blood pressure
  - problematic for Tics?
  - addictive potential?
  - appears to stunt growth
  - appetite
  - sleep problems




PET

PET studies of striatal DAT levels in ADHD

↑ 70% Dougherty et al., 1999
↑ 16% Krause et al. 2000/2002
↑ 30% Cheon et al., 2003 children
↑ 34 % Spencer et al., 2005
↑ 15% Spencer et al., 2007
↑ 17% Dresel et al., 2000
↑ 5% Larisch et al., 2006
↑ 15% responders, non-responders, LaFougere 2006
= van Dyck et al., 2002
= Jucaite et al., 2005
↓ 23 % Hesse et al., 2006/2009
↓ 13 % Volkow et al., 2007, 2009

Mechanisms of Psychiatric Illness

Striatal Dopamine Transporter Alterations in ADHD: Pathophysiology or Adaptation to Psychostimulants? A Meta-Analysis

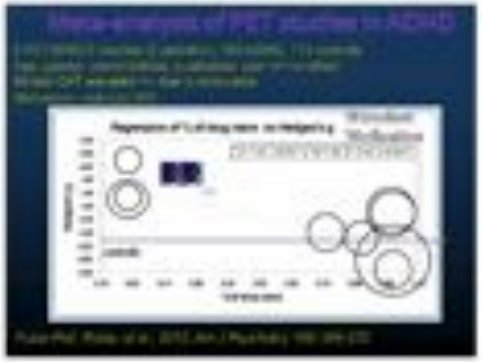
Paolo Fusar-Poli, Ph.D.

Katya Rubia, Ph.D.

Giorgio Rossi, M.D.

Giuseppe Sartori, Ph.D.

Umberto Balottin, M.D., Ph.D.



Background: Striatal dopamine transporter abnormalities are thought to underlie the pathophysiology and psychostimulant treatment of attention deficit hyperactivity disorder (ADHD). However, individual studies using single photon emission tomography (SPECT) or positron emission tomography (PET) have yielded inconsistent results, i.e., both high and low striatal dopamine transporter levels.

Method: Nine SPECT and PET studies investigating striatal dopamine transporter density in ADHD patients (N=169) and age-, gender-, and IQ-matched healthy comparison subjects (N=173) were included in a quantitative meta-analysis. Binding potentials in the striatum and demographic, clinical, and methodological variables were extracted from each publication or obtained directly from authors. Hedges' g was used as a measure of effect size in an analysis using Comprehensive Meta-Analysis software. Publication bias was assessed with funnel plots and Egger's intercept. Heterogeneity was addressed with the Q statistic and I^2 index.

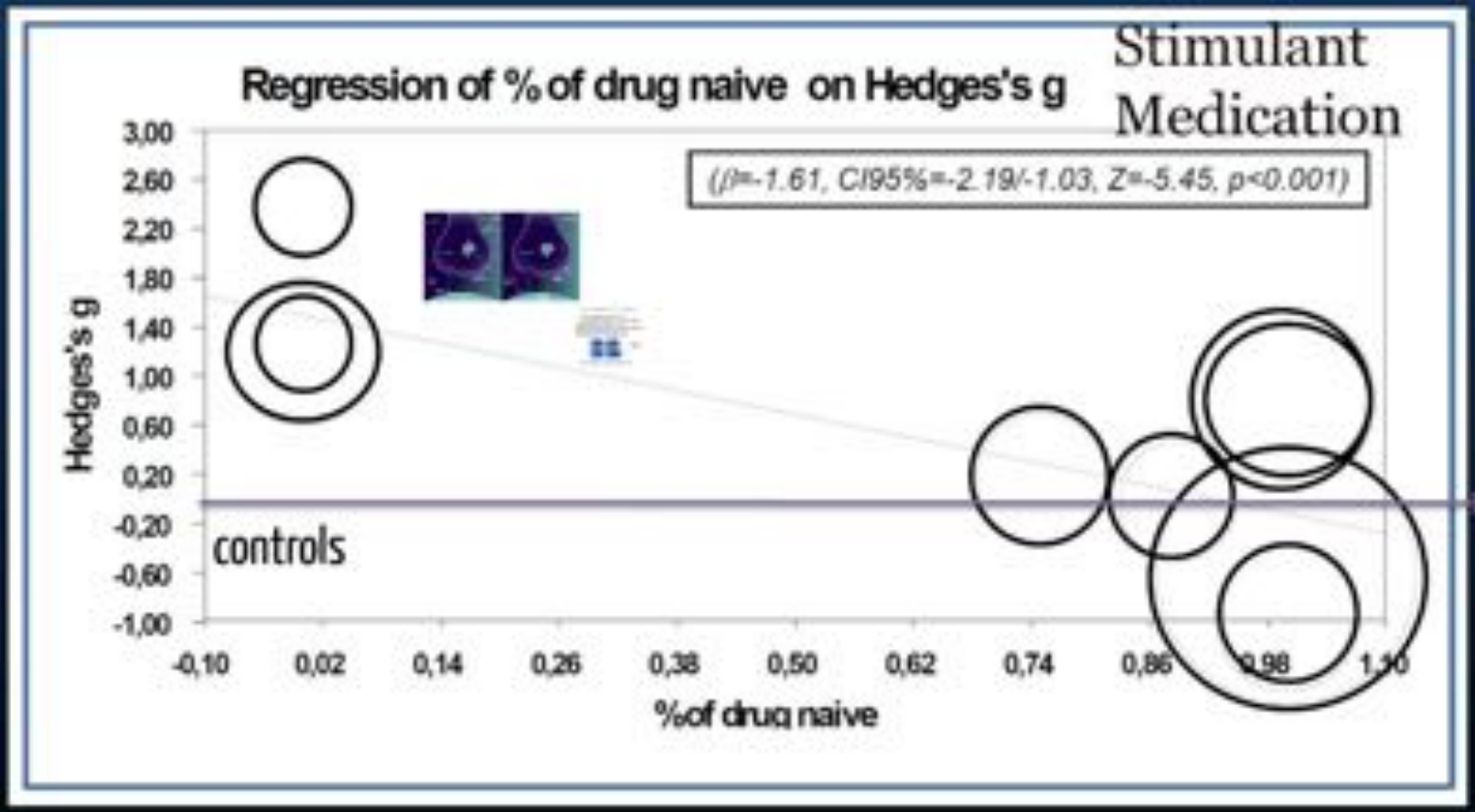
Results: Striatal dopamine transporter density was 14% higher on average in the ADHD group than in the healthy comparison group. However, heterogeneity across studies was large and statistically significant. Meta-regression analyses showed that the percentage of subjects without exposure to psychostimulants was negatively correlated with dopamine transporter density; density was higher in patients with previous medication exposure and lower in medication-naive patients. There was no moderating effect for age, comorbidity, gender, year of publication, or imaging technique. There was no publication bias, and sensitivity analysis confirmed robustness of the results.

Conclusions: Striatal dopamine transporter density in ADHD appears to depend on previous psychostimulant exposure, with lower density in drug-naive subjects and higher density in previously medicated patients.

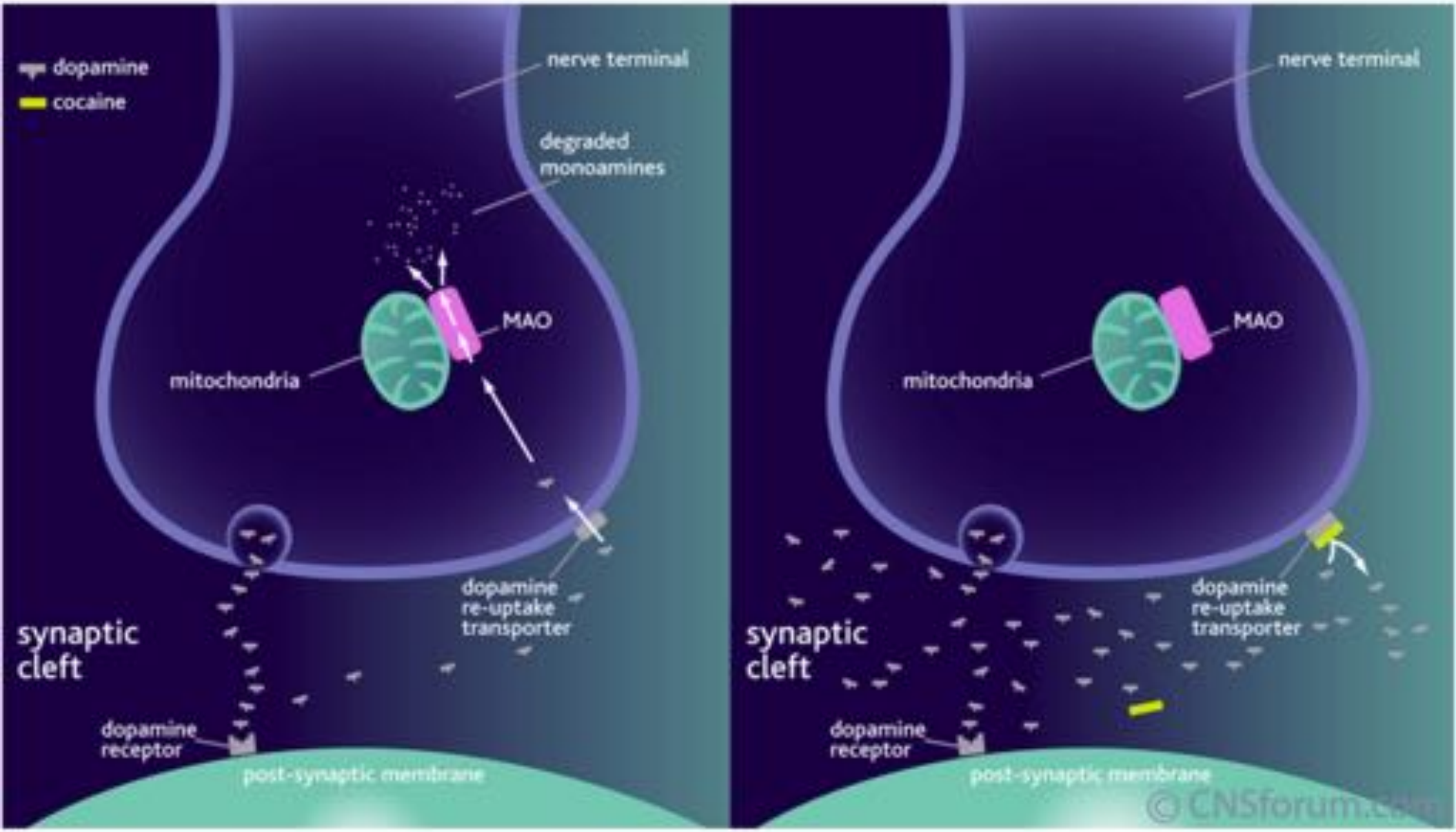
(Am J Psychiatry 2012; 169:264–272)

