Aetiology of ADHD

Ulrich Müller
(um207@cam.ac.uk)

Adult ADHD Research Clinic Cambridge,
Department of Psychiatry, University of Cambridge /
Cambridgeshire & Peterborough NHS Foundation Trust
Overview

- ADHD – a neurodevelopmental disorder
- From genes to clinical phenotypes
- Structural and functional MRI
- Dopamine hypothesis of ADHD – new evidence from neuroimaging
- Noradrenergic modulation of inhibitory control
Attention deficit hyperactivity disorder (ADHD)

Diagnostic criteria

- Inattention
- Hyperactivity / Impulsivity
  - ≥6 symptoms
  - >6 months

- Onset of disorder ≤ 7 years of age

- Children: Problems both at home and at school
- Adults: Clinically significant distress or impairment in social, academic, or occupational functioning
Age-dependent decline of attention deficit hyperactivity disorder: Meta-analysis of follow-up studies

Faraone et al., Psychol Med 2005

Diagram showing the relationship between age at follow-up and persistence of diagnoses.
Attention deficit hyperactivity disorder (ADHD) – comorbidity

- **Other neuro-developmental disorders**
  (dyslexia, autism spectrum, tics / Tourettes etc.)

- **Mood disturbances**
  (mood swings, anxiety, depression, bipolar disorder)

- **Substance abuse**
  (caffeine, nicotine, alcohol, cannabis, amphetamines, ecstasy, cocaine)

- **Personality disorders**
  (antisocial, borderline, obsessive-compulsive)

- **Impulse control disorders**
  (problem gambling, internet addiction, kleptomania, pyromania etc.)
From genes to clinical phenotypes
Evidence-based aetiology of ADHD
Coghill et al., presented at BAP guideline meeting 2011

A: Sufficient Evidence of a Causal Relationship
   No risk factor met these criteria

B: Sufficient Evidence of a Temporal Association
   Premature birth

C: Limited or Suggestive Evidence
   Maternal smoking during pregnancy
   Low birth weight
   DNA variants in SLC6A3, DRD4, DRD5, HTR1B, SLC6A4 and SNAP25

Risk Ratios

- Prematurity
- SNAP25
- HTR1B
- SLC6A4
- DRD5
- DRD4
- SLC6A3
- Low Birth Weight
- Maternal Smoking
Neuroscience of attention-deficit / hyperactivity disorder: the search for endophenotypes

Castellanos & Tannock, Nature Rev Neurosci 2002
Dopamine transporter gene polymorphism moderates the effects of severe deprivation on ADHD symptoms: developmental continuities in gene-environment interplay

Stevens et al., Am J Genet 150B: 753-61

Mean level of sADHD (Rutter Scales/SDQ) across assessment ages as a function of duration of institutional deprivation

Z-standardized sADHD scores at 6, 11, and 15 years (Rutter Scales/SDQ) as a function of early deprivation experience and DAT1 haplotype
Structural MRI in ADHD
(cortical thickness, VBM, DTI)
Brain networks implicated in ADHD
Lister et al., Biological Psychiatry 2011

Replicated structural MRI findings in ADHD:
Total brain volume ↓, cortical thickness ↓, grey matter ↓, ACC ↓, PFC ↓, basal ganglia ↓
Cortical development in typically developing children with symptoms of hyperactivity and impulsivity

Shaw et al., Am J Psychiatry 2011, 168: 143-51
Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication

Nakao et al., Am J Psychiatry 2011

FIGURE 1. Regions of Smaller and Larger Gray Matter Volumes in Individuals With ADHD Compared With Healthy Comparison Subjects

* Smaller volumes are indicated in blue, and larger volumes in orange. Significant clusters have been overlaid to a Talairach template for display purposes only.

FIGURE 2. Results of the meta-regression 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
Regions of reduced white matter density and axial diffusivity in ADHD patients compared to controls in MNI space.

