Neuropsychological and Imaging Endophenotypes of ADHD

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Outlines

- Review of Neuropsychological Theories
- Endophenotype Approach
  - Neuropsychological Functions
  - Imaging Studies
  - Treatment Effects on Neuropsychological/imaging measures
  - DAT/NET genes and neuropsychological functions
Neuropsychological conceptualizations of ADHD

- **Impaired inhibitory control and Executive dysfunction** (Barkley 1997; Doyle 2005; Gau & Shang 2010)

- **Dual pathway** (Sonuga-Barke, 2002) to **triple pathway** (Sonuga-Barke et al., 2011)
  - Reward processing and inhibitory control
  - Temporal processing

- **State regulation deficits** (Sergeant 2005, Sonuga-Barke 2010)
  - Intra-individual variability (IIV)

- **Developmental dynamic theory** (Sagvolden, Johansen et al. 2005)

- **Default-mode network (DMN) interference theory** (Sonuga-Barke and Castellanos 2007)
Behavioral inhibition links to executive dysfunction

Behavioral Inhibition
- Delaying Prepotent Response
- Interrupting Ongoing Responses
- Interference Control

Sensing to the Self
- Retrospective Function
- Prospective Function

Speech to the Self
- Receptive Language
- Expressive Speech

Emotion/Motivation to the Self
- Self-directed Affect
- Intrinsic Motivation

Play to the Self
- Analysis
- Synthesis

Motor Control

Barkley 1997
Dual to triple pathway

Executive Circuit

Inhibitory Deficits

Executive Dysfunction

Reward Circuit

Shortened Delay Reward Gradient

Delay Aversion

Parental Response

AD/HD

ENGAGEMENT

Sonuga-Barke 2002, 2010

Neuro-biological Basis

Psychological Process

Behavioral Expression

DELAY (N=25)
15 (19.5%)

Timing (N=34)
19 (24.7%)

INHIBIT (N=16)
5 (6.4%)

INHIBITION (N=16)

1 (1.3%)

5 (6.5%)

4 (5.2%)

6 (7.8%)

1 (1.3%)
State regulation deficits / Cognitive energetic model

“the engine is intact (i.e. the basic information processing capacity is intact), but there is a problem with the petrol supply (i.e. the utilization of the cognitive capacity depends on state factors such as incentives, event rate and presence/absence of the experimenter)” van der Meere, 2002
Dynamic developmental theory

- Abnormal stimulus-behavioral response
  - dysfunctional meso-limbic dopaminergic circuit
  - Impaired motivational processes, especially reinforcement and extinction of behaviors

Drug • Genetic • Toxins

DYSFUNCTIONING DOPAMINE SYSTEM BRANCHES

Mesocortical • Mesolimbic • Nigrostriatal

Deficient attention and poor behavioral organization
Shorter delay-of-reinforcement gradient and deficient extinction
Clumsiness and poor nondeclarative habit learning

Sagvolden, Johansen et al. 2005
Default mode network interference

Physiological baseline of brain function
Gusnard & Raichle et al. 2001

Dorsal attention network & Default-mode-network (DMN)
Resting-state fMRI connectivity
Fox et al. 2005
Neuropsychological Heterogeneity in ADHD

Data reduction

Community detection

Difference between subgroups

Fair et al. 2012
Candidate neural system of ADHD

Revised from Durston et al. 2011
Large-scale brain systems in ADHD: beyond the prefrontal–striatal model

F. Xavier Castellanos$^{1,2}$ and Erika Proal$^{1,3}$

The etiological model of ADHD shifts from assumed pathology of regional brain abnormalities to dysfunction in distributed network organization (Konrad and Eickhoff, 2010)

Yeo et al. 2011
Revised from Fig 1 in Franke, et al., Hum Genet, 2009
Endophenotype

- Measured at cognitive or neurobiological level, instead of behavioral or molecular level.
- **Potential endophenotypes for ADHD** (Doyle et al., 2005; Nigg et al., 2004):
  - be associated with ADHD in the probands
  - be measured by tools with good psychometric properties, including reliability
  - stable over time, quantifiable
  - appear in unaffected relatives of ADHD probands
  - show familial-genetic overlap with this disorder
- **Endophenotype measurement for ADHD:**
  - Neuropsychological paradigm (Slaats-Willemse et al., 2005)
  - Neuroimaging paradigm (Jucaite et al., 2005)
  - Electrophysiological paradigm (Doyle et al., 2005)
Family Data of ADHD

Genetic Data (trio, sib, case-control)

Neuropsychological Measures (IQ, CANTAB, CPT, time)

Psychopathology (ADHD and other psychiatric disorders (K-SADS-E), ADHD symptoms, comorbidities)

School and Social Function (social adjustment, academic performance, parenting)

Brain Image Data (DSI, task-fMRI, rfMRI)

Treatment Effect (pharmacotherapy and non-pharmacotherapy)

Gene Data (trio, sib, case-control)
Whether Executive Function, Visual Memory, Intra-individual Variability, Interval Timing Can Be Neurocognitive Endophenotypes for ADHD
Impaired Executive Function, Visual Memory, Intra-individual variability, Interval Timing in ADHD
Neuropsychological tests have consistently identified deficits in children (van Mourik, et al, 2005), adolescents (Gau et al., 2009 & 2010) and adults (Hervey, et al., 2004; Schoechlin & Engel, 2005) with ADHD on at least one measure of executive function (EF) or attention with modest effect sizes.