Meta-analysis of PET studies in ADHD

9 PET/SPECT studies (2 pediatric); 169 ADHD, 173 controls
Age, gender, comorbidities, publication year => no effect
Striatal DAT elevated => due to stimulants
Med-naïve: reduced DAT



Fusar-Poli, Rubia, et al., 2012, Am J Psychiatry 169: 264-272

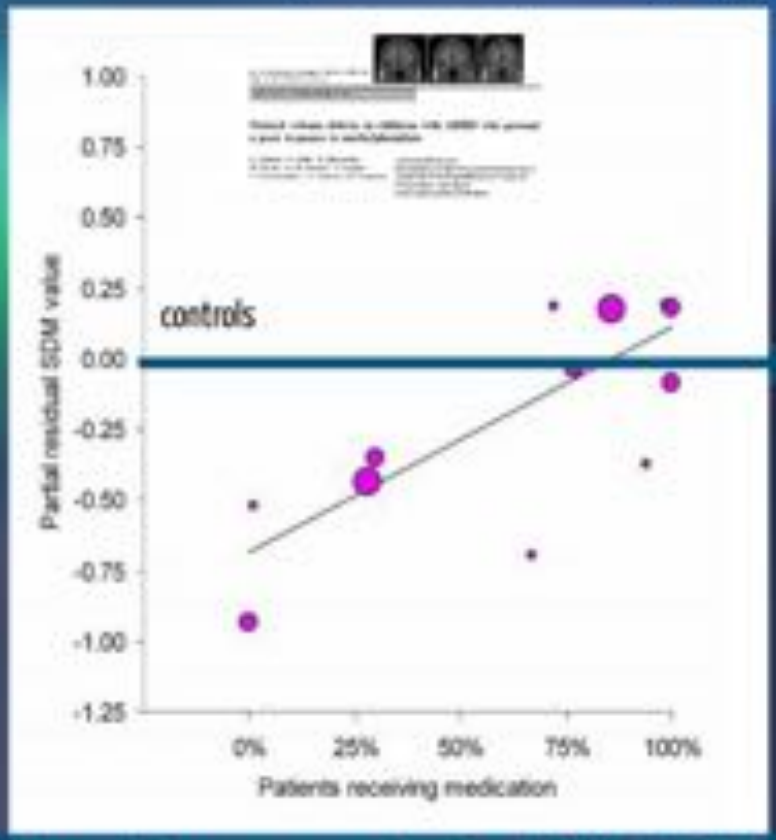

dopamine
cocaine
nerve terminal
degraded monoamines
MAO
mitochondria
dopamine re-uptake transporter
synaptic cleft
dopamine receptor
post-synaptic membrane
nerve terminal
MAO
mitochondria
dopamine re-uptake transporter
synaptic cleft
dopamine receptor
post-synaptic membrane
© CNSforum.com


sMRI

Meta-regression analysis of 14 whole-brain sMRI studies

14 studies (5 adults; 9 children)
N combined: 347 ADHD, 313 Controls
Reduction of GM in:
caudate, putamen, globus pallidus

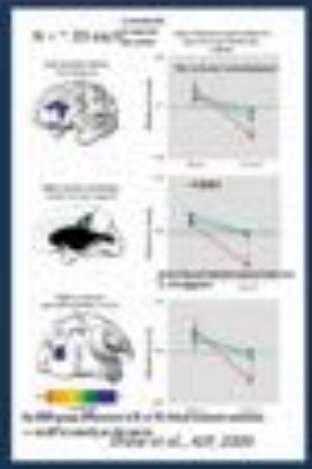
Long-term medication effects (controlled by age)



Not replicated in meta-analysis of 30 sMRI studies

Nakao, Radua, Rubia, Mataix 2011, American J Psychiatry 8:1154-1163

Long-term structural effects



No prospective studies, no RCT, only naturalistic

Longitudinal studies

- Castellanos 2006: med ADHD more normal WM overall
- Shaw 2009: med ADHD more normal GM in L IFC, PMC, PL

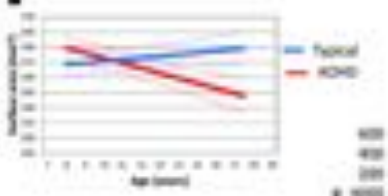
Cross-sectional studies

- Pliszka 2006: med ADHD > normal ACC volume, caud no diff
- Bledsoe 2009: med ADHD more normal post-inf. vermis Cb
- Sobel 2010: med ADHD > normal caudate morphology
- Ivanov 2010, 2014: med ADHD > normal thalamus, L cerebellar lobe
- Schnoebelen 2010: med ADHD > normal CC
- Onnink 2014: med reduced hippocampus (82med;16naiv;107c)
- Hoekzema 2014: med reduced VS volume (adults) longitudinal: med reduces VS transiently in kids (peak:~10m) & adults (~20m)

