Neuropsychological and Imaging Endophenotypes of ADHD

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July 6-10, 2013 ESCAP in Dublin

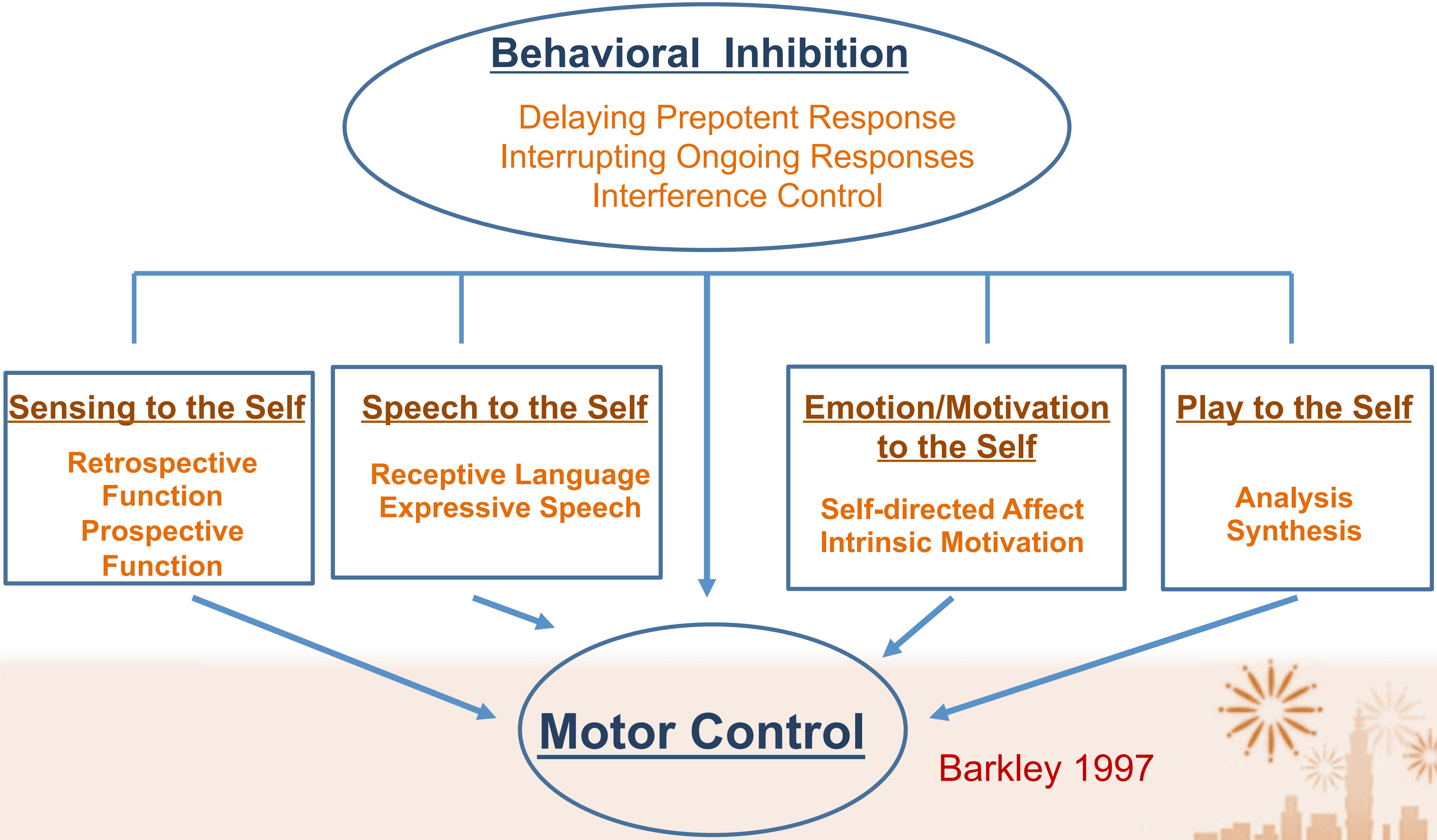
Outlines

- 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

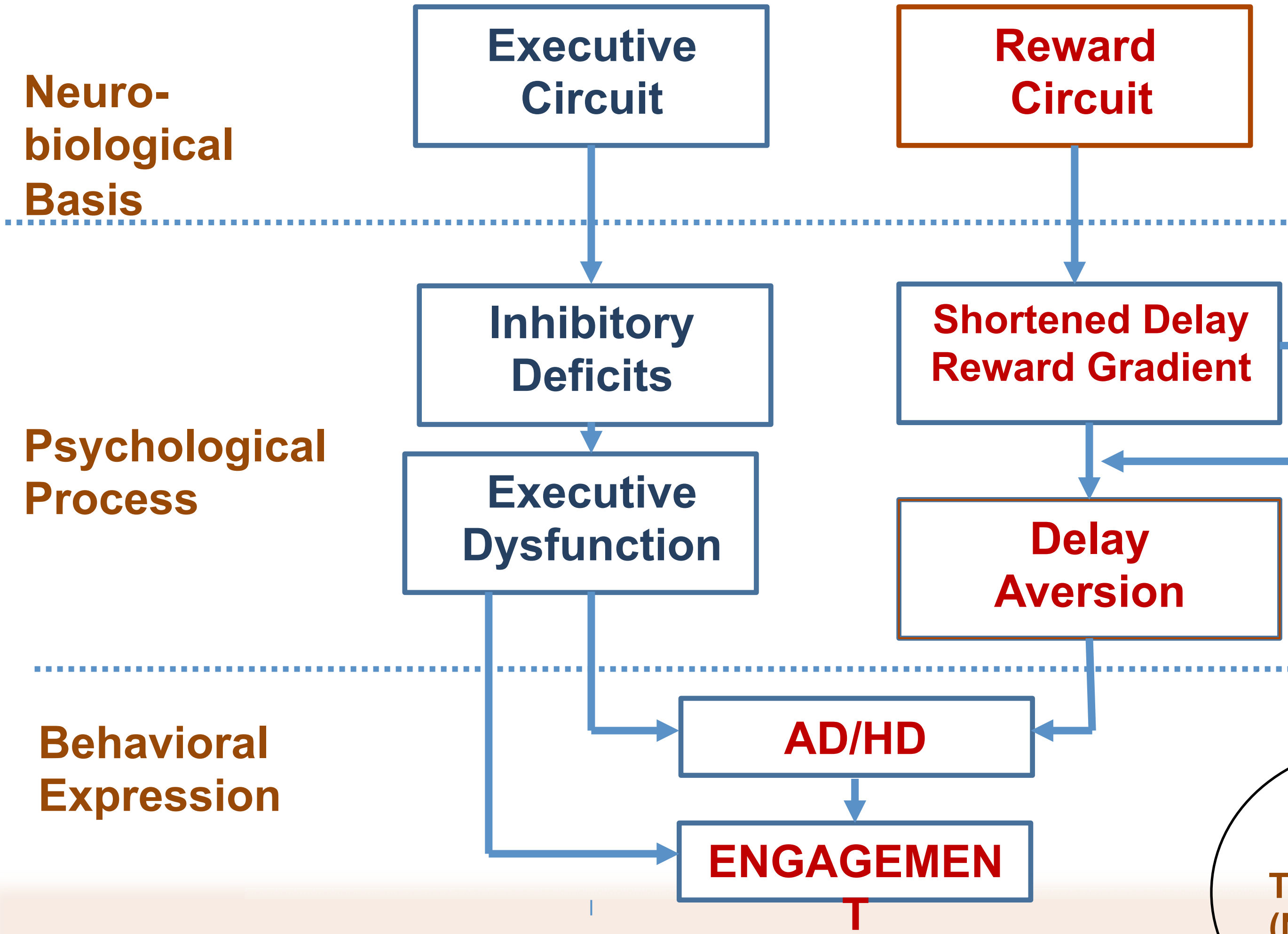
- **Impaired inhibitory control and Executive dysfunction** (Barkley 1997; Doyle 2005; Gau & Shang 2010)
- **Dual pathway** (Sonuga-Barke, 2002) **to triple pathway** (Sonuga-Barke et al., 2011)
  - **Reward processing and inhibitory control**
  - **Temporal processing**
- **State regulation deficits** **(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)