Major theories:
- Inhibitory control deficit (Barkley, 1997) and executive function deficits (Willcutt, et al., 2005)
- Delay aversion theory (de Zeeuw et al., 2008)
- Cognitive-energetic theory (Sergeant, 2000, 2005)
Neuropsychological Findings

- **Executive functions** (Roth et al., 2004):
  - Initiation, response inhibition and execution
  - Working memory and updating
  - Set-shifting and task-switching
  - Interference control
  - Self monitoring, planning /organization

- The inhibitory control theory is supported by increased CPT commission errors (Frazier, et al, 2004), slower stop signal reaction time (SSRT) (Lijffijt et al., 2005) and increased interference in the Stroop test (Hervey, et al, 2004; van Mourik et al., 2005).

- Slower and variable SSRT may be an arousal problem (Alderson et al., 2008; Sergeant, 2000) which supports the cognitive-energetic model (Sergeant, 2000) or the delay aversion model (de Zeeuw et al., 2008) of ADHD.
Neuropsychological Findings

- EFs are assumed to assess the integrity of prefrontal cortex, striatum, and cingulate cortex (Willcutt, et al., 2005).
- EF deficits, particularly WM, predicted impaired academic performance (Gropper 2009), peer relationships, social function (Diamantopoulou 2007), and occupational achievement (Biederman et al., 2007).
- Inattention is significantly associated with EF weaknesses, whereas hyperactivity–impulsivity is not independently associated with EF (Willcutt, et al., 2005).
Neuropsychological Validity of ADHD Subtypes

Using Cohen’s attention model to validate ADHD subtype, we found that ADHD-C performed worse than ADHD-I in most attentional components but ADHD-I scored lower in digit span forward suggesting that ADHD-I children tend to miscue while receiving audio social information (Chiang & Gau, 2008)
Executive Functions (CANTAB)

Spatial Span (SSP)

Intradimension/Extradimension Shift (IED)

Spatial Working Memory (SWM)

Stockings of Cambridge (SOC)
Visual Memory (CANTAB)

- Delayed Matching to Sample (DMS)
- Pattern Recognition Memory (PRM)
- Spatial Recognition Memory (SRM)
- Paired Associates Learning (PAL)
Reaction Time and Attention

Reaction Time (RT)    Rapid Visual Information Processing (RVP)
Executive Dysfunction in ADHD

(Gau et al., 2010)

- Using a matched case control design, we found adolescents with ADHD showed poorer short-term spatial memory, spatial working memory, spatial planning, and response inhibition but not set-shifting, regardless of persistence of ADHD. It suggests symptom improvement did not lead to cognitive improvement.

- An increase in task demands increased the gap of performance difference between ADHD and normal controls.
Reaction Time Variation in ADHD—Based on ex-Gaussian Distribution (Huang & Gau, 2013)

Ex-Gaussian Distribution of Reaction Time assessed by the CPT for the ADHD (n = 206) and Control (n = 94) Groups

Figure 4. The ex-Gaussian probability function with parameters $\mu = 500$, $\sigma = 100$, and $\tau = 250$ (Panel C) resulting from the convolution a Gaussian probability function (Panel A) with an exponential function (Panel B).
A smaller $\mu$, larger $\sigma$ and larger $\tau$ in ADHD.
Greater $\tau$ in ADHD increased with increased ISI.

Means of the three ex-Gaussian parameters [$\mu$ ($\mu$), $\sigma$ ($\delta$), $\tau$ ($\tau$)] plotted across the 1-, 2-, 4-second ISIs for the ADHD and control groups.
The moderating effects of ISIs and blocks on $\tau$ support difficulty in effort allocation in ADHD.

- **Mu ($\mu$), Sigma ($\delta$), Tau ($\tau$)** plotted across the Blocks 1-3
- $\tau$ with inattentive symptoms and omission errors
- $\mu$ correlated with commission errors

![Graphs showing the effects of ISIs and blocks on $\tau$, $\mu$, and $\delta$.](image)
tau would be related to the attention lapses due to the problems of effort regulation, proposed by the cognitive-energetic model

mu would be related to the impulsive response style.

The ex-Gaussian decomposition of RT variability suggests ADHD as an impulsive response style with attentional lapses rather than a cautious response style in CCPT.
In the beginning, the participants heard a bee sound (1000 hz), lasting 100 milliseconds (ms). A green circle, with a diameter of 1.8 cm was shown in the center of a blank screen.

The green circles remained visible for 5, 12 and 17 seconds.

When the screen went blank, participants were asked to key the number of seconds that had lapsed.
The stimuli and the duration are same with the time estimation (5,12,17 sec).

After the screen went blank, participants were instructed “Press the joystick key and let the circle appear and last again, and raise the key when you think the same duration of time has elapsed.”
The temporal stimuli were the same. The concurrent non-temporal task was designed to ask participants to count the number of Arabic numerals.