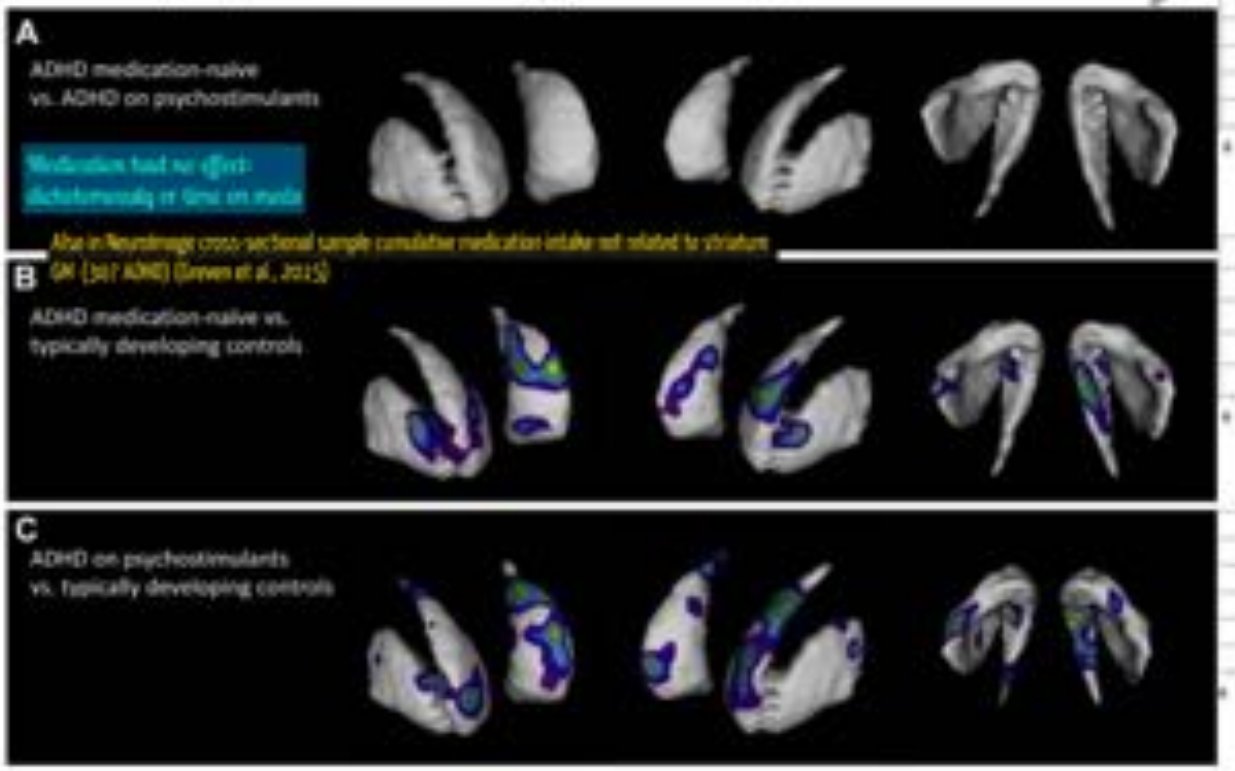
Meta-analysis studies

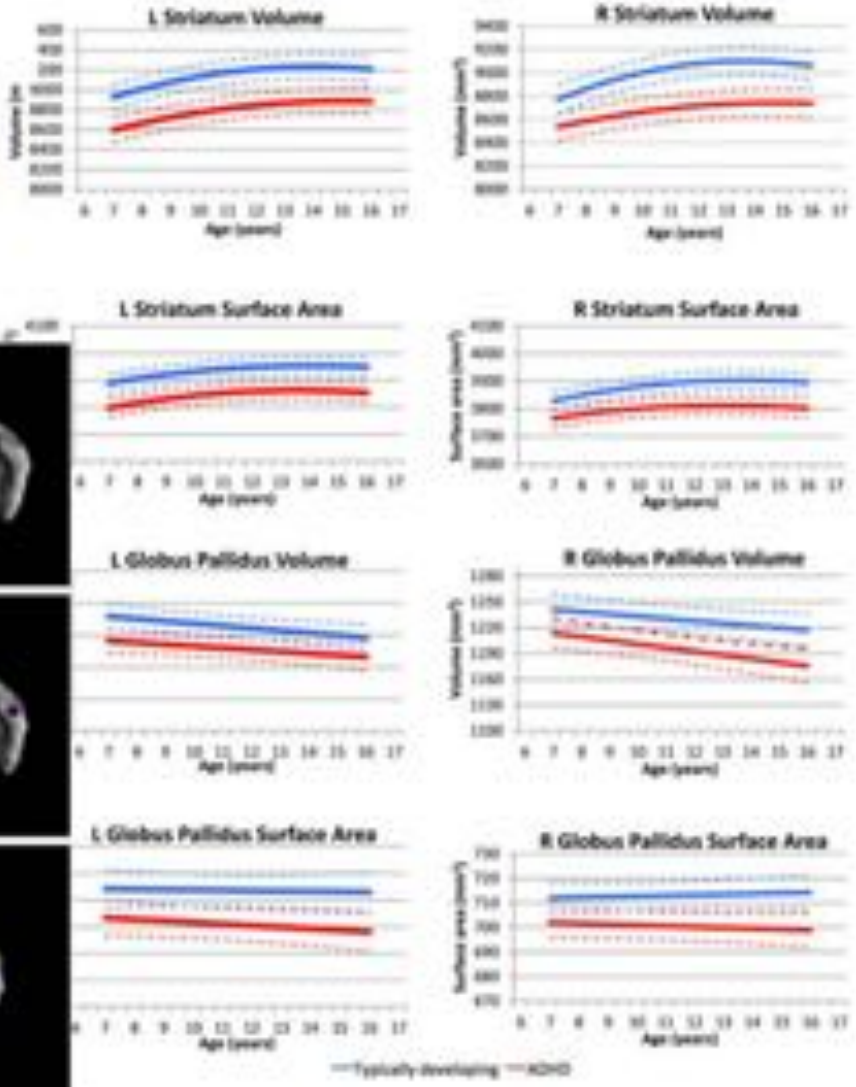
- Nakao et al. 2011: med ADHD > normal lenticular GM
- Frodl et al., 2012: med ADHD > normal lenticular GM, ACC

Mapping the Development of the Basal Ganglia in ADHD



- 270 ADHD (68% male
- 270 age, sex matched controls.
- 40% had two or more scans 99 not on med at entry
- Age at baseline 10.1 (SD 2); range 4-19 yrs.
- Symptomatic throughout study.

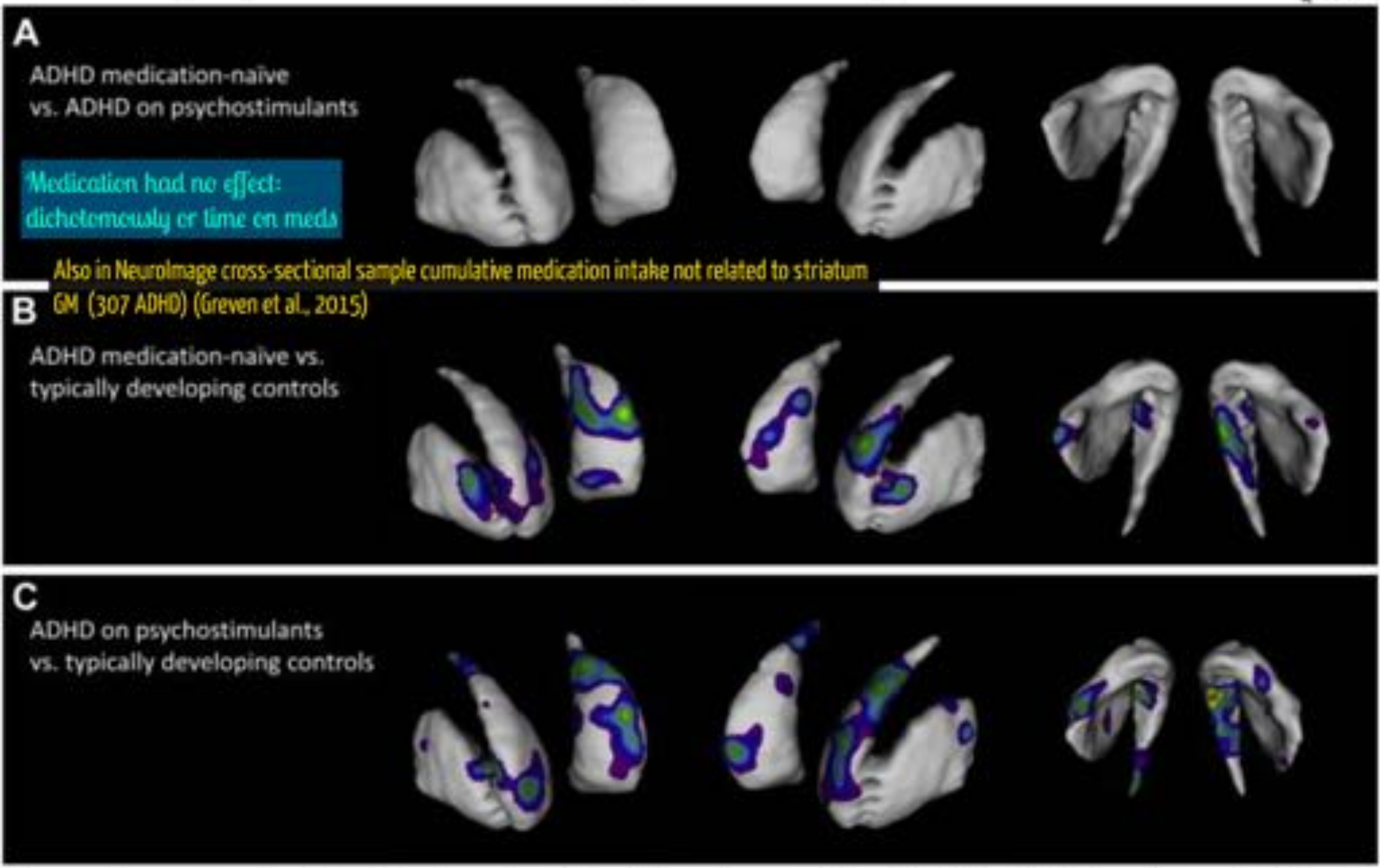




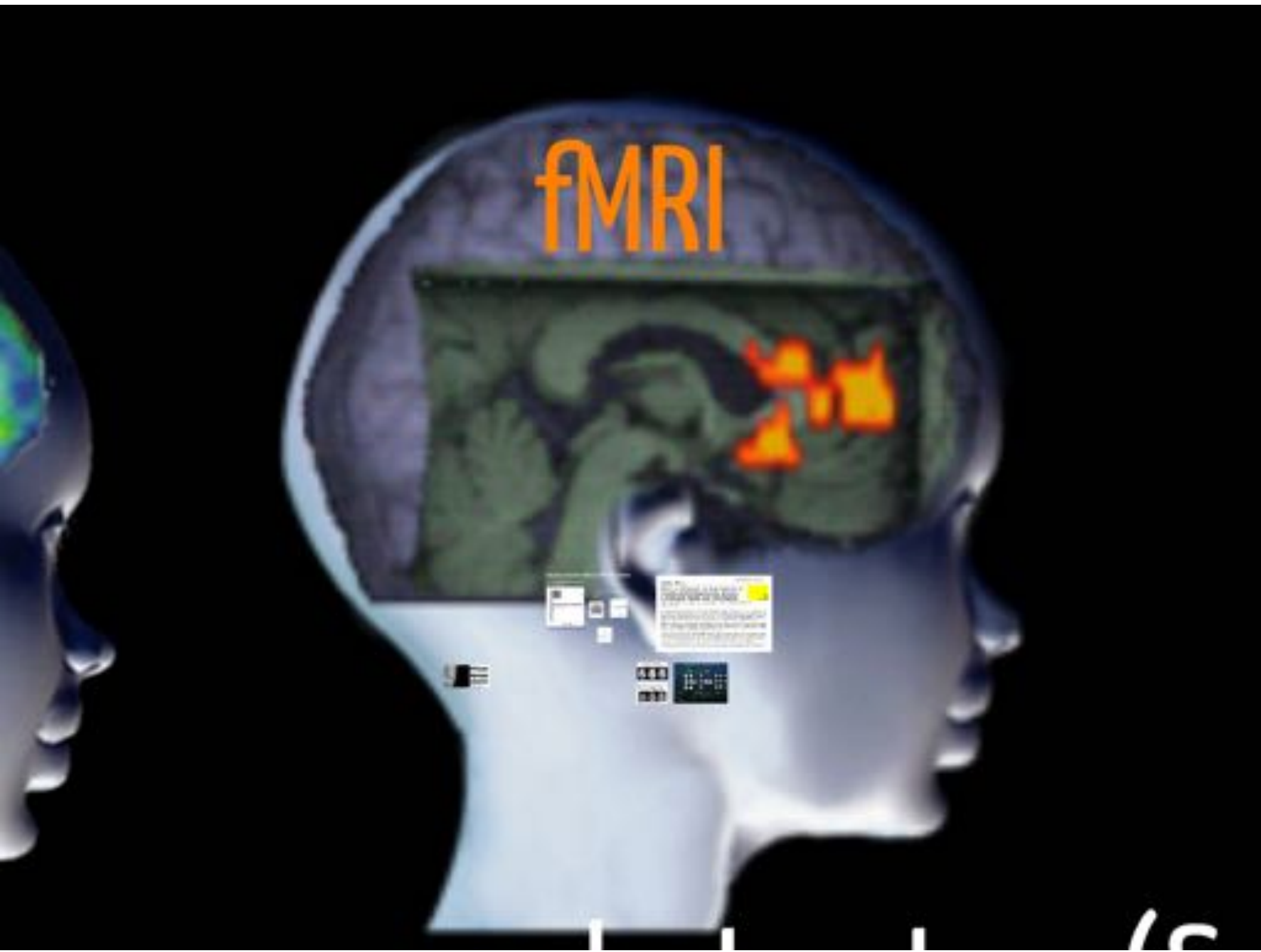
Developmental trajectories (estimates with 95% CI) for the striatal and globus pallidus volumes and total surface areas. Note: There were no significant differences in the shapes of the curves. ADHD have reduced volumes & surface areas. Medication had no effect.

Philip Shaw , et al. 2014, Am Academy Child & Adol Psychiatry, 53: 780 - 78

- Symptomatic throughout study.