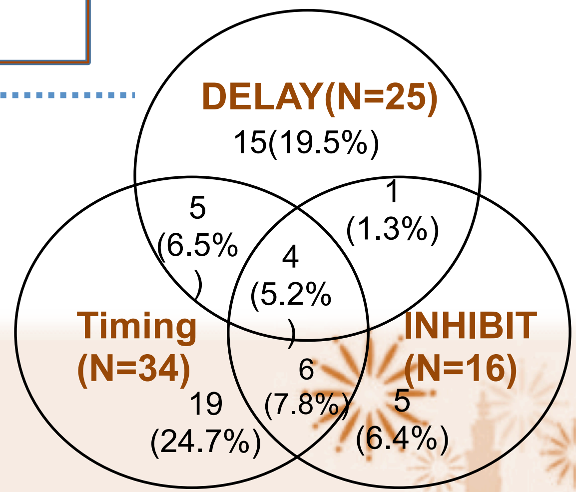
Behavioral inhibition links to executive dysfunction



Barkley 1997

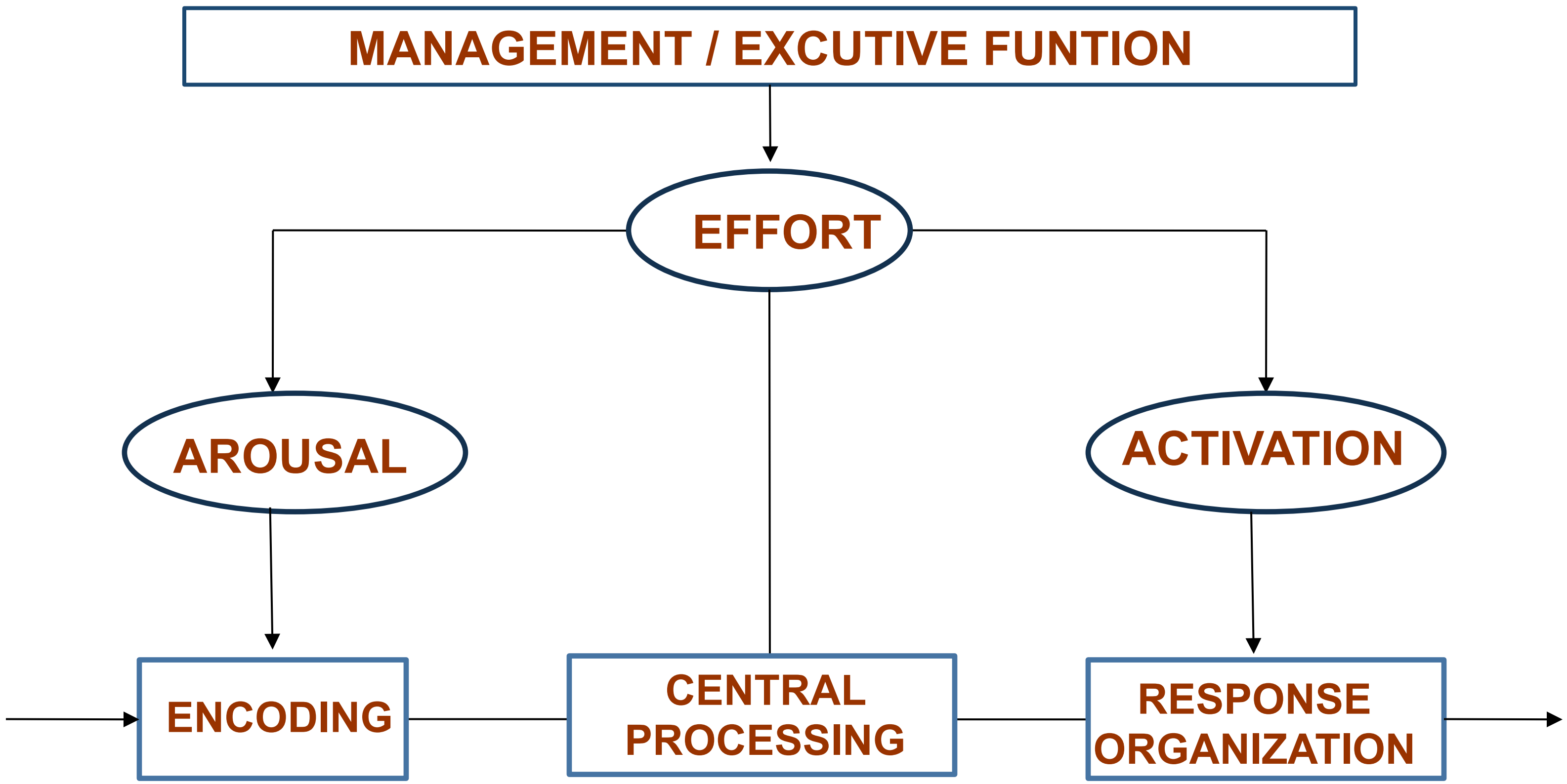