Axial diffusivity ($\lambda_1$) values in these regions were extracted post-hoc from the intersection between the VBM WM2 cluster and the TBSS FA skeleton (green).
Diffusion tensor imaging (DTI) in adult ADHD - correlations with symptoms severity

Del Campo et al., submitted
Dopamine hypothesis of ADHD – new evidence from neuroimaging
First option and other treatment recommendations in 10 national / international ADHD guidelines

Seixas / Weiss / Müller, J Psychopharmacol 2011
PET / SPECT imaging of the dopamine system in ADHD [published studies with healthy controls]

- **Dopamine synthesis**
  - Down: Ernst et al. 1998[^18F-dopa]; Forssberg et al. 2006[^11C-levodopa], Ludolph et al. 2008[^18F-dopa]
  - Up: Ernst et al. 1999[^18F-dopa];

- **Striatal dopamine transporter (DAT) availability**

- **Striatal D2/D3 dopamine receptor density**
  - Down: Volkow et al. 2007b, 2009[^11C-raclopride]

- **Dopamine release (D2/D3 radiotracer displacement)**
  - Down: Volkow et al. 2007b[^11C-raclopride]
  - Up: Del Campo et al. 2011[^18F-fallypride]
Dopaminergic dysfunction in ADHD: 3,4-dihydroxy-6-[18F]fluorophenyl-l-alanine PET
Ludolph et al., Neuroimage 2008; 41: 718-27

ADHD patients [20] < controls [18]:
L/R putamen,
L/R amygdala,
R dorsal midbrain
PET / SPECT imaging of the dopamine system in ADHD [published studies with healthy controls]

- **Dopamine synthesis**
  - ↓ Ernst et al. 1998 \([^{18}F\text{-dopa}]\); Forssberg et al. 2006 \([^{11}C\text{-levodopa}]\), Ludolph et al. 2008 \([^{18}F\text{-dopa}]\)
  - ↑ Ernst et al. 1999 \([^{18}F\text{-dopa}]\)

- **Striatal dopamine transporter (DAT) availability**
  - ↑ Dougherty et al. 1999 \([^{123}I\text{-altropane}]\); Spencer et al. 1999 \([^{11}C\text{-altropane}]\); Krause et al. 2000 \([^{99mTc\text{-TRODAT-1}}]\); Cheon et al. 2003 \([^{123}I\text{-IPT}]\); Larisch et al. 2006 \([^{123}I\text{-FP-CIT}]\); Spencer et al. 2007 \([^{11}C\text{-altropane}]\)
  - ⇧ van Dyck et al. \([^{123}I\text{-β-CIT}]\); Jucaite et al. 2005 \([^{11}C\text{-PE2I}]\)
  - ↓ Volkow et al. 2007a, 2009 \([^{11}C\text{-cocaine}]\); Hesse et al. 2009 \([^{123}I\text{-FP-CIT}]\)

- **Striatal D2/D3 dopamine receptor density**
  - ↓ Volkow et al. 2007b, 2009 \([^{11}C\text{-raclopride}]\)
  - ⇧ Jucaite et al. 2005 \([^{11}C\text{-raclopride}]\); Del Campo et al. 2011 \([^{18}F\text{-fallypride}]\)

- **Dopamine release** (D2/D3 radiotracer displacement)
  - ↓ Volkow et al. 2007b \([^{11}C\text{-raclopride}]\)
  - ⇧ Del Campo et al. 2011 \([^{18}F\text{-fallypride}]\)
Evaluating dopamine reward pathway in ADHD: Clinical implications

Volkow et al., JAMA 2009; 302: 1084-91

[^11C]raclopride PET: DA D2/D3 receptors
ADHD patients [53] < controls [44]:
L N. accumbens, hypothalamus, caudate, midbrain

[^11C]cocaine PET: DA transporter
ADHD patients [53] < controls [44]:
L midbrain, N. accumbens, caudate
Evaluating dopamine reward pathway in ADHD: Clinical implications