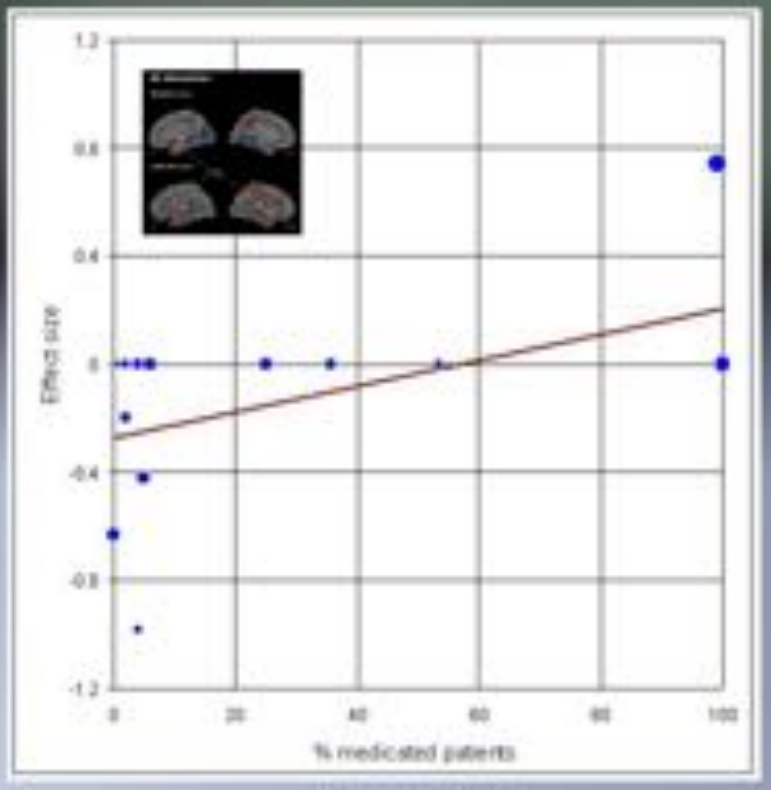


Developmental trajectories (estimates with 95% CI) for the striatal a
surface areas. Note: There were no significant differences in the sh


fMRI

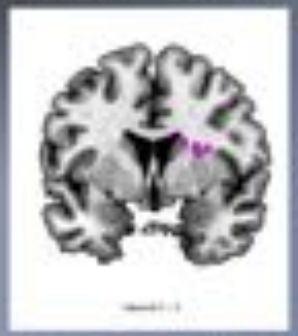
Long-term stimulants effects in fMRI meta-analyses

Caudate in attention meta-regression analysis
Effect of LT medication

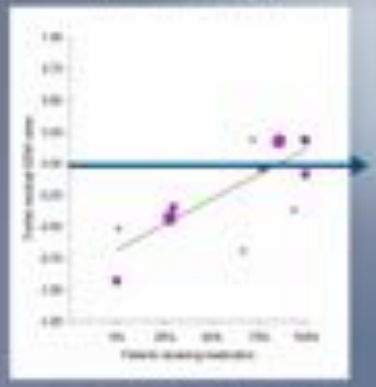


Hart, Radua, Mataix, Rubia, JAMA Psychiatry, 2013, 70: 185-98

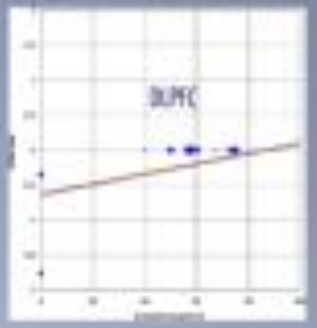
Meta-regression analysis of 14 whole brain sMRI studies



Medication effects (controlled for age)



Nakao, Radua, Rubia, Mataix 2011, American J Psychiatry 8:1059-1063



BIOL PSYCHIATRY 2014;76:616–628

ARCHIVAL REPORT

Effects of Stimulants on Brain Function in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis

Katya Rubia, Analucia A. Alegria, Ana I. Cubillo, Anna B. Smith, Michael J. Brammer, and Joaquim Radua

Background: Psychostimulant medication, most commonly the catecholamine agonist methylphenidate, is the most effective treatment for attention-deficit/hyperactivity disorder (ADHD). However, relatively little is known on the mechanisms of action. Acute effects on brain function can elucidate underlying neurocognitive effects. We tested methylphenidate effects relative to placebo in functional magnetic resonance imaging (fMRI) during three disorder-relevant tasks in medication-naïve ADHD adolescents. In addition, we conducted a systematic review and meta-analysis of the fMRI findings of acute stimulant effects on ADHD brain function.

Methods: The fMRI study compared 20 adolescents with ADHD under either placebo or methylphenidate in a randomized controlled trial while performing stop, working memory, and time discrimination tasks. The meta-analysis was conducted searching PubMed, ScienceDirect, Web of Knowledge, Google Scholar, and Scopus databases. Peak coordinates of clusters of significant effects of stimulant medication relative to placebo or off medication were extracted for each study.

Results: The fMRI analysis showed that methylphenidate significantly enhanced activation in bilateral inferior frontal cortex (IFC)/insula during inhibition and time discrimination but had no effect on working memory networks. The meta-analysis, including 14 fMRI datasets and 212 children with ADHD, showed that stimulants most consistently enhanced right IFC/insula activation, which also remained for a subgroup analysis of methylphenidate effects alone. A more lenient threshold also revealed increased putamen activation.

Conclusions: Psychostimulants most consistently increase right IFC/insula activation, which are key areas of cognitive control and also the most replicated neurocognitive dysfunction in ADHD. These neurocognitive effects may underlie their positive clinical effects.

Meta-analysis of acute stimulant effects

14 whole brain image analysis fMRI datasets: 212 ADHD children

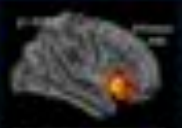
Upregulation within patients MPH > Placebo (ON > OFF-Med)

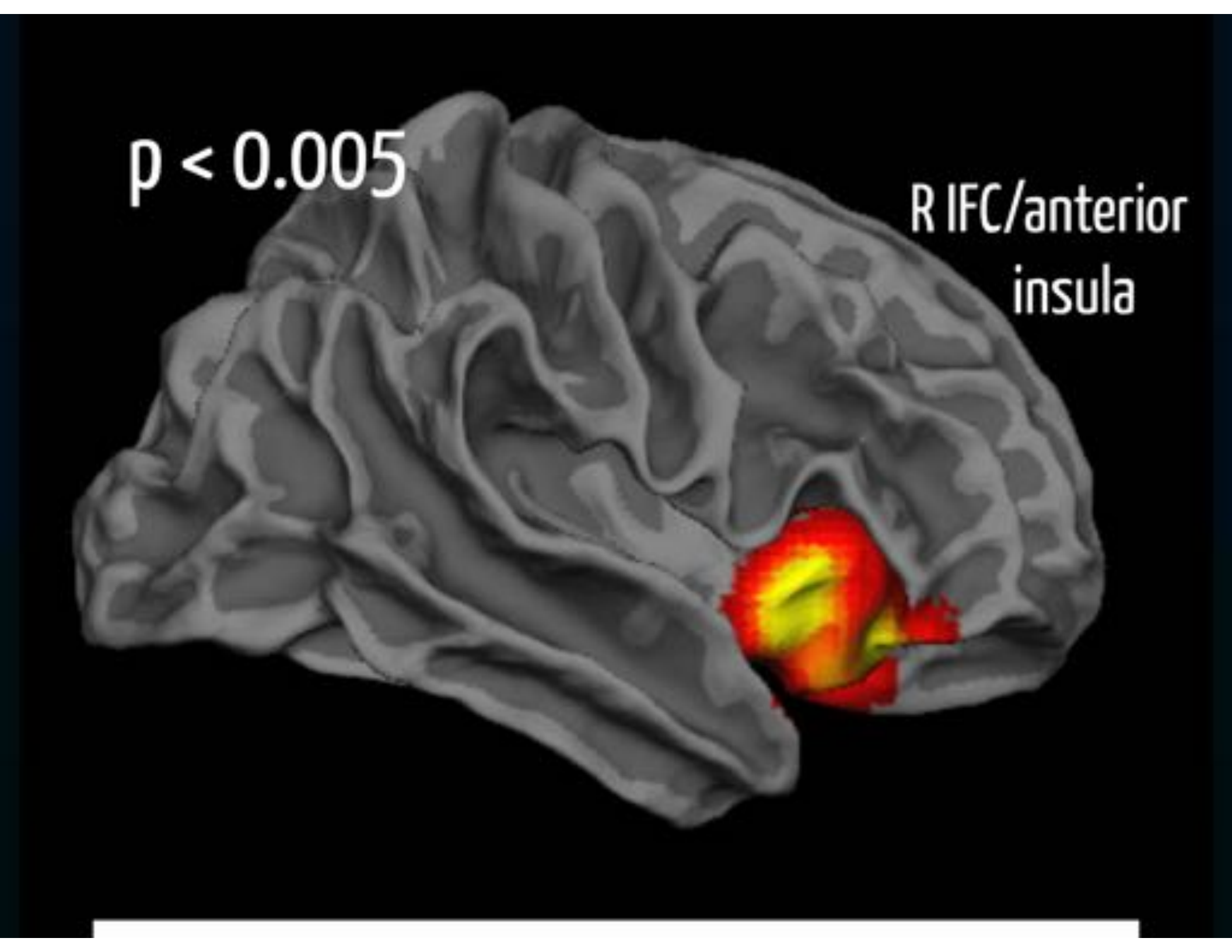
Study	Task	MED	IFC	DLPFC	BG	ACC	PCC	Cb	PL/TL
Rubia 2009a NPP	Attention	No	X				X	X	X
Rubia 2009a NPP	Reward	No			X	X			
Rubia 2011a PP	Simon	No	X					X	X
Rubia 2011b BPS	Stop	No	X	X	X	X	X		X
R: Cubillo 2012 Cer Cx	Stop	No	X		X	X	X	X	X
Rubia 2009b PhilTransB	TD	No	X			X		X	
R: Smith 2013 BPS	TD	No	X		X				
R: Cubillo 2012 PSM	WM	No							
Kobel 2009 EurPedNeur	WM	Yes							
Peterson 2009 AJPsych	Stroop	Yes							
Posner 2011 Psych Res	Emot. Stroop	Yes		X					

