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

Prof Katya Rubia  Dep Child & Adol Psychiatry

Brain deficits
ADHD have cognitive domain-specific functional deficits in several frontal-striatal-cortical networks & problems with switching off DMNs — both CFT deficits
Most prominent abnormality is in RFLP: frontal, basal ganglia, anterior insula, cerebellum, delay in left cortical thickness & gray matter.

Specificity
ADHD have disorder-specific abnormality in structure & function (inhibition) of VLPF/VS relative to OCD & ASO (△)
PC dysfunction is dissociated between ADHD (△) & ASO (△)
Putamen & AI GM reduction is disorder-dissociated
GM in ADHD (△) vs ASO

Translation
Diagnosis & prognosis?

Medication
Long-term standard treatment △: more erratic activity (δ frequency) of the basal ganglia (not replicated in recent studies) but with abnormal high striatal D2 levels.
Microscopy: FEF, cingulate, & intrastriatal dopamine excretion △
GTS (Guanidine) & clozapine △: GM & FEF activity

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ESCAP June 2015
Brain imaging in ADHD: disorder-specificity, medication effects & clinical translation

Prof Katya Rubia  
Dep Child & Adol Psychiatry

Brain deficits

ADHD have disorder-specific abnormality in structure & function (inhibition) of IFC/Nu/NG relative to OCD & XSD & CI
UTC dysfunction is dissociated in ADHD (+) & ASB (+)
Putamen & AI GM reduction is disorder-dissociated in ADHD (+) & OCD (+)
Cto-GM is smaller in ADHD vs XSD

Translation

Diagnosis/progress?

Medication

Long-term stimulant medication -> normalization structure & function of the basal ganglia (not replicated in recent studies)
but with abnormally high CSF levels
Meta-analysis: acute stimulants consistently 
result in IFG & NAc & deactivation BAs
4/5 & fluoxetine also medication C5/8

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ESCAP June 2015
Disclosures

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

COOL
- Working memory
  - Visuo-Spatial
  - Verbal
- Inhibition
  - Motor inhibition
  - Interference inhibition
  - Cognitive switching
- Attention
  - Sustained
  - Selective
  - Attention allocation
- Temporal processing

EXECUTIVE FUNCTIONS

HOT
- Reward-related decision making
  - Reward anticipation
    - Temporal discounting
- Delay of reward
- Motor timing

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
   - Medial view:
     - 21 fMRI studies; 187 ADHD
     - ACC/SMA
   - Lateral view:
     - Thalamus
     - IFC
   Hart, Radua, Mataix, Rubia, 2013
   JAMA Psychiatry 70: 185.

B. Meta-analysis of attention
   - Medial view:
     - 13 fMRI studies; 171 ADHD
     - PL
   - Lateral view:
     - DLPFC
     - Basal ganglia
   Hart et al., Neurosci Behav Brain Res 36:2248.

C. Meta-analysis of timing
   - Medial view:
     - 11 fMRI studies; 178 ADHD
     - PCC/Precuneus
   - Lateral view:
     - Cb
     - IFC

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
Meta-analyses of whole brain fMRI studies in ADHD

A. Meta-analysis of inhibition
   Medial view: 21 fMRI studies; 187 ADHD
   ACC/SMA
   Lateral view: Thalamus, basal ganglia
   IFC

B. Meta-analysis of attention
   Medial view: 13 fMRI studies; 171 ADHD
   PL
   Lateral view: Basal ganglia, DLPFC

C. Meta-analysis of timing
   Medial view: 11 fMRI studies; 178 ADHD
   PCC/Precuneus, Cb
   Lateral view: PL, IFC

Hart, Radua, Mataix, Rubia, 2013
JAMA Psychiatry 70: 185.

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
Reduced deactivation of the default mode network

Parametric sustained attention task:
3 difficult levels

10

40

- 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
Meta-analyses of whole brain fMRI studies in ADHD

A. Meta-analysis of inhibition
   Medial view: 21 fMRI studies; 187 ADHD
   ACC/SMA
   Lateral view: Prefrontal cortex; basal ganglia

B. Meta-analysis of attention
   Medial view: 13 fMRI studies; 171 ADHD
   PL
   Lateral view: DLPFC; basal ganglia

C. Meta-analysis of timing
   Medial view: 11 fMRI studies; 178 ADHD
   PCC/Precuneus; Cb
   Lateral view: IFC; PL


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
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

Most consistent brain abnormalities in ADHD

Task-related activation

- DLPFC
- IFC
- dACC
- SMA

Default mode network

- MFC
- ACC
- Inferior parieto-temporal
- PCC
- Superior temporal

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
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

Dysfunctions specific to CD (ADHD; C)