Volkow et al., JAMA 2009; 302: 1084-91 / Mol Psychiatry 2011; 16: 1147-54
**Meta-analysis of striatal DAT density in ADHD patients and healthy comparison subjects employing random-effects model**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges' g</th>
<th>p</th>
<th>Hedges' g and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dougherty et al., 1999 (16)</td>
<td>2.37</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>van Dyck et al., 2002 (17)</td>
<td>-0.02</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Cheon et al., 2004 (32)</td>
<td>1.26</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Jucaite et al., 2005 (33)</td>
<td>0.16</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>la Fougere et al., 2006 (34)</td>
<td>1.19</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Larisch et al., 2006 (35)</td>
<td>0.75</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Spencer et al., 2007 (36)</td>
<td>0.81</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Volkow et al., 2009 (10)</td>
<td>-0.62</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Hesse et al., 2009 (37)</td>
<td>-0.99</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.23</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Circle size reflects the weight a study obtained in the meta-regression.

Lower effect sizes were detected in studies involving drug-naive ADHD patients

(b=−1.61, 95% CI=−2.19 to −1.03, z=−5.45, p<0.001).

PET / SPECT imaging of the dopamine system in ADHD [published studies with healthy controls]

- **Dopamine synthesis**
  - Ernst et al. 1998 $[^{18}F$-dopa]; Forssberg et al. 2006 $[^{11}C$-levodopa], Ludolph et al. 2008 $[^{18}F$-dopa]
  - Ernst et al. 1999 $[^{18}F$-dopa]

- **Striatal dopamine transporter (DAT) availability**
  - Dougherty et al. 1999 $[^{123}I$-altropane]; Spencer et al. 1999 $[^{11}C$-altropane]; Krause et al. 2000 $[^{99mTc}$-TRODAT-1]; Cheon et al. 2003 $[^{123}I$-IPT]; Larisch et al. 2006 $[^{123}I$-FP-CIT]; Spencer et al. 2007 $[^{11}C$-altropane]
  - van Dyck et al. $[^{123}I$-β-CIT]; Jucaite et al. 2005 $[^{11}C$-PE2I]
  - Volkow et al. 2007a, 2009 $[^{11}C$-cocaine]; Hesse et al. 2009 $[^{123}I$-FP-CIT]

- **Striatal D2/D3 dopamine receptor density**
  - Volkow et al. 2007b, 2009 $[^{11}C$-raclopride]
  - Jucaite et al. 2005 $[^{11}C$-raclopride]; Del Campo et al. 2011 $[^{18}F$-fallypride]

- **Dopamine release** (D2/D3 radiotracer displacement)
  - Volkow et al. 2007b $[^{11}C$-raclopride]
  - Del Campo et al. 2011 $[^{18}F$-fallypride]
**[¹⁸F]fallypride PET study – D2/D3 receptor binding potentials on placebo day**

Del Campo et al., Neuroimage 2011 / Del Campo, ..., Müller, *submitted*

---

**Figure 2.** Coronal T1-weighted MRI brain slice of one representative volunteer with bilateral striatal ROIs superimposed. Top portion of the figure shows pre-commissural ROIs. The red line (1) helped to divide the caudate and putamen into ventral and dorsal. ROIs are: ventral striatum (2,3), pre-commissural dorsal putamen (4,5) and pre-commissural dorsal caudate (6,7). Bottom portion of the figure shows post-commissural putamen (8,9) and post-commissural caudate (10,11).

---

No displacement differences between ADHD patients and healthy controls.
Correlations between ADHD symptoms and $[^{18}\text{F}]\text{fallypride}$ binding

Del Campo, ..., Müller, submitted

$r = -0.516, p = 0.020$

$r = -0.542, p = 0.019$

$r = -0.126, p = 0.320$

$R = -0.596, p = 0.010$
[18F]fallypride PET study – D2/D3 receptor binding potentials on placebo day

Del Campo, ..., Müller, submitted

**Figure 8.** Low performers had (A) decreased [18F]fallypride BP in left pre-commissural caudate on placebo [F (1,28) = 4.63, p = 0.04], as well as (B) decreased BP % change in substantia nigra following methylphenidate (relative to placebo) [F(1,28) = 9.351, p = 0.005].