Dual to triple pathway





Sonuga-Barke 2002, 2010

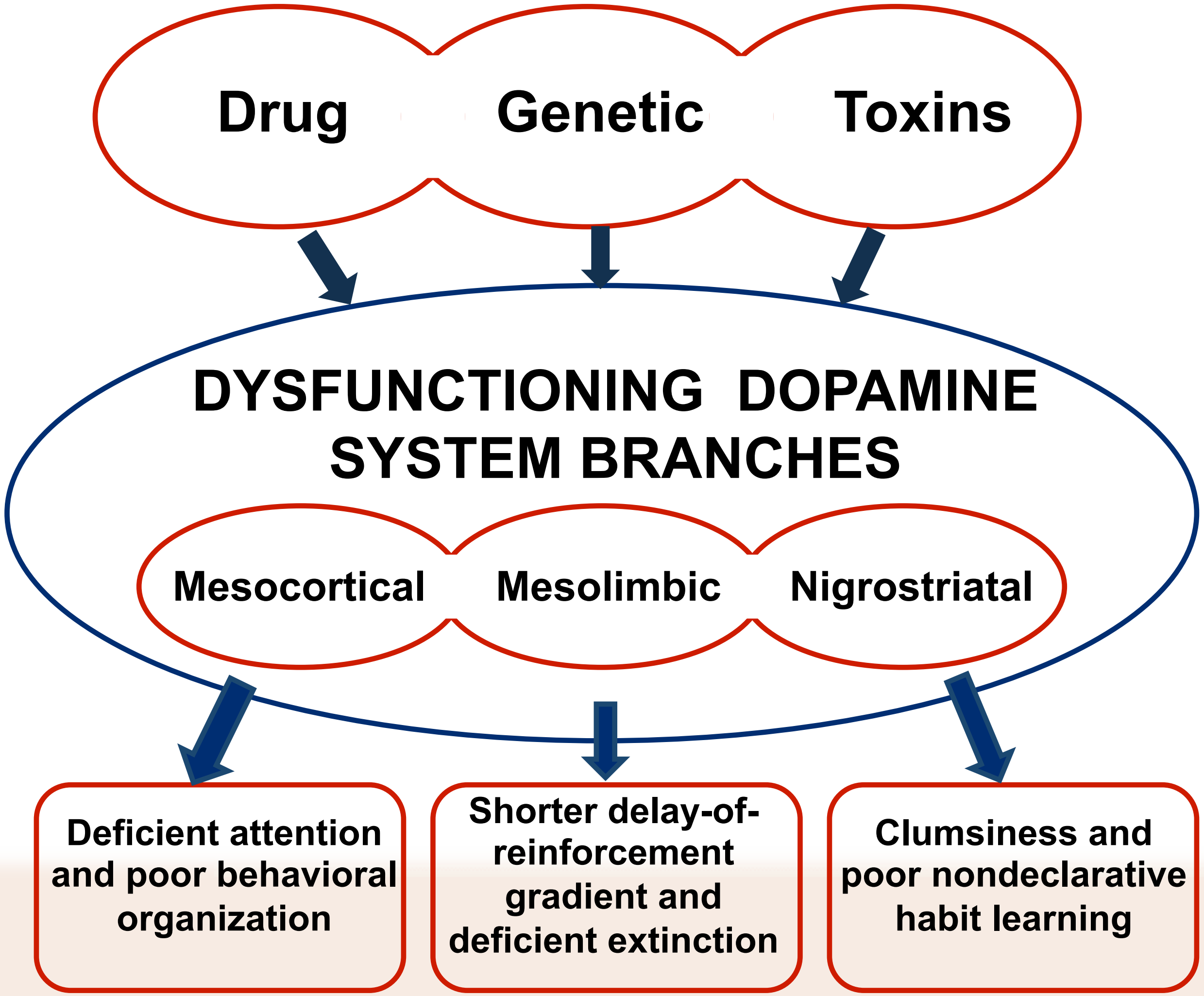
State regulation deficits / Cognitive energetic model