The participants were asked to count all the numerals shown on the screen in the non-temporal task of the simple version, and to count only the odd numerals in the difficult version.
Using the time reproduction dual task to explore the role of the attentional resource in time perception deficits in ADHD, our findings suggest that impaired timing processing in ADHD during long time intervals may be explained by the limited attentional capacity rather than a primary problem in timing per se.
Which Neuropsychological Functions are Potential Endophenotypes for ADHD
From Fig 1 in Franke, et al., Hum Genet, 2009
Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB)

Susan Shur-Fen Gau and Chi-Yung Shang
Department of Psychiatry, National Taiwan University Hospital & College of Medicine, Taipei, Taiwan

Graphs showing comparisons between ADHD, unaffected siblings, and control groups in various tasks:
- **Spatial Span (Stocking of Cambridge)**
  - ADHD, Sib > Control
  - ADHD, Sib < Control
- **Spatial Working Memory**
- **Problems solved in minimum moves**
- **Total usage errors**
- **Total errors**
- **Number of Errors**
- **Number of boxes**
Visual memory as a potential cognitive endophenotype of attention deficit hyperactivity disorder

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² Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan
Rapid visual information processing as a cognitive endophenotype of attention deficit hyperactivity disorder

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\textsuperscript{2}Department of Psychology, Graduate Institute of Clinical Medicine, Graduate Institute of Brain and Mind Sciences, and Graduate Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan
\textsuperscript{3}Department of Psychiatry, National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin, Taiwan

Rapid Visual Information Processing

- ADHD < Sib < Control

Reaction Time

- ADHD, Sib > Control
- ADHD, Sib > Control
• ADHD had faster mu (μ) and larger sigma (σ) than the other two groups. Both ADHD and unaffected sibling groups had larger tau (τ) than TD across the 3 ISIs and 3 Blocks.
• The attention lapse in tau could be a candidate endophenotype for ADHD.
Deficit in Interval Timing May be a Candidate Endophenotype for ADHD (1/2)

Both ADHD and unaffected Sib had more discrepancy errors than controls.

More discrepancy errors in ADHD.
More discrepancy errors in ADHD and unaffected Sib in both Time Reproduction Dual Tasks without 3 group difference in no-temporal task
Conclusions

- Unaffected siblings may perform worse than controls or performed at the intermediate position in the Time Estimation and Time Reproduction Dual Task.
- Findings suggest that inadequate attention capacity measured by the time reproduction paradigm with dual tasks may be a potential endophenotype of ADHD.
From Fig 1 in Franke, et al., Hum Genet, 2009
Brain Image Studies

--Structural and Functional Connectivity
Magnetic Resonance Imaging

**Task fMRI**
Mapping function

**Resting fMRI**
Mapping functional link (connectivity)

And magnetic resonance spectroscopy (MRS), arterial spin labeling, etc...

**Diffusion tractography**
Mapping wiring (DTI, DSI)

**Mapping structure**
Voxel-based morphometry, cortical thickness, cortical surface area, cortical gyrification
Using MRI, We Can Investigate…

Functional connectivity fMRI
functional interactions
(temporal correlation between BOLD signals)

Cortical area

Effective connectivity fMRI
Influence of functional interactions

Diffusion - tractography
Qualitative and quantitative definition of structural links

Does not require the participant to complete functional tasks
DSI Acquisition Scheme

- Diffusion weighted image
- 3D Fourier Transform
- ODF
- 3D q-space $E(q)$

$\int r^2 P(r) \, dr$
Reconstruct fiber tracts and quantify integrity

- Fiber Integrity
  - myelination
  - directional coherence
  - axonal density

Generalized fractional anisotropy

\[ GFA = \frac{\text{std}(\psi)}{\text{rms}(\psi)} = \sqrt{\frac{n \sum_{i=1}^{n} (\psi(u_i) - \langle \psi \rangle)^2}{(n - 1) \sum_{i=1}^{n} \psi(u_i)^2}} \]

tractography

GFA mapping

ODF
Hypothesis

- **Decreased** fronto-striatal circuits in ADHD:
  - Dorsolateral prefrontal cortex - Caudate
  - Medial prefrontal cortex-Caudate
  - Ventrolateral prefrontal cortex- Caudate
  - Orbitofrontal cortex-Caudate

- **Impaired** executive functions: cognitive inhibition, set-shifting, working memory, planning, etc

_Biological Psychiatry, 2005; 57 (11), pp. 1273-1284_
Lower GFA of bilateral 4 fronto-striatal fiber tracts in children with ADHD
White Matter Tract Integrity of Frontostriatal Circuit in Attention Deficit Hyperactivity Disorder: Association with Attention Performance and Symptoms

Yi-Huan Wu, Susan Shur-Fen Gau, Yu-Chun Lo, and Wen-Yih Isaac Tseng


[Epub ahead of print]
Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder

C. Y. Shang¹, Y. H. Wu², S. S. Gau¹,³* and W. Y. Tseng³,⁴,⁵*

[Epub ahead of print]
Conclusion

- Disturbed structural connectivity of the frontostriatal circuitry in children with ADHD
- Loss of the leftward asymmetry in the dorsolateral and medial prefrontal tracts
- New evidence of associations between integrity of the frontostriatal tracts, particularly the left orbitofrontal and ventrolateral tracts, and measures of core symptoms of ADHD and a wide range of executive dysfunctions in both groups.
Neural Substrates of Behavioral Variability in ADHD: Based on ex-Gaussian Reaction Time Distribution and Diffusion Spectrum Imaging Tractography