Partial replication of Volkow et al. 2007 when comparing high and low performing participants (independent of patient status)
Summary – $^{[18\text{F}]}$fallypride PET study

Single oral dose of MPH displaces $^{[18\text{F}]}$fallypride.

**No difference** in baseline D2/D3 R availability between ADHD and controls (in striatum, globus pallidus, thalamus and substantia nigra)

**No difference** in magnitude of DA increase following oral MPH.

D2/D3 receptor availability modulates attention, working memory and trait impulsivity similarly in ADHD and controls.

MPH effects are less pronounced in low performing participants –> implications for continuity model of DA (NA) deficits in ADHD.
Noradrenergic modulation of inhibitory control
Stop-signal reaction time task (SSRT)

This task measures the participant’s ability to inhibit a pre-potent response.

Horse-race model
Stop-signal reaction time is increased in ADHD

Aron et al., Biol Psychiatry 2003
Methylphenidate, modafinil, and atomoxetine improve stop-signal inhibition in adults with ADHD

Aron et al., Biol Psychiatry 2003

Methylphenidate 30mg

Modafinil 200mg

Atomoxetine 60mg

Turner et al., Biol Psychiatry 2004

Chamberlain et al., Biol Psychiatry 2007

SSRT (ms)

ADHD unmedicated

Controls unmedicated

ADHD medicated

Placebo

Drug

Placebo

Drug

p=0.016

p=0.028

p=0.016

*p >
Atomoxetine modulates right inferior frontal activation during inhibitory control – a pharmacological fMRI study

Chamberlain, Hampshire, Müller, et al., Biol Psychiatry 2009

Scatter plots showing plasma atomoxetine levels against mean RIFG activation during successful inhibition

Atomoxetine 40mg enhances the inhibition-related BOLD signal
(second level CamBA analysis of drug effect: cluster wise, permutational ANOVA)
Stopping and Shifting in Adult ADHD

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>6:13</td>
<td>6:13</td>
</tr>
<tr>
<td>Age</td>
<td>29.11</td>
<td>28.58</td>
</tr>
<tr>
<td>NART</td>
<td>115.65</td>
<td>116.03</td>
</tr>
<tr>
<td>MADRS*</td>
<td>9.79</td>
<td>5.05</td>
</tr>
<tr>
<td>ASRS-inatt*</td>
<td>26.00</td>
<td>14.26</td>
</tr>
<tr>
<td>ASRS-hyp/im*</td>
<td>22.53</td>
<td>10.68</td>
</tr>
<tr>
<td>ASRS*</td>
<td>48.53</td>
<td>24.89</td>
</tr>
<tr>
<td>CAARS*</td>
<td>49.33</td>
<td>20.00</td>
</tr>
</tbody>
</table>

Dodds et al., Cereb Cortex 2010

Morein-Zamir et al., in preparation
ADHD patients had slower responses and increased commission errors

No differences in the neural correlates of shifting between patients and controls

ADHD patients under-activate the anterior Insula / frontal Operculum (al/fO), a key region associated with stopping

This activation correlated negatively with ADHD symptom severity

Morein-Zamir, Müller et al., in preparation
Aetiology of ADHD – Conclusions

- "ADHD genes" and perinatal factors have small effects
- Recent neuroimaging evidence supports
  - maturational delay hypothesis
  - catecholamine deficit hypothesis and
  - continuum model
- We need better integration of neuro-developmental and psychopharmacological research
Thank you for your attention!
Disclosures

**Competitive grants**
- Alexander von Humboldt Foundation; Clare Hall / Isaac Newton Trust, University of Cambridge; Medical Research Council (MRC); Mental Health Research Network (MHRN)