Sergeant 2000

"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,

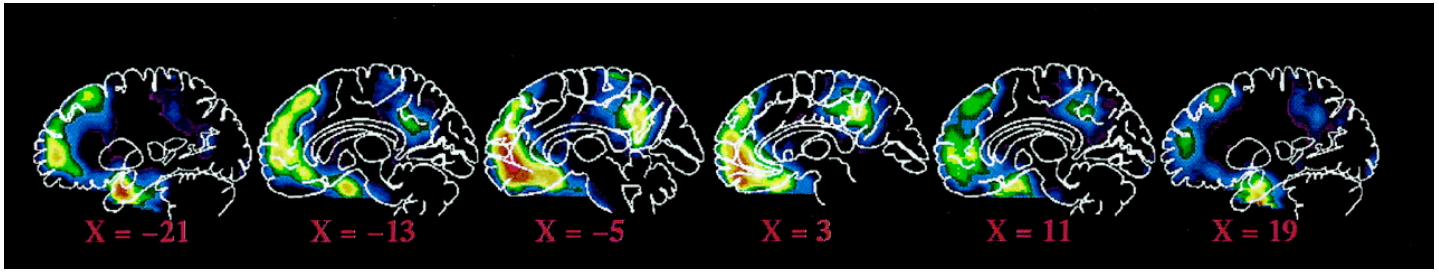
Dynamic developmental theory



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

Sagvolden, Johansen et al. 2005

Default mode network interference

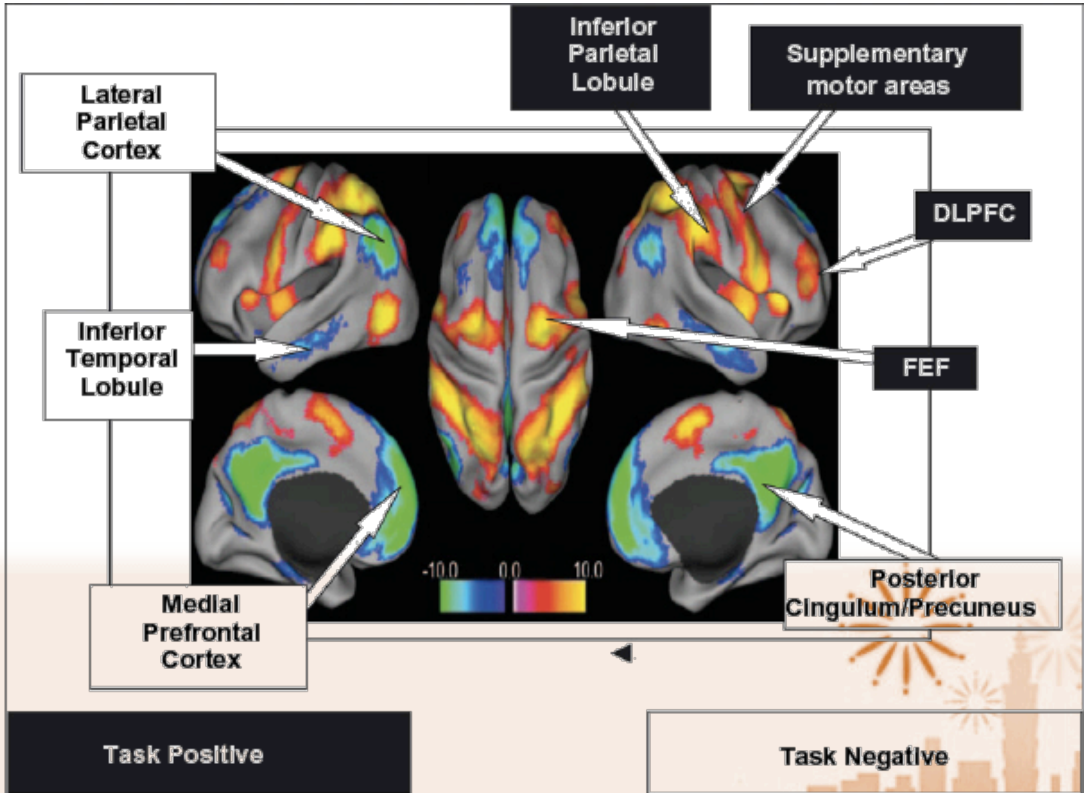


Physiological baseline of brain function

Gusnard & Raichle et al. 2001

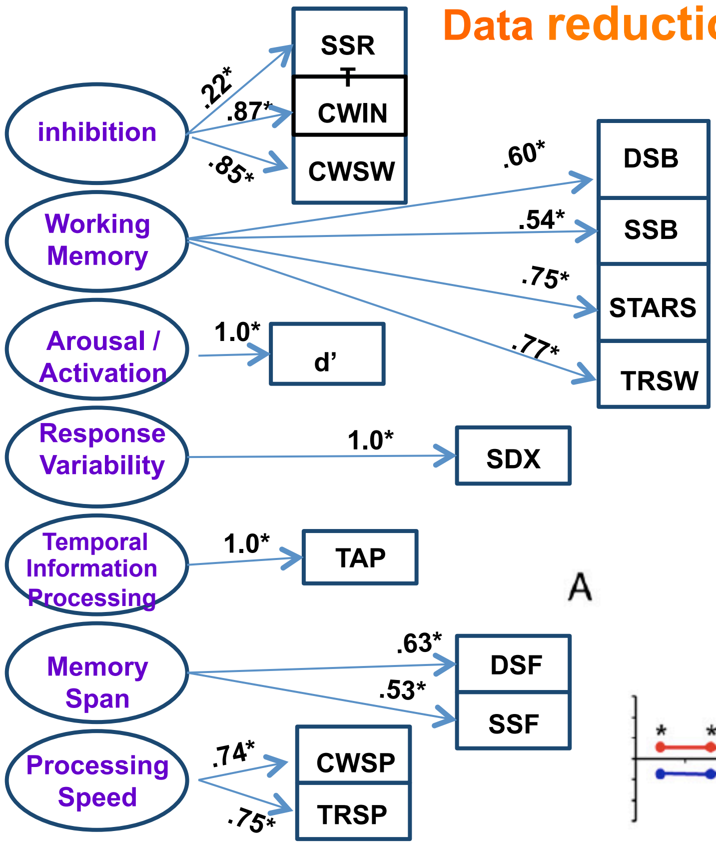
Dorsal attention network & Default-mode-network (DMN) Resting-state fMRI connectivity

Fox et al. 2005

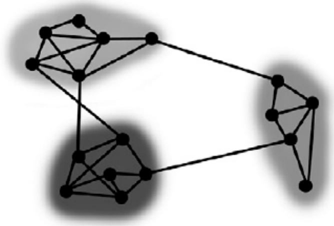


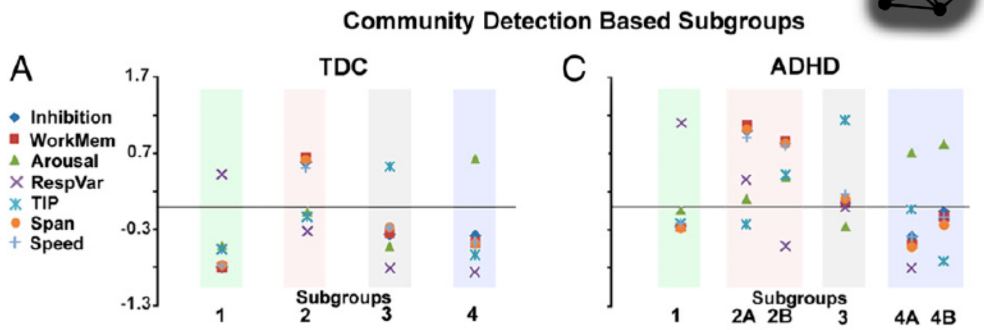
Neuropsychological Heterogeneity in ADHD