Hsiang-Yuan Lin, Susan Shur-Fen Gau et al

*Psychological Medicine (accepted)*
Intraindividual variability (IIV) and ex-Gaussian distribution

- **Increased IIV in ADHD**
  
  "One ubiquitous finding in ADHD research across a variety of speeded-reaction-time tasks, laboratories and cultures", Castellanos and Tannock, NRN, 2002

- **Ex-Gaussian distribution of RT indexes IIV**
  - $\mu$ (mu) and $\sigma$ (sigma): mean and SD of Gaussian portion of distribution
  - $\tau$ (tau): mean of exponential portion of the distribution

- **Larger $\tau$ in ADHD, across choice RT task** (Leth-Steensen et al. 2000), Conner’s continuous performance test (Hervey et al. 2006, Gu-Huang & Gau et al. 2012), and working memory task (Buzy et al. 2009)
Microstructural integrity of frontostriatal tracts and cingulum bundle

- Based on top-down control and DMN interference model accounting for IIV in ADHD
ex-Gaussian Parameters across 3 ISI

- 28 children with ADHD and 28 pair-wise age, gender, handedness, intelligence matched typically developing control
- Conners’ CPT RT → Ex-Gaussian parameters
Integrity of cingulum bundle plays an important role in RT variability in ADHD children, while frontostriatial circuitry integrity may mediate RT variability in TD children.

<table>
<thead>
<tr>
<th></th>
<th>Mu (μ)†</th>
<th>Sigma (σ)†</th>
<th>Tau (τ)†</th>
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<tr>
<td></td>
<td>β</td>
<td>p</td>
<td>β</td>
</tr>
<tr>
<td>ADHD</td>
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<tr>
<td>Medial prefrontal L’t</td>
<td>-2521.40</td>
<td>.039</td>
<td>-</td>
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<tr>
<td>Orbitofrontal   L’t</td>
<td>3605.18</td>
<td>.020</td>
<td>-</td>
</tr>
<tr>
<td>Ventrolateral   L’t</td>
<td>-</td>
<td>-</td>
<td>2685.16</td>
</tr>
<tr>
<td>Cingulum        L’t</td>
<td>-527.35</td>
<td>.004</td>
<td>-1482.21</td>
</tr>
<tr>
<td>R’t</td>
<td>-1195.27</td>
<td>.026</td>
<td>-341.18</td>
</tr>
<tr>
<td>F values</td>
<td>F(3,22)= 4.68</td>
<td>p = .011</td>
<td>F(2,21)= 8.72</td>
</tr>
<tr>
<td>R-square</td>
<td>0.39</td>
<td>0.45</td>
<td>0.28</td>
</tr>
<tr>
<td>Typically Developing Children</td>
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<td></td>
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<tr>
<td>Dorsalateral    R’t</td>
<td>-</td>
<td>-</td>
<td>-2195.92</td>
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<tr>
<td>Orbitofrontal   L’t</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>R’t</td>
<td>-1846.37</td>
<td>.065</td>
<td>-</td>
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<tr>
<td>Ventrolateral   L’t</td>
<td>2695.73</td>
<td>.006</td>
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<tr>
<td>R’t</td>
<td>2156.81</td>
<td>.059</td>
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<tr>
<td>Cingulum        L’t</td>
<td>-73.46</td>
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<tr>
<td>F values</td>
<td>F(3,22)= 5.26</td>
<td>p = .007</td>
<td>F(1,22)= 0.61</td>
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<tr>
<td>R-square</td>
<td>0.42</td>
<td>0.03</td>
<td>0.29</td>
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†Sum of ISI-1S, ISI-2S and ISI-4S.
Altered resting-state frontoparietal control network in children with attention-deficit hyperactivity disorder

Lin HY, Tseng WY, Lai MC, Matsuo K, Gau SS*

2013, Human Brain Mapping, under review
Anatomically interposed between the default and dorsal attention networks
Cognitive control & goal-directed integration of information (Spreng et al. 2010)

Anterior prefrontal cortex (aPFC)
- Cognitive control

Dorsal lateral prefrontal cortex (DLPFC)
- Hierarchical organization of control process

Dorsal anterior cingulate cortex (dACC)
- Error detection

Anterior insula/ frontalopercular (aIfO)
- Salience processing

Anterior inferior parietal lobule (aIPL, also named supramarginal gyrus)
- Control of attention

Cerebellum

Caudate

Vincent et al. 2008
Sample and rfMRI connectivity analysis

- 25 pairs of ADHD-TDC matched individually for age, sex, handedness, and performance IQ for final analysis
- Also matched in framewise displacement (TDC 0.164 ± 0.05; ADHD 0.170 ± 0.06)
- Seed: bilateral anterior prefrontal cortex

Seed-based analysis

ADHD Endophenotype, Susan SF Gau, MD, PhD, ESCAP 2013 in Dublin
Aberrant FPCN in ADHD

left aPFC seed:  ADHD > TDC: left dorsolateral prefrontal cortex
TDC > ADHD: right inferior parietal lobule

right aPFC seed:  TDC > ADHD: right ventrolateral prefrontal cortex
Aberrant connectivity within FPCN correlated with clinical symptoms of impulsivity and opposition-defiance, and sustained attention and response inhibition assessed by the CCPT in ADHD