Inhibition failure
- TL

Sustained attention
- Hippocampus
- Insula
- ACC

Reward
- vmOFC

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
ADHD vs OCD & C

Stop
C, OCD > AD
C > AD, OCD

Switch
C > AD (OCD)

Oddball
C, OCD > AD

corr with severity
Rubia et al., HBM, 2010, HBM 2011
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
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

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
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
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/Al & BG & deactivate DMN [ATX & Fluoxetine also modulate R IFG/Al]
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

- Disadvantages
  - Heart rate & blood pressure
  - problematic for Tics?
  - addictive potential?
  - appears to stunt growth
  - appetite
  - sleep problems
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
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 I² 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-naïve 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-naïve 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-naive: reduced DAT

Regression of % of drug naive on Hedges's g

Stimulant Medication

\[ \beta = -1.61, \text{CI}95\% = -2.19/-1.03, Z = -5.45, p < 0.001 \]

controls

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-sectionalal 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
- Onnik 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.

• Symptomatic throughout study.

A
ADHD medication-naïve vs. ADHD on psychostimulants

Medication had no effect: dichotomously or time on meds

Also in NeuroImage cross-sectional sample cumulative medication intake not related to striatum GM (307 ADHD) (Greven et al., 2015)

B
ADHD medication-naïve vs. typically developing controls

C
ADHD on psychostimulants vs. typically developing controls

Developmental trajectories (estimates with 95% CI) for the striatal and surface areas. Note: There were no significant differences in the shape of the GM surfaces.
Long-term stimulants effects in fMRI meta-analyses

Caudate in attention meta-regression analysis
Effect of LT medication

Meta-regression analysis of 14 whole brain sMRI studies

- 24 studies (7 adults, 9 children)
- R-amphetamine 34/7
- 12/sulpiride 12
- Reduction of LA
- Reduction of DR
- Reduction of PR
- Caudate, putamen, globus pallidus

Medication effects (controlled for age)

Hart, Radua, Mataix, Rubia, JAMA Psychiatry. 2013, 70: 185-98
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-naive 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)**

<table>
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<th>Task</th>
<th>MED</th>
<th>IFC</th>
<th>DLPFC</th>
<th>BG</th>
<th>ACC</th>
<th>PCC</th>
<th>Cb</th>
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</table>

**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
Deactivation

$\text{dmACC}$

$p < 0.005$
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

A R C H I V A L  R E P O R T

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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.

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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.
Atomoxetine vs Methylphenidate

Working memory
- R DLPFC
  - C > ADHD Plac
  - C > ADHD MPH
  - C > ADHD ATX
  - Accuracy improved with both drugs

Stop task
- IFC – correlated SSRT
  - Only MPH improved SSRT
  - Normalisation sign for both in L IFG
  - Sign for MPH in R IFG + Cb (trend for ATX)

Time discrimination
- Go process
  - 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, Giampeetro, Brammer, Simmons, Rubia in submission

Within-Patient Comparisons
C. Group by Medication Interaction Effects

Chantiluke, Barrat, .... Rubia, Psychopharmacology 232(12):2071-82.
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 → clinical improvement
- No region-specificity

Neurofeedback
Diagnosis/prognosis?

Multivariate pattern recognition analyses have the potential to aid in clinical diagnosis & prognosis.
Traditional MRI analysis:
- mass
- univariate

\[ \Rightarrow \]

Multivariate pattern recognition analyses
- designed to identify spatial/temp patterns that discriminative between groups
- combinatorial effects $\Rightarrow$ more sensitive
- generalise categorization to new individual data
  $\Rightarrow$ diagnostic & prognostic indicators of individuals $\Rightarrow$ groups
# Applications of MVPR in MRI

## Diagnosis:
- ADHD: ~61% sMRI/rfMRI  
  (ADHD200)
- Autism: 80-90%: sMRI/DTI  
- 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% Schizophrenia  
  (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

MVPA: accuracy: 77%; sensitivity: 90% (ADHD=30); specificity: 63% (C=30)

Univariate analyses: ADHD < controls

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

Time discrimination

MVPA: accuracy: 75%; sensitivity: 80% (ADHD=20); specificity (C = 20): 70%

Univariate analysis: ADHD < C

Hart et al., 2013, JAACAP, 53; 569-578
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 from the GE MR750 3T MR scanner. => 6s delay

NF calculation: \((\text{ROIEXP} - \text{ROIREF}) - (\text{ROIEXPPrevious} - \text{ROIREFPrevious})\) => progressively more difficult to move rocket. Can win 10 points (\% of video covered) = £10

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)
THANK YOU!

All participants

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Somerset House and King’s College before the Thames Embankment was made.