Data reduction

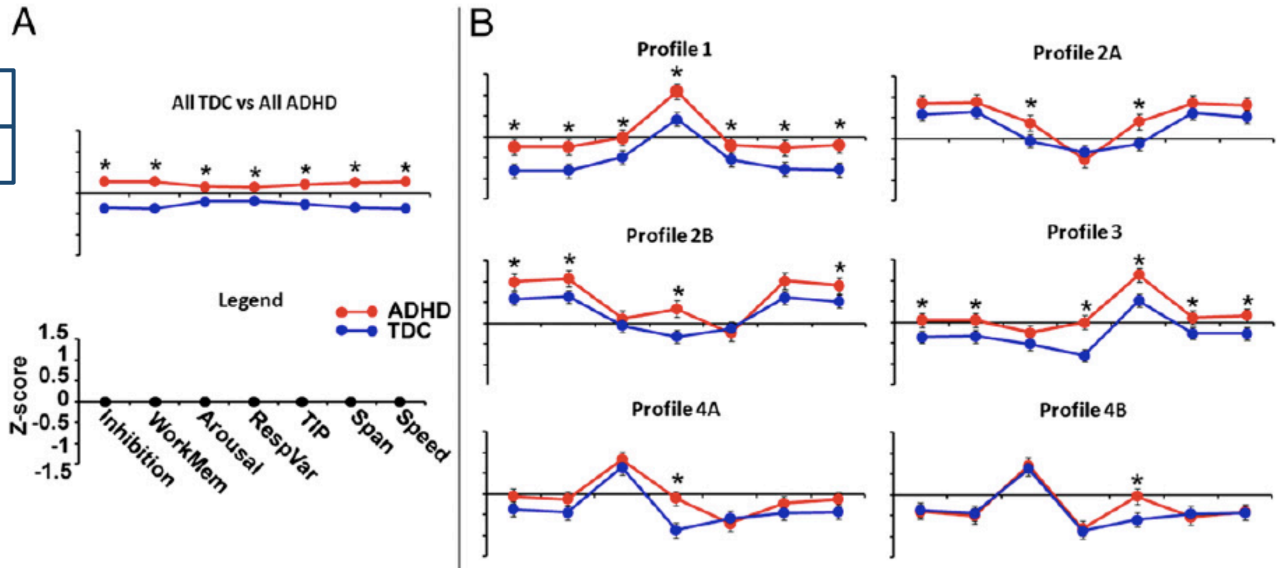


Community detection



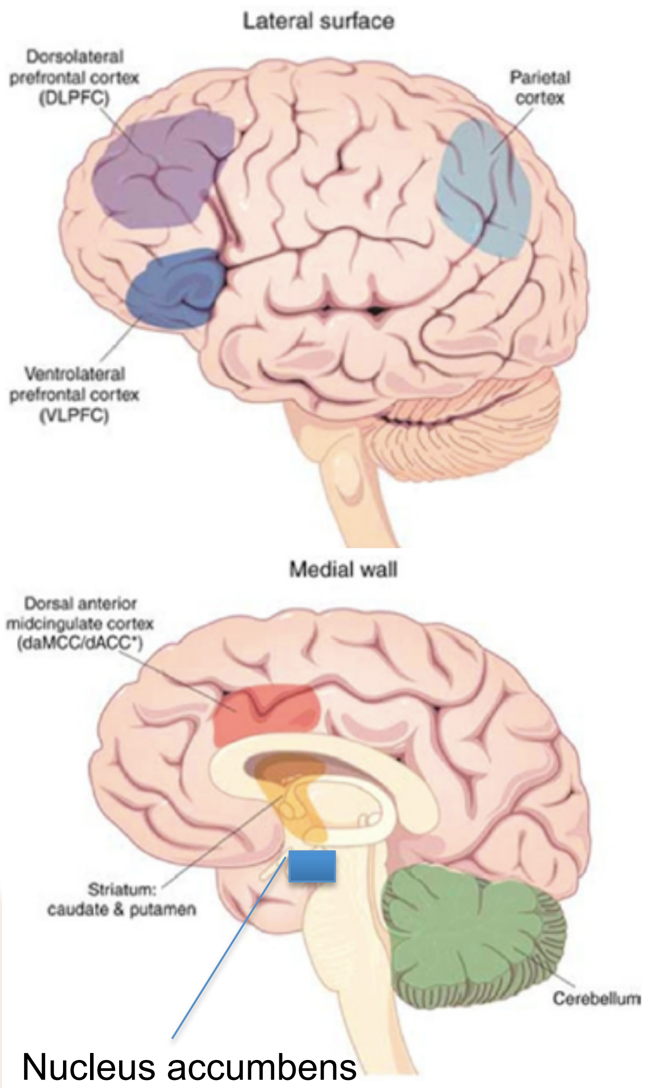


Difference between subgroups

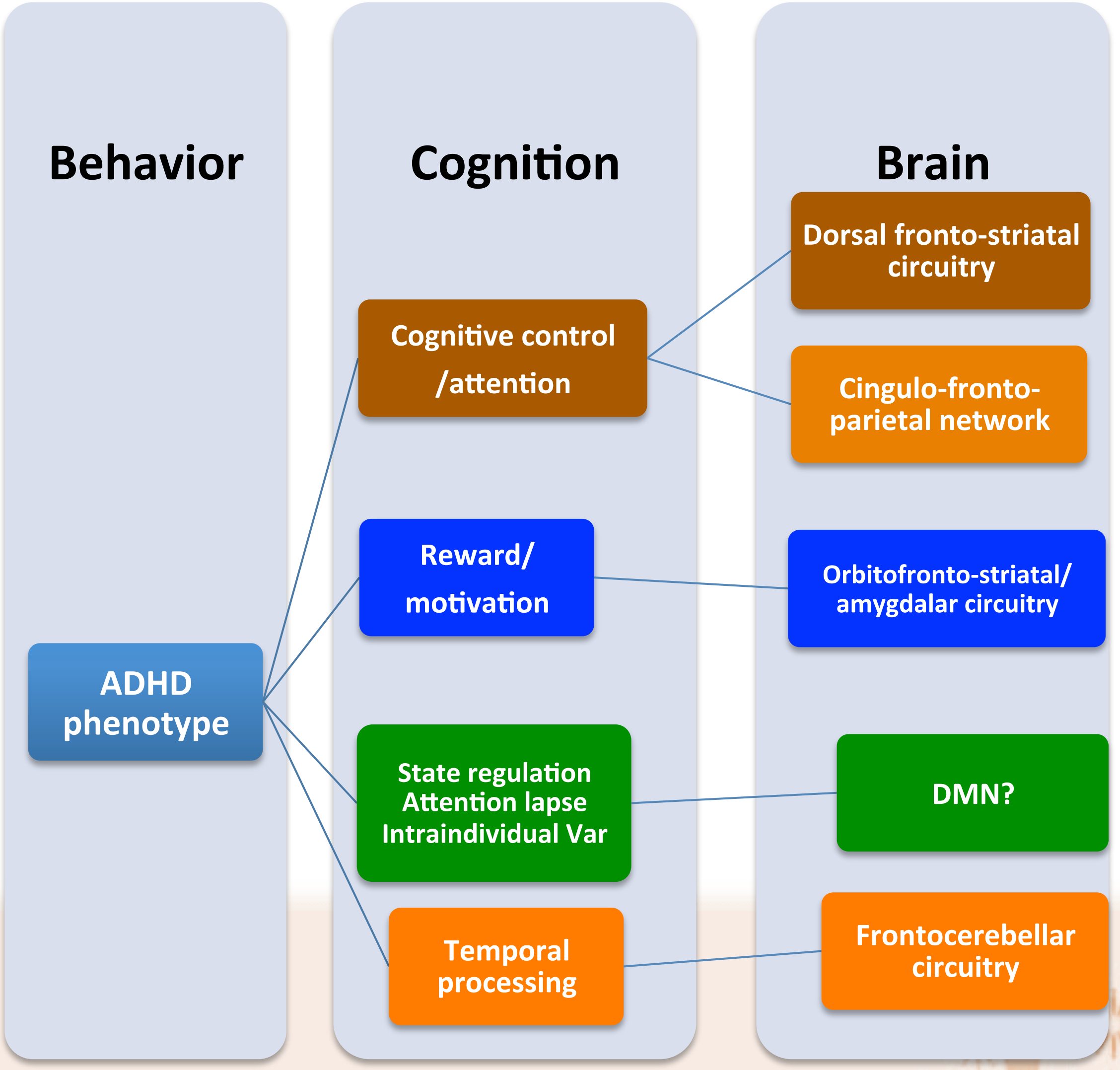