<table>
<thead>
<tr>
<th></th>
<th>laPFC-raIPL</th>
<th></th>
<th>laPFC-lDLPFC</th>
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<th>raPFC-rVLPFC</th>
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<td></td>
<td>r</td>
<td>B</td>
<td>r</td>
<td>B</td>
<td>r</td>
<td>B</td>
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<tr>
<td>ADHD (n=25)</td>
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<tr>
<td>Inattention</td>
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<td>.43</td>
<td>-0.01</td>
<td>.31</td>
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<td>Hyperactivity</td>
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<td>-0.02</td>
<td>.32</td>
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<td>Impulsivity</td>
<td>-0.41*</td>
<td>3.93</td>
<td>-0.01</td>
<td>.31</td>
<td>-0.11</td>
<td>.47</td>
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<td>Oppositional</td>
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<td>.47</td>
<td>-0.13</td>
<td>.52</td>
<td>-0.50*</td>
<td>12.24</td>
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<table>
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<tr>
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<th>laPFC-raIPL</th>
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<tr>
<td>Sustained attention</td>
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<td></td>
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<tr>
<td>Omissions</td>
<td>-0.08</td>
<td>0.45</td>
<td>-0.07</td>
<td>0.26</td>
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<td>0.12</td>
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<tr>
<td>Hit RT SE</td>
<td>-0.54*</td>
<td>23.67</td>
<td>0.24</td>
<td>1.03</td>
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<td>0.37</td>
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<td>Variability</td>
<td>-0.47*</td>
<td>8.41</td>
<td>0.36</td>
<td>2.55</td>
<td>0.03</td>
<td>0.30</td>
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<tr>
<td>Detectability (d’)</td>
<td>0.34</td>
<td>2.14</td>
<td>-0.55*</td>
<td>28.01</td>
<td>0.01</td>
<td>0.34</td>
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<td>Response inhibition</td>
<td></td>
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<tr>
<td>Commissions</td>
<td>-0.33</td>
<td>1.97</td>
<td>0.48*</td>
<td>9.61</td>
<td>-0.07</td>
<td>0.43</td>
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<td>Perseverations</td>
<td>-0.45*</td>
<td>6.56</td>
<td>0.30</td>
<td>1.56</td>
<td>-0.31</td>
<td>1.68</td>
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</table>
Key Points of the Study

The FPCN connectivity is aberrant in children with ADHD supporting ADHD as a brain network disorder.

Atypical connectivity is associated with impulsivity, opposition-defiance, and executive dysfunctions of sustained attention and response inhibition.
Neural correlates of sustained attention, inhibitory control and visuo–spatial memory in youths with ADHD

Fan LY, Gau SS, Chou TL (under review)

- 25 ADHD and 25 age-, sex-, handedness- and IQ-matched controls
- The counting Stroop task during fMRI
- RVP and PRM tasks of the CANTAB
Sustained attention and inhibitory control

- Increasing activation in right inferior frontal gyrus (IFG) was correlated with poorer performance in the RVP for youths with ADHD.

$p < .05$, 10 voxels, FWE corrected
Increasing activation in left superior parietal lobule (SPL) was correlated with better performance in the PRM for neurotypical youths, implying a better visual–spatial ability to process global information (i.e., number in counting Stroop fMRI).
Youths with ADHD might need more inhibitory control to suppress local influences, and may involve less visuo-spatial memory to process global information than neurotypical youths.
Treatment Effect

Neuropsychological functions:
- Child Study (Atomoxetine, ATX)
  - Executive Function: Int J Neuropsychopharm, 2010
  - Visual Memory: J Child Adolesc Psychopharm, 2012
- Adult Study (Methylphenidate vs. ATX)
  - Int J Neuropsychopharm, 2013

Imaging measures:
- Adult Study (ATX vs Placebo)
  - Resting-state fMRI
  - Counting Stroop fMRI
- Child Study (ATX vs. Methylphenidate)
  - Counting Stroop fMRI
Cognitive effects of Atomoxetine (ATX) (1/2)

- ATX improves inhibitory control in a single dose
  - Decreased stop signal test RT in healthy adults (Chamberlain et al. 2006)
  - Increased in failed inhibition during Eriksen flanker test under 80mg ATX in healthy adults (Graf et al. 2011)
  - Decreased stop signal test RT and reduced commission errors in sustained attention test in adults with ADHD (Chamberlain et al. 2007)
Long-term ATX improves executive functions and life functioning

– Improved flexibility, inhibition, sustained attention, spatial working memory, visual memory in drug-naïve ADHD boy, 12 weeks treatment (Gau and Shang 2010; 2012)

– School functioning in ADHD children (Gau and Shang 2012)

– Driving performance in ADHD adults (Sobanski et al. 2012)
ATX modulates right inferior frontal gyrus during inhibitory control in adults

Within-subject, double-blind, placebo-controlled design; 19 healthy adults; single dose of 40mg ATX
Stop-signal task fMRI

Chamberlain et al. 2009
ATX modulates bilateral inferior frontal gyrus and supplementary motor area during error monitoring