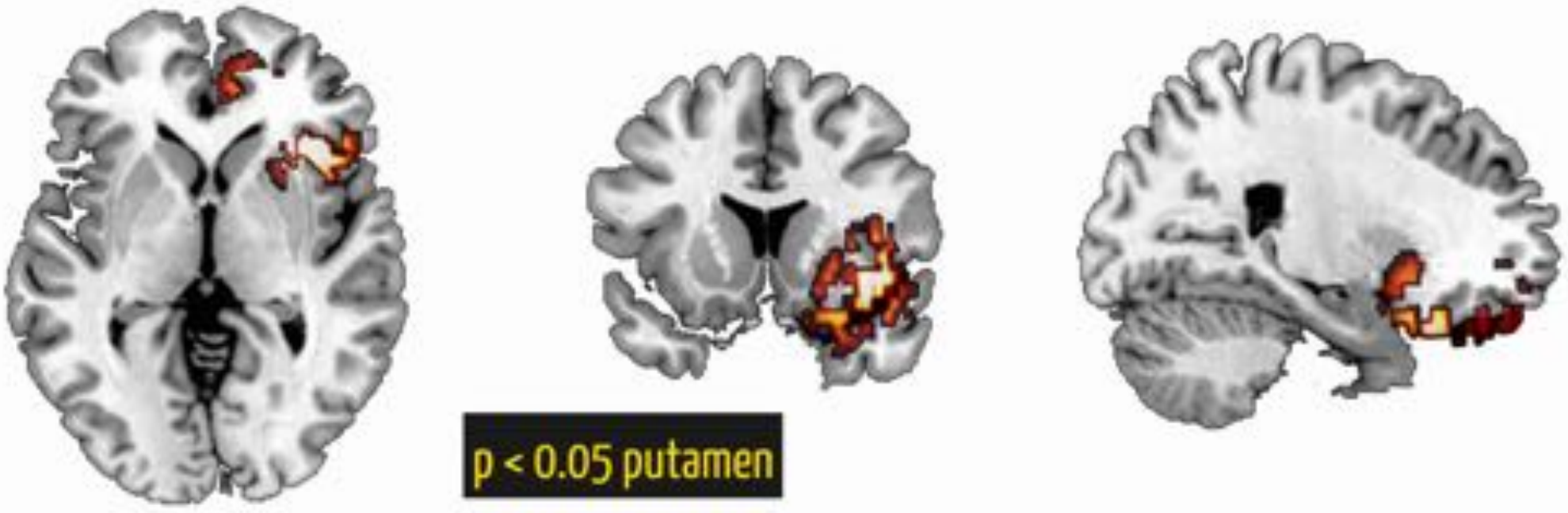
MPH > Placebo in randomised controlled design in med-naïve ADHD

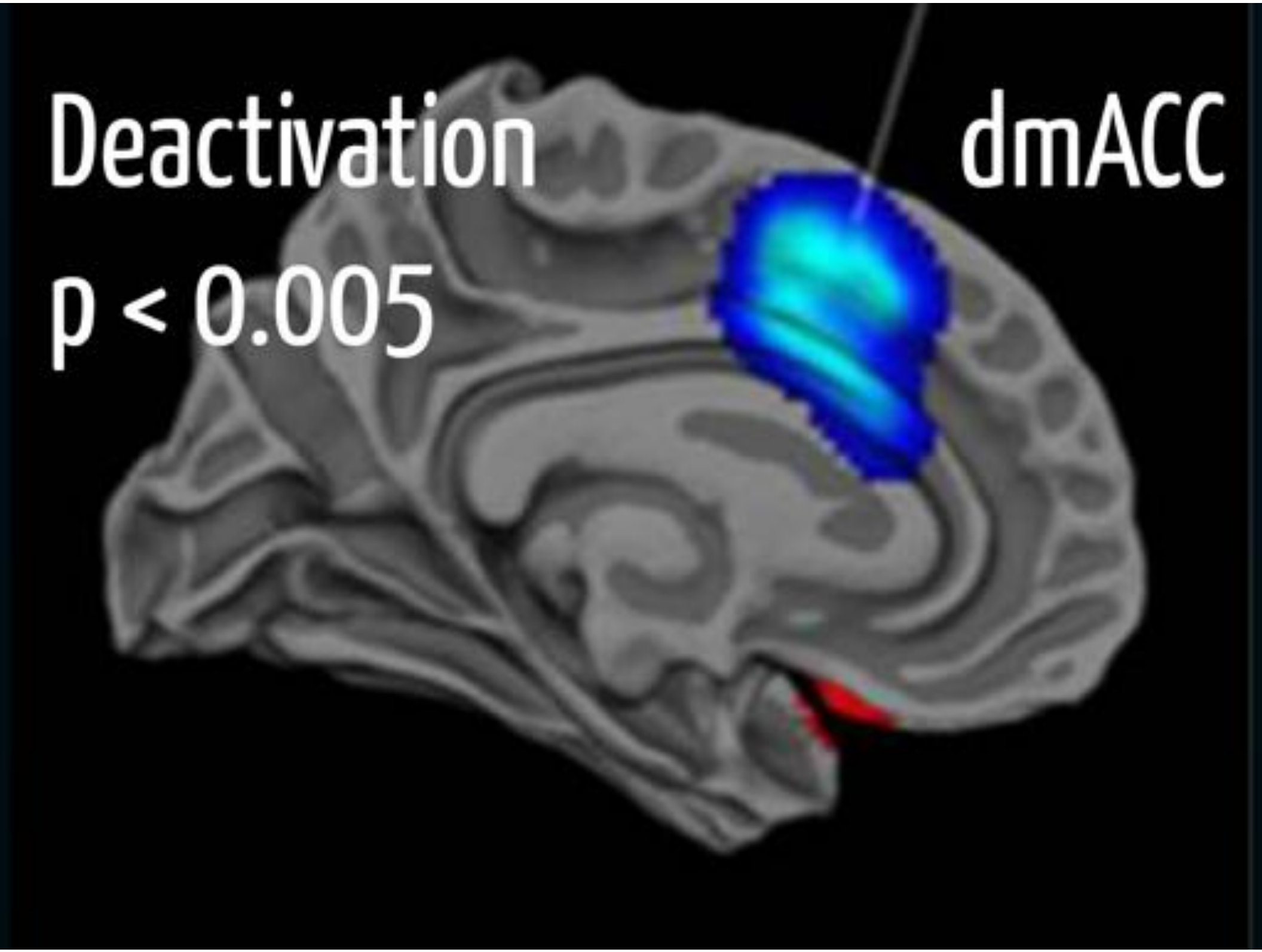
MPH On > MPH Off in chronically treated ADHD

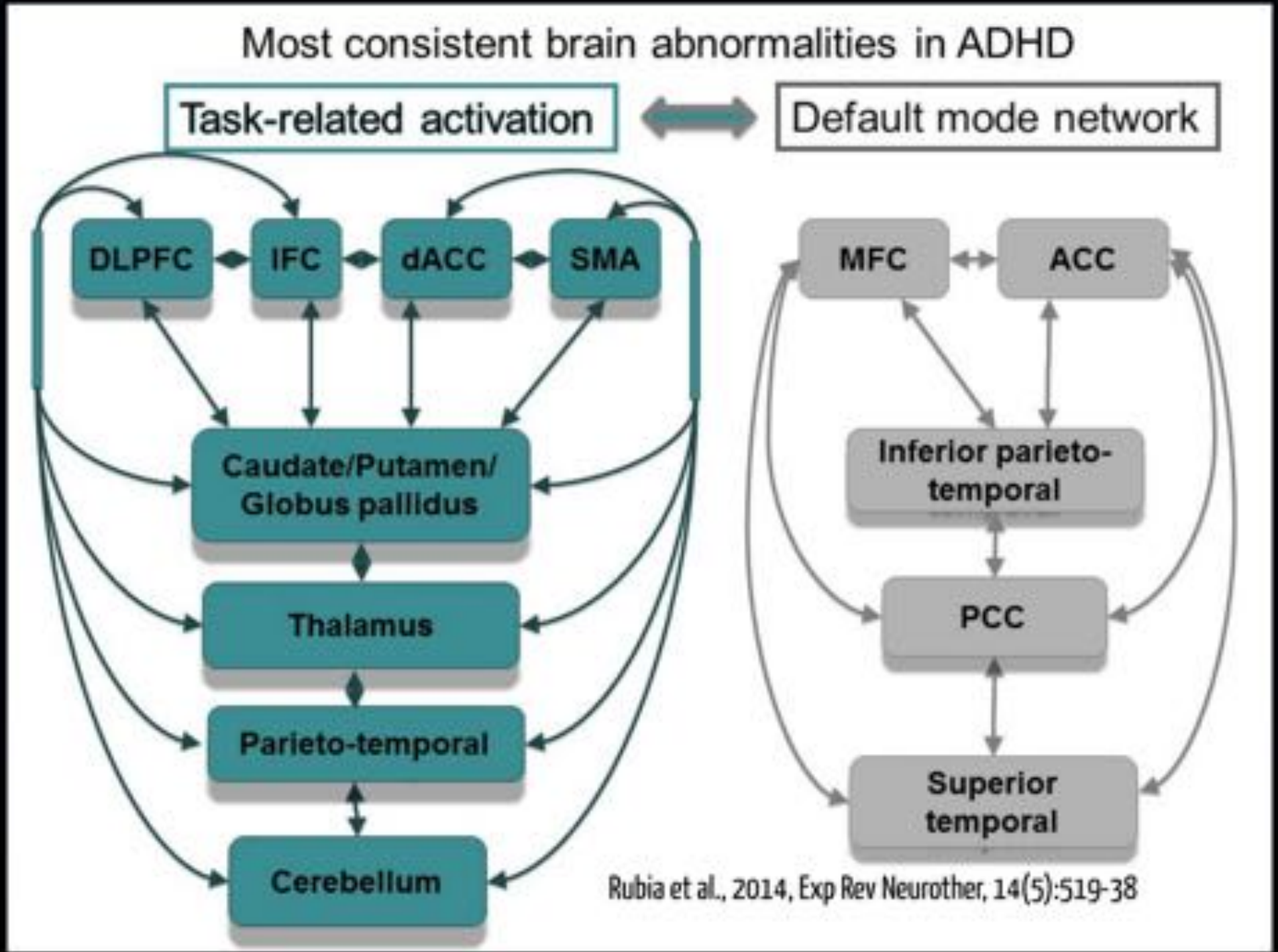
Rubia, Alegria, Radua, Biol Psych, 2014: 76:616




p < 0.005
R IFC/anterior
insula


p < 0.05 putamen


Deactivation
dmACC
p < 0.005


Most consistent brain abnormalities in ADHD
Task-related activation
Default mode network
DLPFC
IFC
dACC
SMA
Caudate/Putamen/
Globus pallidus
Thalamus
Parieto-temporal
Cerebellum
MFC
ACC
Inferior parieto-
temporal
PCC
Superior
temporal
Rubia et al., 2014, Exp Rev Neurother, 14(5):519-38