Fair et al. 2012

Candidate neural system of ADHD



Revised from Bush, 2011



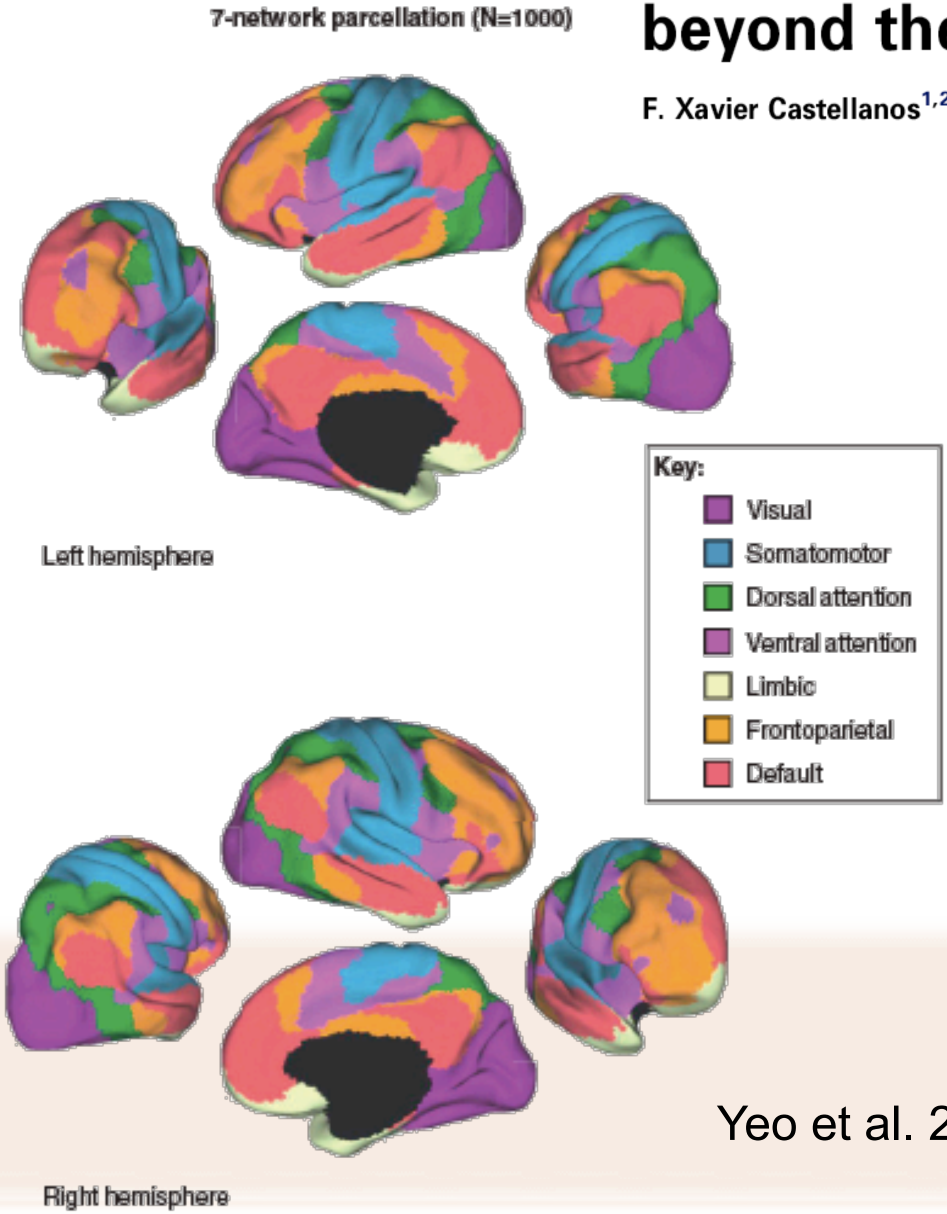
Revised from Durston et al. 2011

Review

Special Issue: Cognition in Neuropsychiatric Disorders