**Educational grants**
- Janssen-Cilag

**Speaker honoraria / travel support**
- Bristol-Myers Squibb (BMS); Janssen-Cilag; Lundbeck; Pharmacia-Upjohn; UCB Pharma

**Advisory board**
- Janssen-Cilag
- Eli Lilly

Some medicinal products discussed in this talk have been used in non-licensed indications (exempted by BfArM / MHRA)
UK Adult ADHD Network

- Prof. Philip Asherson (IoP, London)
- Dr Marios Adamou (Wakefield)
- Dr Muhammad Arif (Leicester)
- Dr Blanca Bolea (Bristol)
- Dr David Coghill (Dundee)
- Prof. Gisli Gudjohnsson (IoP, London)
- Dr Ulrich Müller (Cambridge)
- Mark Pitts (SLAM, London)
- Dr Susan Young (IoP, London)
The genetics of attention deficit/hyperactivity disorder in adults, a review

B Franke\textsuperscript{1,2}, SV Faraone\textsuperscript{3}, P Asherson\textsuperscript{4}, J Buitelaar\textsuperscript{5}, CHD Bau\textsuperscript{6,7}, JA Ramos-Quiroga\textsuperscript{8}, E Mick\textsuperscript{9}, EH Grevet\textsuperscript{7}, S Johansson\textsuperscript{10,11}, J Haavik\textsuperscript{11,12}, K-P Lesch\textsuperscript{13,14}, B Cormand\textsuperscript{15,16,17} and A Reif\textsuperscript{18}, on behalf of the International Multicentre persistent ADHD CollaboraTion (IMpACT)

The adult form of attention deficit/hyperactivity disorder (aADHD) has a prevalence of up to 5% and is the most severe long-term outcome of this common neurodevelopmental disorder. Family studies in clinical samples suggest an increased familial liability for aADHD compared with childhood ADHD (cADHD), whereas twin studies based on self-rated symptoms in adult population samples show moderate heritability estimates of 30–40%. However, using multiple sources of information, the heritability of clinically diagnosed aADHD and cADHD is very similar. Results of candidate gene as well as genome-wide molecular genetic studies in aADHD samples implicate some of the same genes involved in ADHD in children, although in some cases different alleles and different genes may be responsible for adult versus childhood ADHD. Linkage studies have been successful in identifying loci for aADHD and led to the identification of \textit{LPHN3} and \textit{CDH13} as novel genes associated with ADHD across the lifespan. In addition, studies of rare genetic variants have identified probable causative mutations for aADHD. Use of endophenotypes based on neuropsychology and neuroimaging, as well as next-generation genome analysis and improved statistical and bioinformatic analysis methods hold the promise of identifying additional genetic variants involved in disease etiology. Large, international collaborations have paved the way for well-powered studies. Progress in identifying aADHD risk genes may provide us with tools for the prediction of disease progression in the clinic and better treatment, and ultimately may help to prevent persistence of ADHD into adulthood.
Cortical thickness correlated with impulsivity in healthy adults

Schilling et al., NeuroImage 2012; 59: 824-830

(A) Impulsiveness total score

(B) Impulsiveness attention

(C) Impulsiveness motor

(D) Impulsiveness nonplanning
Brain gray matter deficits at 33-year follow-up in adults with ADHD established in childhood

Proal et al., Arch Gen Psychiatry 2011, 68: 1122-34
Ventro-striatal reductions underpin symptoms of hyperactivity and impulsivity in ADHD

Carmora et al., Biol Psychiatry 2009

Volumetric differences in the right and left ventral striatum between attention-deficit/hyperactivity disorder (ADHD) and control subjects. Error bars represent the SEM. VStr/TBV, volume of ventral striatum corrected for total brain volume