BIOL PSYCHIATRY 2014;76:616–628

ARCHIVAL REPORT

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Atomoxetine vs Methylphenidate

Working memory

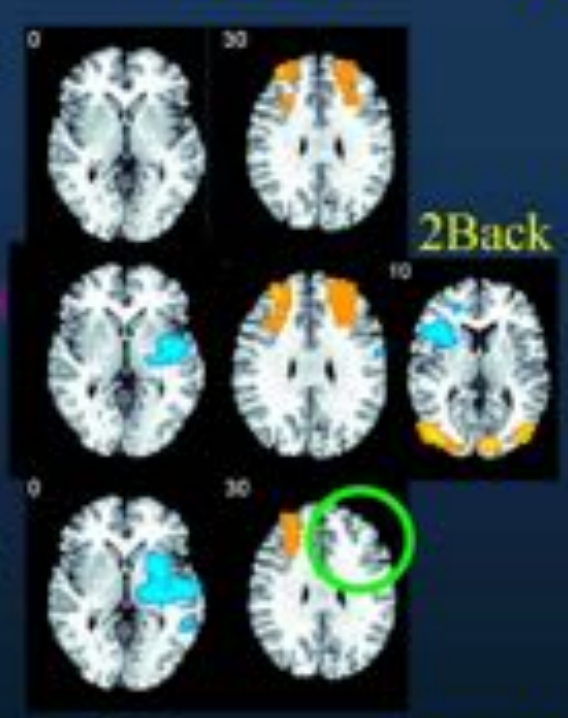
R DLPFC

2Back

C > ADHD Plac

C > ADHD MPH

C > ADHD ATX



Accuracy improved
with both drugs

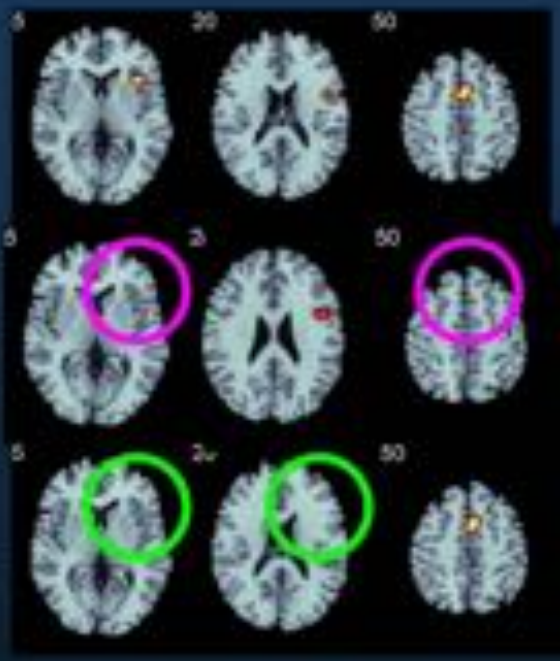
Stop task

IFC –correlated SSRT

Go process

Only MPH improved SSRT
Normalisation sign for both in L IFG
Sign for MPH in R IFG + Cb (trend for ATX)

Time discrimination



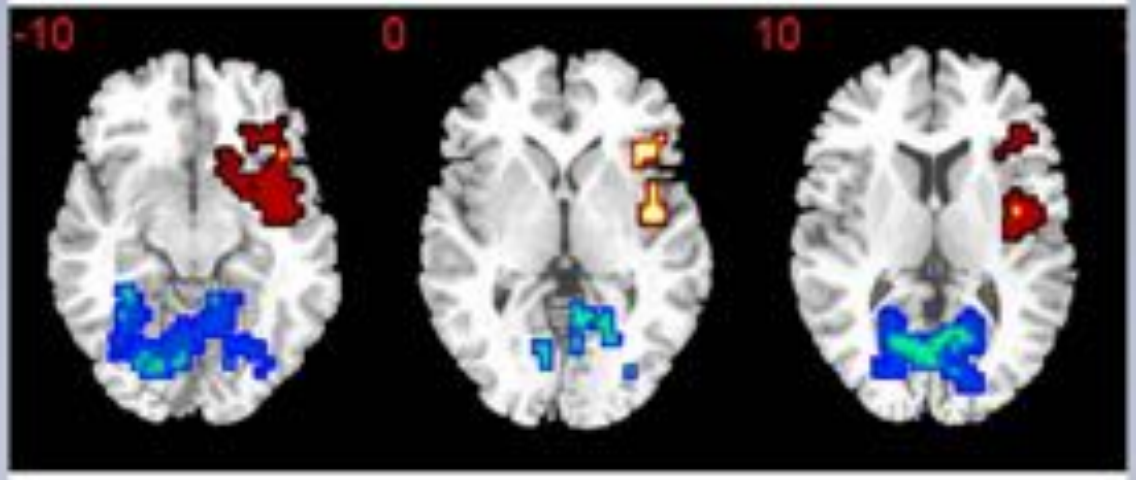
Only MPH normalised

TD errors

Cubillo et al., 2013, Cerebral Cortex, Cubillo et al., Psychol Med, 19: 1-14
Smith et al., 2013, Biol Psych, 74(8):615-22
24(1):174-85

Fluoxetine > Placebo

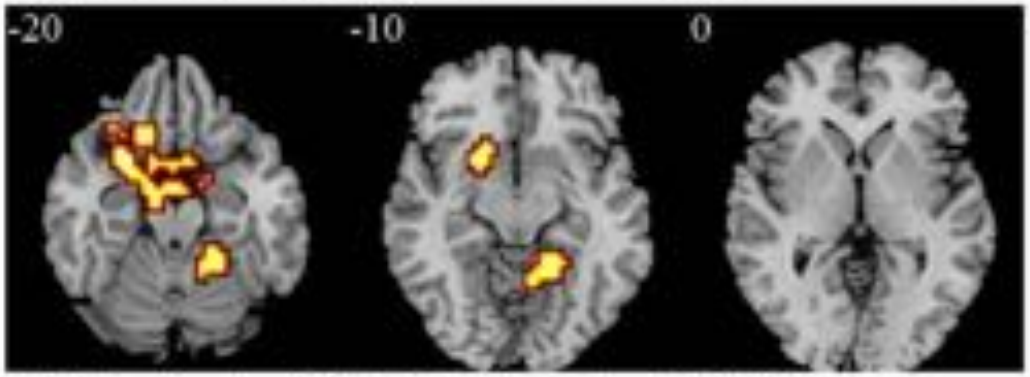
Temporal discounting: delayed > immediate



Carlisi, Chantiluke, Norman, Giampietro, Brammer, Simmons, Rubia in submission

Within-Patient Comparisons

C. Group by Medication Interaction Effects



Chantiluke, Barrat, ... Rubia, Psychopharmacology 232(12):2071-82.

C > ADHD P

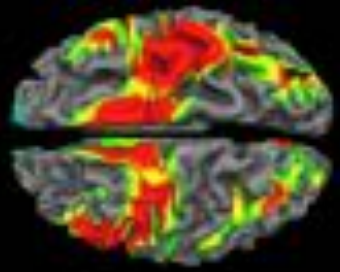
C > ADHD M

C > ADHD A

Accuracy in
with both d

Cubillo e
Smith e

Translation



=>

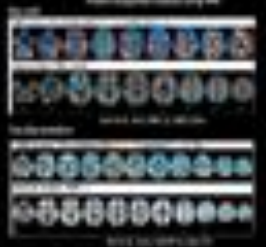
Diagnosis/ prognosis?

Multivariate pattern recognition analyses have the potential to aid in clinical diagnosis & prognosis

Neurotherapy

Children with ADHD can self-regulate brain activation -> clin improvement no region-specificity

Diagnosis/ prognosis?



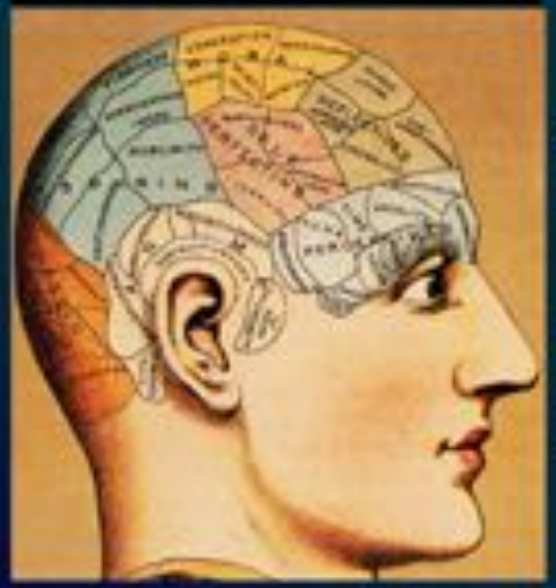
Multivariate pattern recognition analyses have the potential to aid in clinical diagnosis & prognosis

Analucia Al

Helen Brin

Traditional MRI analysis:
mass
univariate

=>



Multivariate pattern recognition analyses

- designed to identify spatial/temp patterns that discriminative between groups
- combinatorial effects=> more sensitive
- generalise categorization to new individual data