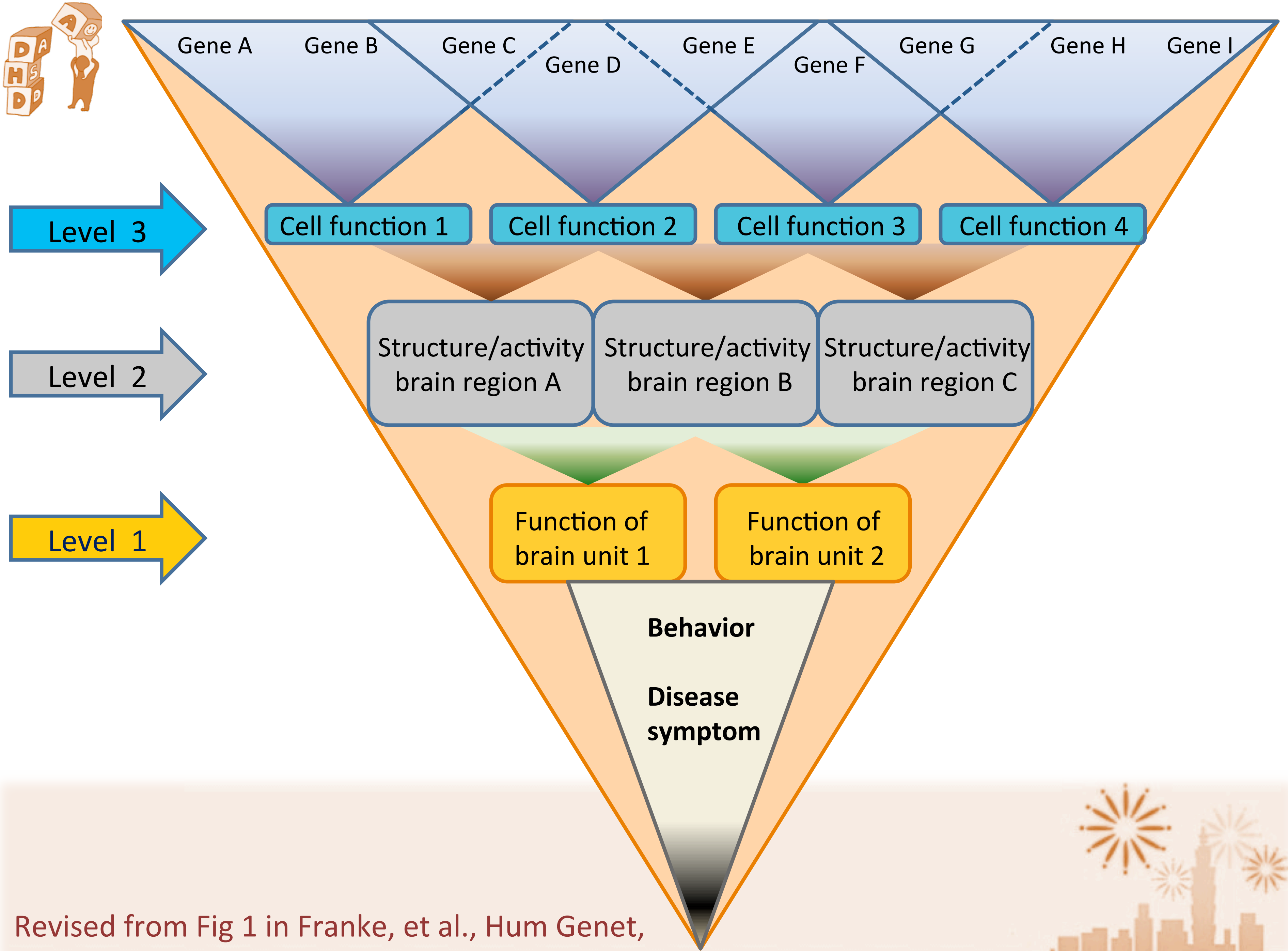
Large-scale brain systems in ADHD: beyond the prefrontal–striatal model

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)