Correlations between the relative volume of the right ventral striatum (VStr/TBV) and clinical ratings of hyperactivity / impulsivity (HI) according to the mother.
Catecholaminergic profiles of the major drugs used in the treatment of ADHD

Heal et al., Pharmacol Biochem Behav 2008: 90: 157-69

Atomoxetine | Methylphenidate \n| Amphetamines \n| Bupropion \n
Noradrenaline | Noradrenaline + Dopamine | Dopamine

Efficacy in ADHD
- Cognitive function ↑
- Attentiveness ↑
- Distractibility ↓
- Hyperactivity ↓
- Behavioural disruption ↓

Adverse effects
- Insomnia ↑
- BP/HR ↑
- Nausea/vomiting ↑
- Abdominal pain ↑
- Tics ↑?
- Appetite ↓
- Bodyweight ↓
- Growth rate ↓
Moderators of methylphenidate efficacy for adults with ADHD: a meta-regression analysis

Castells et al., CNS Drugs 2011; 25: 157-69
Adult ADHD compared to psychiatric and general medicine medication

Leucht et al., Br J Psychiatry 2012; 200: 97-106
PET study – Behavioural differences between ADHD patients and controls

<table>
<thead>
<tr>
<th>Self-rating scales</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASRS</strong> Total</td>
<td>56</td>
<td>0.00</td>
</tr>
<tr>
<td>Inattention</td>
<td>34.3</td>
<td>0.00</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>46.7</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Barratt</strong> Total</td>
<td>21.86</td>
<td>0.00</td>
</tr>
<tr>
<td>Attention</td>
<td>43</td>
<td>0.00</td>
</tr>
<tr>
<td>Motor</td>
<td>6.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-planning</td>
<td>13.43</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive measures (CANTAB)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Visual Information Processing</strong></td>
<td></td>
</tr>
<tr>
<td>RVP A'</td>
<td>6.25</td>
</tr>
<tr>
<td>RVP B'</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Spatial Working Memory</strong></td>
<td></td>
</tr>
<tr>
<td>Between errors</td>
<td>4.6</td>
</tr>
<tr>
<td>Double errors</td>
<td>6.1</td>
</tr>
<tr>
<td>Strategy</td>
<td>1.5</td>
</tr>
<tr>
<td>Total errors</td>
<td>4.8</td>
</tr>
<tr>
<td>Within errors</td>
<td>5.5</td>
</tr>
</tbody>
</table>
[^18F]fallypride PET study – D2/D3 receptor binding potentials on placebo day

Del Campo, ..., Müller, submitted

Figure E.2: MPH increased endogenous DA levels not only in striatum and midbrain, but also in globus pallidus, limbic regions (hippocampus and amygdala) and temporal cortices (p<0.01, corrected for family-wise errors).
Diffusion tensor imaging (DTI) in adult ADHD

Del Campo et al., *submitted*

Regions of reduced **white matter density** and **axial diffusivity** in ADHD patients compared to controls in MNI space.

Axial diffusivity ($\lambda_1$) values in these regions were extracted post-hoc from the intersection between the VBM WM2 cluster and the TBSS FA skeleton (green).
Diffusion tensor imaging (DTI) in adult ADHD - correlations with symptoms severity

Del Campo et al., submitted

![Graph 1: Axial diffusivity (λ1) in the left middle frontal cortex vs. ASRS (total scores)](image1)

- Controls
- ADHD patients
- Fit line for Total

![Graph 2: Grey matter density in left middle frontal cortex vs. ASRS (total scores)](image2)

R Sq Linear = 0.169
Dopaminergic dysfunction in ADHD: 3,4-dihydroxy-6-[18F]fluorophenyl-l-alanine PET

Ludolph et al., Neuroimage 2008; 41: 718-27

Treated [12] < untreated [8] ADHD patients:

L/R putamen,
L/R amygdala,
L/R insula,
R anterior cingulate
Dopamine transporter imaging in adult patients with attention-deficit / hyperactivity disorder
Hesse et al., Psychiatr Res Neuroimaging 2009; 171: 120-28