⇒ diagnostic & prognostic indicators of individuals
⇔ groups

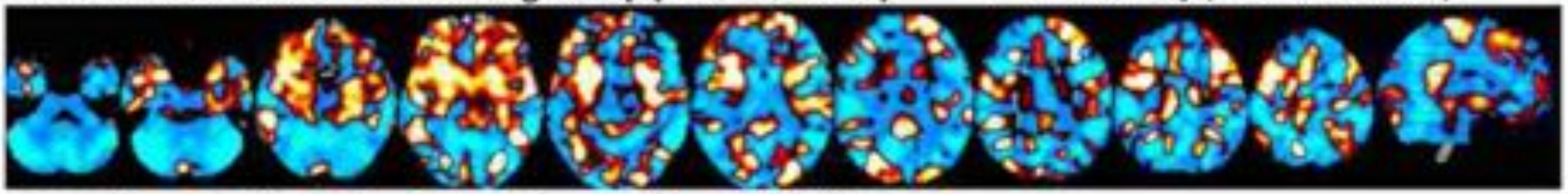
Applications of MVPR in MRI

Diagnosis:			
ADHD:	~61%	sMRI/rfMRI	(ADHD200)
Autism:	80-90%:	sMRI/DTI	(Ecker 2009, 2010, Ingalhalikar 2010)
Schizophrenia:	81-92%:	sMRI/fMRI/DTI	(Davatsikos 2005, Costafreda 2011, Ingalhalikar 2010)
MDD:	68-90%	sMRI/fMRI	(Fu, 2008, Marquand 2008, Mwangi 2012)
Prognosis:			
ARMS:	82-92%	sMRI	(Koutsouleris 2009, 2011)
PS-CP:	70	sMRI	(Mirao-Miranda 2011)
Treatment response prediction:			
MDD:	69-89%	sMRI/fMRI	(Fu 2008, Costafreda 2009a,b, Gong 2011)
Schizophrenia:	85%	EEG	(Khodayari-Rostamabad 2010)
Multimodal MVPR:			
f/sMRI & NPS:	80%	reading	(Hoeft 2007)
sMRI& PET	65-100%	MCI	(Fan 2008, Zhang 2011, Cui 2011)
sMRI & DTI	91-98%	MCI	(Fan 2008, Haller 2010)
fMRI & genes:	87%	Schizophr.	(Yang 2010)

Pattern recognition analysis using grey matter

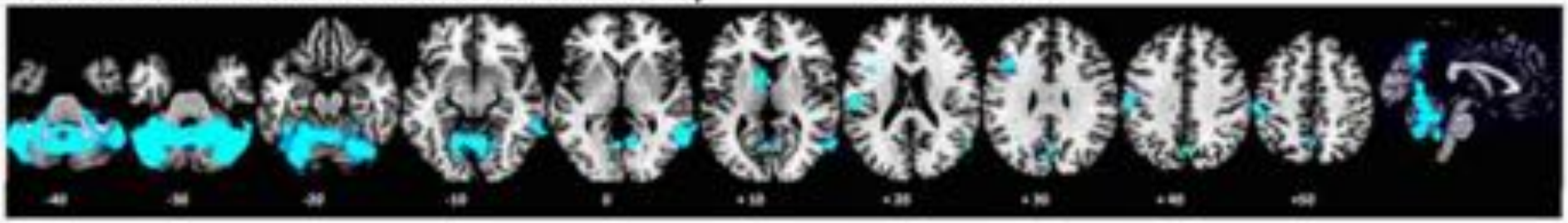
29 ADHD; 33 Controls

A. Multivariate discrimination weight map (unthresholded) 79.3% accuracy (76% ADHD; 83% C)



B. Multivariate discrimination weight map (thresholded)

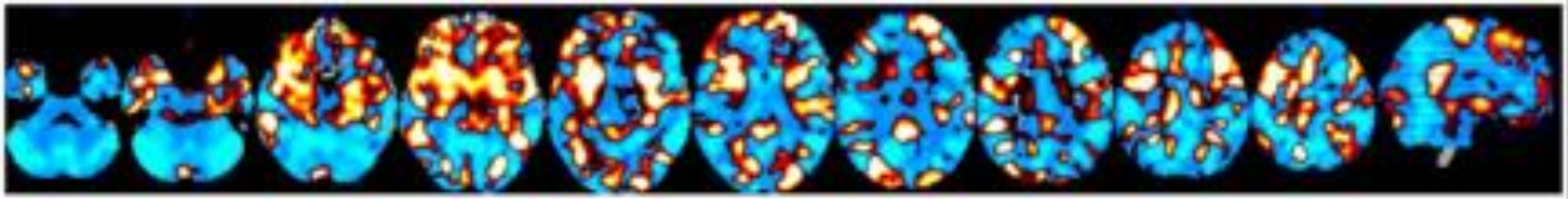
C. Conventional mass-univariate t-statistic map Controls > ADHD



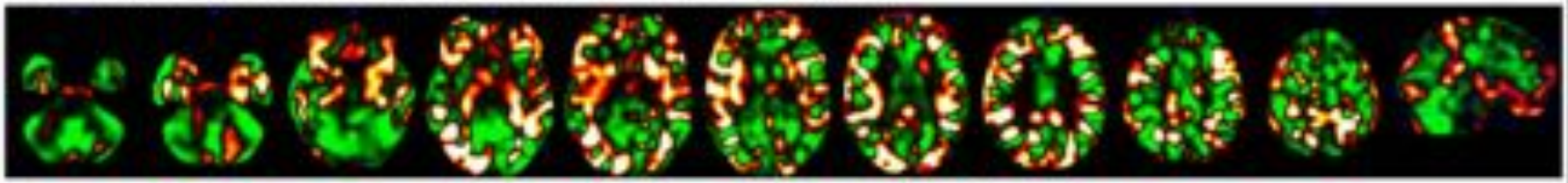
Lim, Marquand, Chantiluke, Mehta, Simmons, Rubia, PLOS One, 8(5): e63660

Disorder-specific pattern classification in GM: ADHD vs ASD

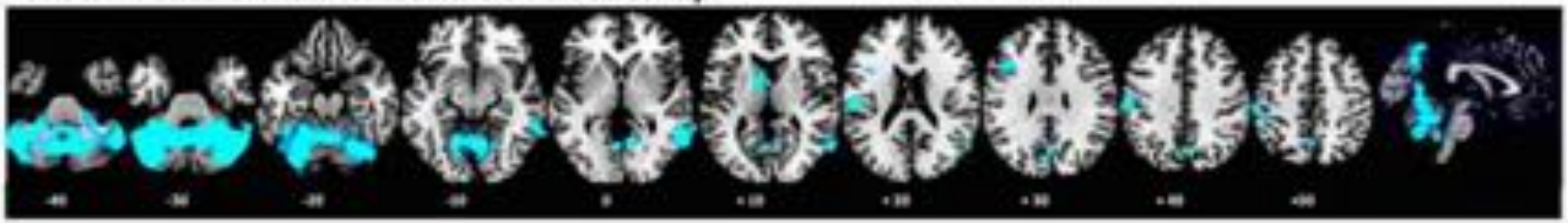
29 ADHD (orange) versus 33 healthy controls (blue): Accuracy: 79.3 %, sensitivity 74% (ADHD); specificity 83% (controls)



29 ADHD (orange) versus 19 ASD (green): Accuracy 83%, 93% (ADHD), 68% (ASD)



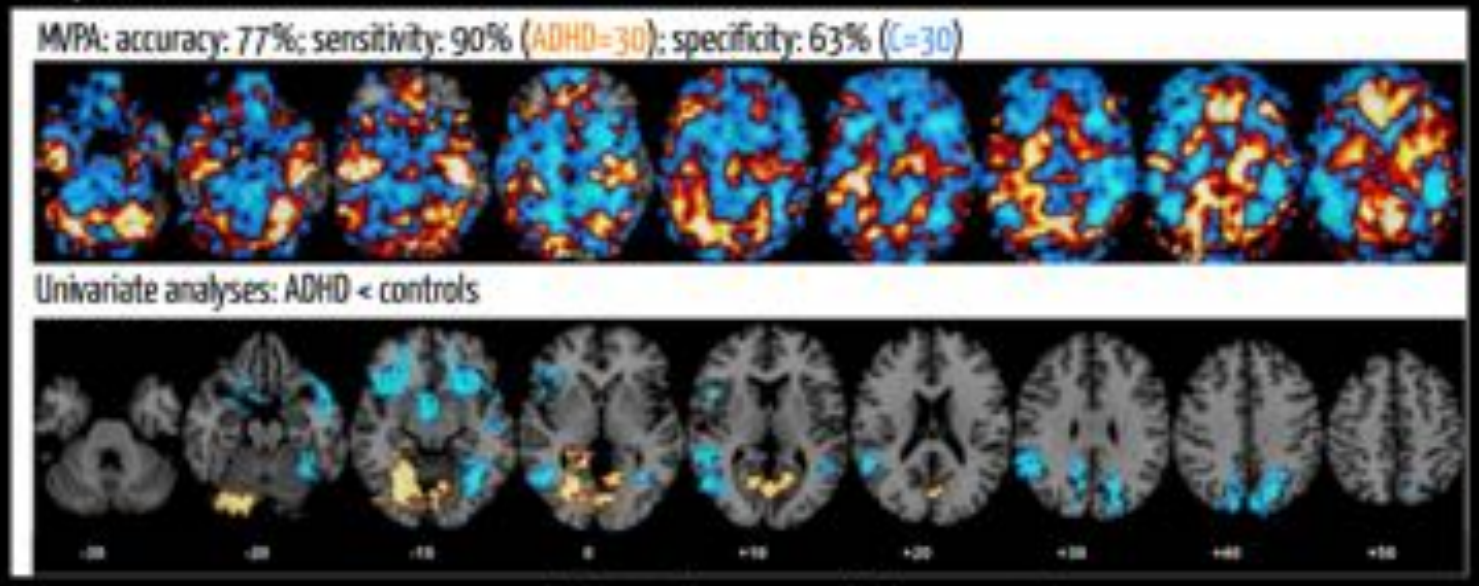
C. Conventional mass-univariate t-statistic map Controls > ADHD