- Within-subject, double-blind, placebo-controlled design; 12 healthy adults; single dose of 80mg ATX
- Eriksen flanker-Go/NoGo task fMRI

Graf et al. 2011
Improvement of executive functions in boys with attention deficit hyperactivity disorder: an open-label follow-up study with once-daily atomoxetine

Susan Shur-Fen Gau\textsuperscript{1,2} and Chi-Yung Shang\textsuperscript{1,2}

\begin{itemize}
  \item Improving sustained attention (RVIP), inhibitory ability (RVIP), and attentional set shifting (IED) noted at Week 4; and spatial short-term memory (SSP), spatial working memory (SWM), spatial planning (SOC) and spatial problem solving (SOC) mainly noted at Week 12.
  \item Moreover, the magnitude of improvement in \textbf{spatial planning} and \textbf{problem solving} was a function of treatment duration of atomoxetine and task difficulties.
\end{itemize}
Improving Spatial Planning and Problem Solving at Week 12

Stockings of Cambridge (Cohen’s $d$, * $p < .05$)
A head-to-head randomized clinical trial of methylphenidate and atomoxetine treatment for executive function in adults with attention-deficit hyperactivity disorder

Hsing-Chang Ni¹,²,³, Chi-Yung Shang⁴, Susan Shur-Fen Gau¹,⁴,⁵, Yu-Ju Lin¹,⁶, Hui-Chun Huang⁷ and Li-Kuang Yang¹,⁸
Key Findings

- In general, both MPH and ATX were equally effective in reducing ADHD core symptoms and improving psychosocial functions, quality of life and executive functions.

- However, we found ATX is superior to IR-MPH in improving hyperactivity/impulsivity and ADHD severity at week 4 and spatial working memory, spatial short-term memory, and spatial sustained attention at week 8, which deserves further investigations.
Atomoxetine modulates resting fMRI connectivity in adults with attention-deficit hyperactivity disorder

(in preparation)

- **Study Design:** 8-week double blind placebo-controlled
- **Treatment Arms:** Atomoxetine (n=12) vs Placebo (n=12)
- **Seed-based analysis:** Bilateral VLPFC
  - BA 44 (A, posterior VLPFC)
  - BA 45 (B, mid-VLPFC)
  - BA 47 (C, anterior VLPFC)
Objectives

- To date, no rsfMRI study on ATX effects, neither under single dose nor long-term treatment condition, neither in healthy volunteers nor in patients group

- We hypothesized ATX would modulate intrinsic functional connectivity of right VLPFC seeds, especially mid- and posterior VLPFC (mainly involved in inhibitory control), but not in left VLPFC seeds, in adults with ADHD
ATX effects on right post-VLPFC seed (group by time interaction)

<table>
<thead>
<tr>
<th></th>
<th>MNI coordinate</th>
<th>Cluster size</th>
<th>Interaction term</th>
<th>Treatment period</th>
<th>Connection strength, mean (SD)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atomoxetine</td>
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<tr>
<td>Left precuneus (BA 7)</td>
<td>-6, -72, 57</td>
<td>136</td>
<td>F=17.30 P&lt;0.001</td>
<td>Post</td>
<td>0.281 (0.2229)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre</td>
<td>0.124 (0.2221)</td>
</tr>
<tr>
<td>Right orbitofrontal cortex (BA 11)</td>
<td>12, 51, -21</td>
<td>121</td>
<td>F=23.38 P&lt;0.001</td>
<td>Post</td>
<td>0.301 (0.1905)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre</td>
<td>0.086 (0.1967)</td>
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</table>
ATX effects on right mid-VLPFC seed (group by time interaction)

<table>
<thead>
<tr>
<th>MNI coordinate</th>
<th>Cluster size</th>
<th>Interaction term</th>
<th>Treatment period</th>
<th>Connection strength, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right inferior temporal lobe (BA 20)</td>
<td>51, -12, -27</td>
<td>207</td>
<td>Post</td>
<td>Atomoxetine: 0.469 (0.1504) Placebo: 0.304 (0.2162)</td>
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<tr>
<td></td>
<td></td>
<td>F=30.4 P&lt;0.001</td>
<td>Pre</td>
<td>Atomoxetine: 0.209 (0.2445) Placebo: 0.441 (0.1209)</td>
</tr>
<tr>
<td>Left orbitofrontal cortex (BA10)</td>
<td>-24, 54, -3</td>
<td>158</td>
<td>Post</td>
<td>Atomoxetine: 0.303 (0.2034) Placebo: 0.158 (0.2389)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F=22.26 P&lt;0.001</td>
<td>Pre</td>
<td>Atomoxetine: 0.137 (0.1644) Placebo: 0.349 (0.247)</td>
</tr>
</tbody>
</table>
Neural correlates of atomoxetine improving executive functions and visuo–spatial memory in adults with ADHD (in preparation)

**Study Design:** 8-week double blind placebo-controlled

**Participants:** 24 drug-naïve ADHD adults

**Treatment Arms:** Atomoxetine (n=12) vs Placebo (n=12)

**Neuropsychological Assessments:**
- IED and SOC
  - executive function
- SSP and DMS
  - visual spatial memory

**Counting Stroop - fMRI Assessment**
Hypothesis

Based on previous fMRI studies in ADHD (Cortese et al., 2012), we hypothesized that pre-treatment group may show greater activation relative to post-treatment group in right prefrontal cortex (PFC).