ADHD patients [17] < controls [14]:
L/R head of caudate,
L/R putamen
Dopamine release in the caudate nucleus after intravenous methylphenidate is reduced in adults with ADHD

Volkow et al., Arch Gen Psychiatry 2007

Regressions slopes between changes in dopamine (DA) in caudate and in putamen and scores on Conners Adult ADHD Rating Scales (CAARS) section E (DSM-IV symptoms of inattention) in adults with ADHD. Correlations correspond for left caudate ($r=-0.49$, $P=0.04$), right caudate ($r=-0.56$, $P=0.02$), left putamen ($r=-0.61$, $P=0.008$), and right putamen ($r=-0.71$, $P=0.001$).
PET study – Relationship between cognitive and $[^{18}F]$fallypride BP changes

A. Right ventral striatum
B. Right substantia nigra

MPH-induced $[^{18}F]$fallypride displacement

MPH-induced % change in RVP A' score

group
- Controls
- ADHD patients
- Fit line for Total

MPH-induced $[^{18}F]$fallypride displacement
($BP_{ND}$ % change)
Limitations of PET studies in ADHD

- Small sample sizes
- High rate of co-morbidity
- Confounding effects of long-term medication
- Often retrospective diagnosis of childhood onset
- Medication naïve vs. off / on medication (possible withdrawal effects)
Correlations between DA imaging parameters and ADHD symptoms

- **Striatal dopamine synthesis** with
  - DSM-IV inattention (Forssberg et al. 2006)
  - DSM-III / Conners’ hyperactivity (Ernst et al. 1999)

- **Striatal / midbrain DAT availability** with
  - SWAN inattention / MPQ motivation (Volkow et al. 2009 / 2010)
  - Treatment response (Krause et al. 2005)

- **Striatal D2/D3 dopamine receptor density** with
  - ASRS inattention / hyperactivity (Del Campo et al., submitted)
  - SWAN inattention / MPQ motivation (Volkow et al. 2009 / 2010)
  - head movements (Jucaite et al. 2005)

- **DA release** (D2/D3 radiotracer displacement) with
  - RVIP attention (Del Campo et al. submitted)
  - CAARS inattention (Volkow et al. 2007b)
Effects of noradrenergic drugs on SSRT

healthy volunteers

Chamberlain et al., Science 2006

Rats

Robinson et al., Neuropsychopharmacology 2008

Müller et al., Psychopharmacology 2005

Eagle et al., Psychopharmacology 2008
(S,S)-[^{11}C]methylreboxetine
[^{11}C]MRB

"the most promising C-11 labeled positron-emission tomography (PET) radioligand for NET developed to date"

Yu-Shin Ding 2010
Displacement of $[^{11}\text{C}]\text{MRB}$ by methylphenidate (MPH) and atomoxetine (ATX)

Logan et al., Nucl Med Biol 2007; 34: 667-679
Hannestad et al., Biol Psychiatry 2010, 68: 854-860
PET Imaging of the effects of age and cocaine on the NET in the human brain using $^{[11}C]MRB$

Ding et al., Synapse 2011; 64: 30-38
Design of $[^{11}C]$MRB PET study in adults with ADHD

20 never medicated ADHD patients / 20 controls
- Age 18-40 years / male and female
- No major co-morbidity
- Unmedicated (SSRI and contraceptive pill allowed)
- Recruitment in Leipzig, Cambridge, Rostock etc.

Standardised clinical and cognitive assessment
- DIVA, MINI 5.0, Wender-Utah, ASRS, DAST-20
- Personality questionnaires (Barratt, SSS-V, Kirby)
- CANTAB battery (SSRT, SWM, RVIP)

$[^{11}C]$MRB PET / resting state fMRI
- PET/MRT scanner?

Hypothesis: Reduced MRB availability / connectivity in / with Locus coeruleus, hypothalamus/thalamus, PFC