Lim, Marquand, Mehta, Rubia, PLOS One, 8(5): e63660

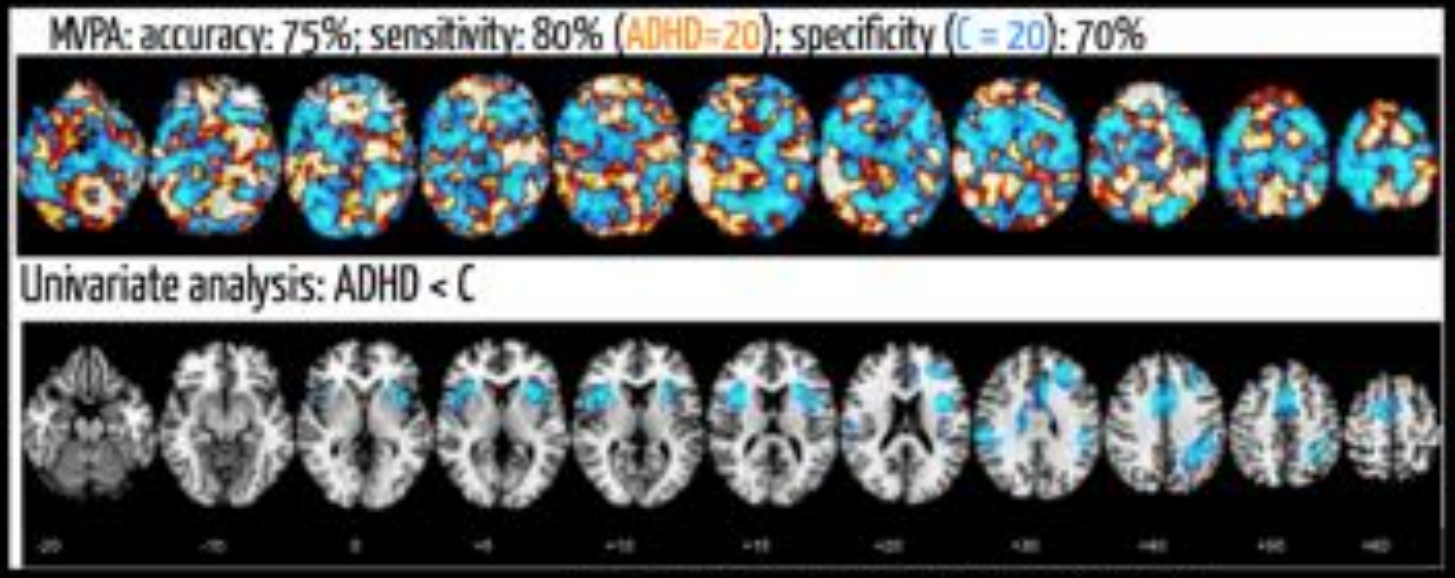
Pattern recognition analysis using fMRI

Stop task



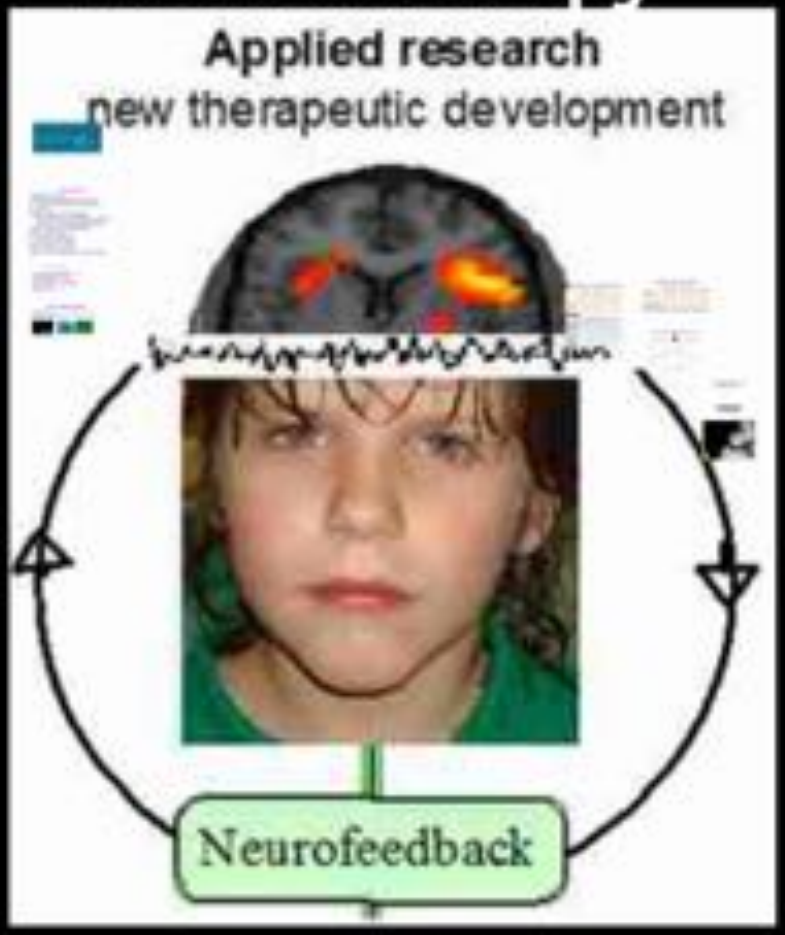
Hart et al., 2013, HBM, 35: 3083-3094

Time discrimination



Hart et al., 2013, JAACAP, 53: 569-578

Neurotherapy



Analucia Alegria

Helen Brinson

Children with ADHD can self-regulate
brain activation -> clin improvement
no region-specificity

Neuroscience-based neurotherapy for ADHD:

rIFC underactivated, disorder-specific & modulated by stimulants =>

fMRI NF for self-upregulating rIFC activation

EEG Neurofeedback in ADHD

Beta-theta ratio upregulation; slow cortical potentials

Meta-analyses: medium ES for prob blinded parent ratings to improve inattention & hyp/imp & smaller ES for teacher ratings (Micouloud-Francis 2014).

Several head-to-head RCT studies find similar effects to stimulants.

Advantage of fMRI NF

Better spatial resolution => better learning

fMRI-NF requires fewer sessions (4 of 10min) (EEG: 30-40 sessions of 50min)

Can target deep regions that are key to ADHD neuropathology: rIFC

Can easily control for region-specificity (<=>sham NF)

Can measure learning (brain act) & how it relates to outcomes

fMRI-NF study design

First fMRI-NF study in children

Single-blind RCT (parents/patients blind, not researcher)

N = 31 ADHD (combined) boys; stable medicated/med-naive

Age: 12-18 years

Controlling for region-specificity of upregulation

- 18 Active Grp: R IFC : pars triangularis/orbitalis (BA 44/45/47)
- 13 Control Grp: L middle parahippocampal gyrus (L PHG)

Training: 4 scan visits of 3-4 NF sessions of 8.5min

Total: 14 sessions of 8.5min NF

Last session: Transfer session (no NF)

In 1st & last session: Stop task fMRI

Offline training with a cue-card (daily)

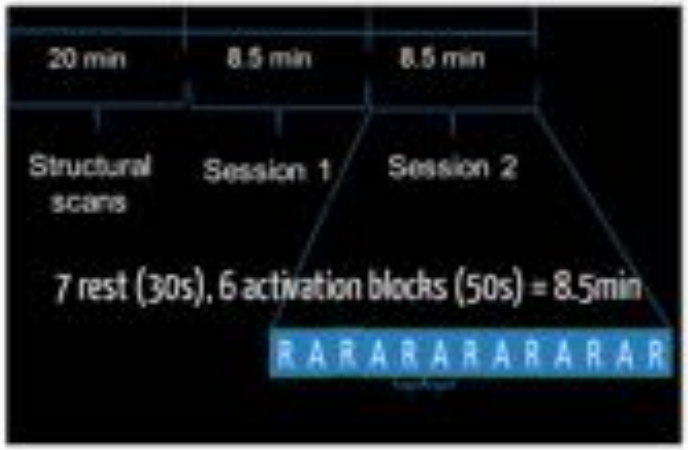
Instructions: free but we suggested concentration as an option

Outcome measures/hypotheses:

Children with ADHD can self-regulate R IFG with fMRI-NF - feasibility
Clinical ADHD symptoms (ADHD-RS) (CPRS) -reduction
Progressive increase in rIFC activity - increased ↗
Cognitive functions MARS (GNG, CPT, time discr, TD)-improvement
rIFG activation during fMRI stop task -increase in active group
Side effect scale: no side effects
Long-term effects: 6 months persistence

Real-time fMRI Neurofeedback

Real-time fMRI software in AFNI that provides immediate access to the fMRI images as they are reconstructed
GE MR750 3T MR scanner. => 6s delay
NF calculation: (ROIEXP - ROIREF) - (ROIEXPPrevious - ROIREFPrevious) => progressively more difficult to move rocket.
Can win 10 points (% of video covered) = €10



Bodurka, J. & Bandettini, P (2008) Real-time software for monitoring MRI scanner operation. Neuroimage, 41(S1): p. S85.

Conclusions

Disorder-specificity

Reduced GM & activation in right IFC/BG & AI is disorder-specific to ADHD vs OCD & ASD
Reduced GM in Cb is disorder-specific to ADHD vs ASD
Dissociated abnormalities in BG/AI GM in ADHD (<) vs OCD (>) & in IFC activation in ADHD (<) vs ASD (>)

Medication

LT stimulants are associated with more normal BG structure & function (not replicated in recent studies), but with abnormally high striatal DAT levels.
Acute stimulant in fMRI: consistent upregulation in R IFC/AI/putamen & deactivation of DMN
Some evidence that Atomoxetine & Fluoxetine have comparable IFC upregulation/normalisation effects

Brain-based diagnosis

Machine learning based methods for NI are promising & may be able to aid with diagnosis (& prognosis) - higher classification accuracy & replication across scanners & samples necessary for clinically use.

Neurotherapy

fMRI-Neurofeedback is feasible in ADHD children. They can self-regulate specific brain regions and this is associated with clinical improvement (region-specificity needs to be further investigated)


Institute of Psychiatry
at The Maudsley
Fundación Alicia Koplowitz
MRC Medical Research Council
NHS National Institute for Health Research
THANK YOU!
KIDSCOMPANY
Lilly
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