Based on previous fMRI findings of atomoxetine in adults with ADHD (Bush et al., 2013), we hypothesized that post-treatment with atomoxetine may enhance parietal activation.
Results—Executive functions

- Increasing right inferior frontal gyrus (IFG) with thinking time of SOC and errors in IED

Results—visuo-spatial memory

- Increasing left precuneus activation with total usage errors in SSP and mean correct latency in DMS

Pre-treatment > Post-treatment

Post-treatment > Pre-treatment

\( p < .05, 10 \text{ voxels, FWE corrected} \)

Taken together, 8-week treatment with atomoxetine might improve executive functions and visuo-spatial memory in adults with ADHD.
Neural correlates of **atomoxetine** and **methylphenidate** improving executive functions and visuo–spatial memory in children with ADHD (in preparation)

- **Study Design:** 12-week head-to-head ATX vs MPH RCT
- **Participants:** 28 drug-naïve ADHD adults
- **Treatment Arms:** Atomoxetine (n=14) vs Methylphenidate (n=14)

- **Neuropsychological Assessments:**
  - IED and SOC
  - executive function
  - SSP and DMS
  - visual spatial memory

- **Counting Stroop - fMRI Assessment**
Incongruent vs. Congruent
Pre-ATX > Post -ATX

Downregulation of rDLPFC after ATX treatment is correlated with performance in both counting stroop test & clinical symptoms.

![Brain Image with Right DLPFC highlighted](image)

- **Changes in DLPFC activation (after-before)**
  - **Improvement in stroop task (accuracy of incongruent trial)**
    - $R^2 = 0.47347$
    - $P = 0.007$

- **Changes in DLPFC activation (after-before)**
  - **Improvement in clinical symptom (CGI-severity)**
    - $R^2 = 0.31258$
    - $P = 0.038$
Upregulation of activation in rIFG after MPH treatment is correlated with performance in clinical symptoms

Incongruent vs. Congruent
Post-MPH > Pre-MPH

R² = 0.34553

P=0.027

Right IFG
Downregulation of activation in rSPL after MPH treatment was correlated with performance in Counting Stroop task.

Digits (3&4) > Digits (1&2)
Pre-MPH > Post-MPH
Summary of results

- Behavioral result showed only main effect of time and condition.

- Inhibitory control:
  - ATX decreased activation in DLPFC significantly (correlated with both Stroop performance & clinical symptoms-severity).
  - MPH increased activation in IFG significantly (correlated with clinical symptoms-severity).

- Visuospatial:
  - MPH decreased activation in SPL significantly (correlated with Stroop performance)
Impaired attention control (Chiang & Gau, 2008), EF (Gau, et al., 2009 & 2010e), visual memory (Shang & Gau, 2011), time reproduction (Hwang, et al., 2009), and variability of reaction time (Hwang & Gau), in ADHD with effect sizes ranging from 0.4 to 0.7.

EF (Gau & Shang, 2010), visual memory measured by the Delayed Matching to Sample task (Shang & Gau, 2011), sustained attention assessed by RVP (Gau & Huang, 2013), Tau of ex-Gaussian parameter of RT, interval timing measured by the Time Reproduction test with dual tasks (Hwang & Gau), may be neurocognitive endophenotypes for ADHD.

Children with ADHD had fronto-striatal, and fronto-parietal networks that may be associated with executive dysfunction.
Teri A. Manolio et al., Nature, 2009, Oct 8, 461: 749, Fig1

Effect size
50.0

High
Intermediate
Modest
Low

Rare alleles causing Mendelian disease

Low-frequency variants with intermediate effect

Rare variants of small effect very hard to identify by genetic means

Very rare
Rare
Low frequency
Common

Few examples of high-effect common variants influencing common disease

Common variants implicated in common disease by GWA
From Fig 1 in Franke, et al., Hum Genet, 2009
Association between the dopamine transporter gene and the inattentive subtype of attention deficit hyperactivity disorder in Taiwan

Chi-Yung Shang \textsuperscript{a,b}, Susan Shur-Fen Gau \textsuperscript{a,b,c,d,*}, Chih-Min Liu \textsuperscript{a,b,e}, Hai-Gwo Hwu \textsuperscript{a,b,c}

\textbf{DAT1} gene was significantly associated with the inattentive subtype of ADHD and the severity of inattentive symptoms.

Linkage Disequilibrium of the 15 Variants in the \textit{DAT1} gene
Association between Spatial Working Memory and \textit{DAT1} Gene in ADHD

\textit{International Journal of Neuropsychopharmacology} (accepted)

Sample: 382 ADHD families (n=1320)
3 SNPs (rs2617605, rs403636, and rs37020) and Haplotype Bock 1 were Significantly Associated with SWM Double Errors

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Allele</th>
<th>Allele Frequency</th>
<th>N</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2937639</td>
<td>G</td>
<td>0.145</td>
<td>49</td>
<td>1.94</td>
<td>0.052345</td>
</tr>
<tr>
<td>rs2617605</td>
<td>G</td>
<td>0.172</td>
<td>55</td>
<td>3.053</td>
<td>0.002265**</td>
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<tr>
<td>rs403636</td>
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<td>rs463379</td>
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<td>0.761</td>
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<tr>
<td>rs393795</td>
<td>C</td>
<td>0.462</td>
<td>86</td>
<td>0.847</td>
<td>0.396898</td>
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<tr>
<td>rs37020</td>
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<td>0.675</td>
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<td>2.858</td>
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<tr>
<td>rs40358</td>
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<td>0.656</td>
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<tr>
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<tr>
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<td>0.768</td>
<td>0.44235</td>
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<tr>
<td>rs27072</td>
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<tr>
<td>3VNTR</td>
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<td>0.918</td>
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<td>1.042</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SNP, Haplotype frequency, Number of Informative Families, Z, P, P_2 side by haplotype permutation test, Minimal P</th>
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<tbody>
<tr>
<td>rs403636, rs463379, rs393795, and rs37020</td>
</tr>
<tr>
<td>G/G/A/G 0.521 90 -0.784 0.432779 0.43314</td>
</tr>
<tr>
<td>T/C/C/T 0.3 91 -1.869 0.061641 0.06031</td>
</tr>
<tr>
<td>G/C/C/G 0.137 54 3.382 0.000719* 0.00042*</td>
</tr>
<tr>
<td>G/C/C/T 0.023 12 -1.265 0.205903 0.2179</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>rs27048 and rs429699</td>
</tr>
<tr>
<td>C/C 0.58 100 0.383 0.70201 0.710977</td>
</tr>
<tr>
<td>C/T 0.244 76 -1.235 0.216752 0.201410</td>
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<tr>
<td>T/C 0.176 68 0.866 0.386571 0.408862</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>rs27072, and 3VNTR</td>
</tr>
<tr>
<td>C/10 0.643 77 -0.328 0.742711 0.760067</td>
</tr>
<tr>
<td>T/10 0.273 64 1.042 0.297393 0.348993</td>
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<tr>
<td>C/9 0.061 30 -0.386 0.699722 0.738255</td>
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<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>0.0014*</td>
</tr>
<tr>
<td>0.456697</td>
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<tr>
<td>0.918624</td>
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</tbody>
</table>
2 SNPs (rs2937639, and rs2617605) and Haplotype Block 1 were Significantly Associated with SWM within Errors.

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Allele</th>
<th>Frequency</th>
<th>N</th>
<th>Z</th>
<th>P</th>
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<tr>
<td>rs2937639</td>
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<td>0.145</td>
<td>68</td>
<td>1.968</td>
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<tr>
<td>rs2617605</td>
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<td>0.172</td>
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<table>
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<tbody>
<tr>
<td>rs403636, rs463379, rs393795, and rs37020</td>
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<td>0.061</td>
<td>36</td>
<td>-0.509</td>
<td>0.610812</td>
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The NET gene and visual memory in the ADHD family genetic study

- The human NET gene localizes on 16q12.2 and consists of 14 exons spanning 48 kb.
- Association of ADHD with nucleotide polymorphisms (SNPs) in the NET gene has been reported (Brookes et al., 2006).
- Our recent work has found that atomoxetine can improve the visual memory deficits of children with ADHD (Shang and Gau, 2012).
Method

- We recruited 382 children with ADHD and their families, resulting in 1298 subjects in total.
- A total of 22 genetic polymorphisms in the NET gene were investigated, and all of them were compatible with the Hardy-Weinberg equilibrium distribution.
- Two visual memory tasks from the CANTAB were employed to measure executive functions
  - Pattern Recognition Memory (PRM)
  - Spatial Recognition Memory (SRM)
22 SNPs and 6 haplotype blocks in the NET gene

- In the single marker analysis, our findings provided evidence for the association between ADHD and rs36011 of the NET gene.

- Haplotype block 5 (rs36011 T/ rs1566652 G) was significantly associated with
  - ADHD (minimal $P = 0.045$)
  - Pattern Recognition Memory (minimal $P = 0.019$)
  - Spatial Recognition Memory (minimal $P = 0.014$)
In the single marker analysis, our findings provided evidence for the association between ADHD and rs36011 of the NET gene.

In the haplotype analysis, our findings showed that one variant (TG) of block 5 (rs36011 / rs1566652) was significantly associated with visual memory.

Our findings suggested that the NET gene may mediate the performance in visual memory in children with ADHD and their families.
Revised from Fig 1 in Franke, et al., Hum Genet, 2009
Net Steps

- Unaffected sibling designs for imaging studies and genomic imaging research are our next step to identify imaging endophenotype.
- Further pharmacogenetic studies for personalized treatment is also our ongoing research.
Acknowledgements

Grants: NSC, NHRI
Clinic/genetic/neuropsychological Team: P. Gau, SS, Dr. Shang, CY
Imaging Team: DSI: P. Tseng, WY; fMRI: P. Chou, TL; frMRI: Lin HY
Graduate Students: LY Fang, YF Wu, HY Lin, CY Shang, YJ Lo, Huang SL
Research Assistants:
   WL Tseng
   HY Lo
   MF Chen
   CM Lee
   YL Lin
   SL Hsu