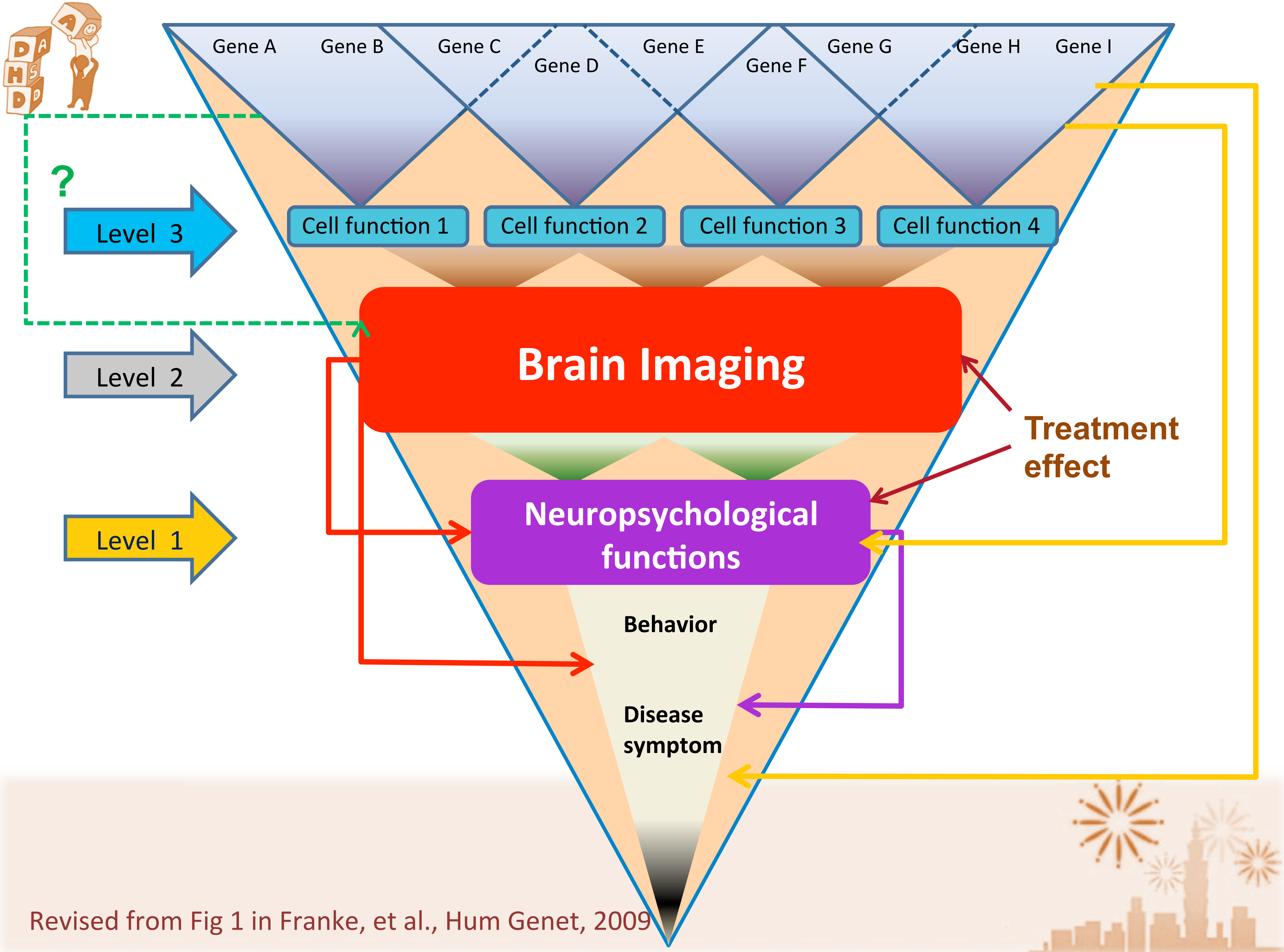
Yeo et al. 2011



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

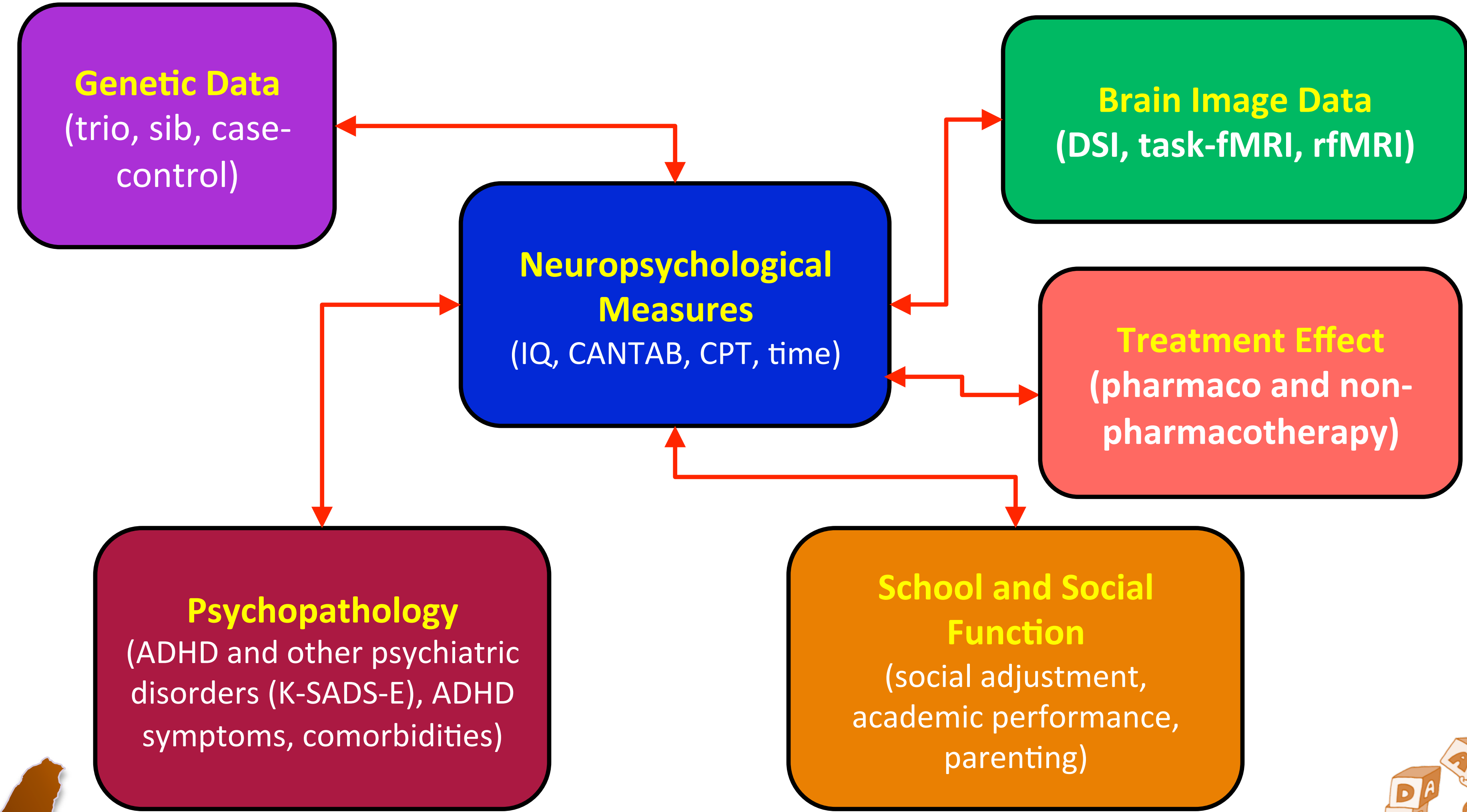
Endophenotype

- 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)



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

Family Data of ADHD



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 Findings 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

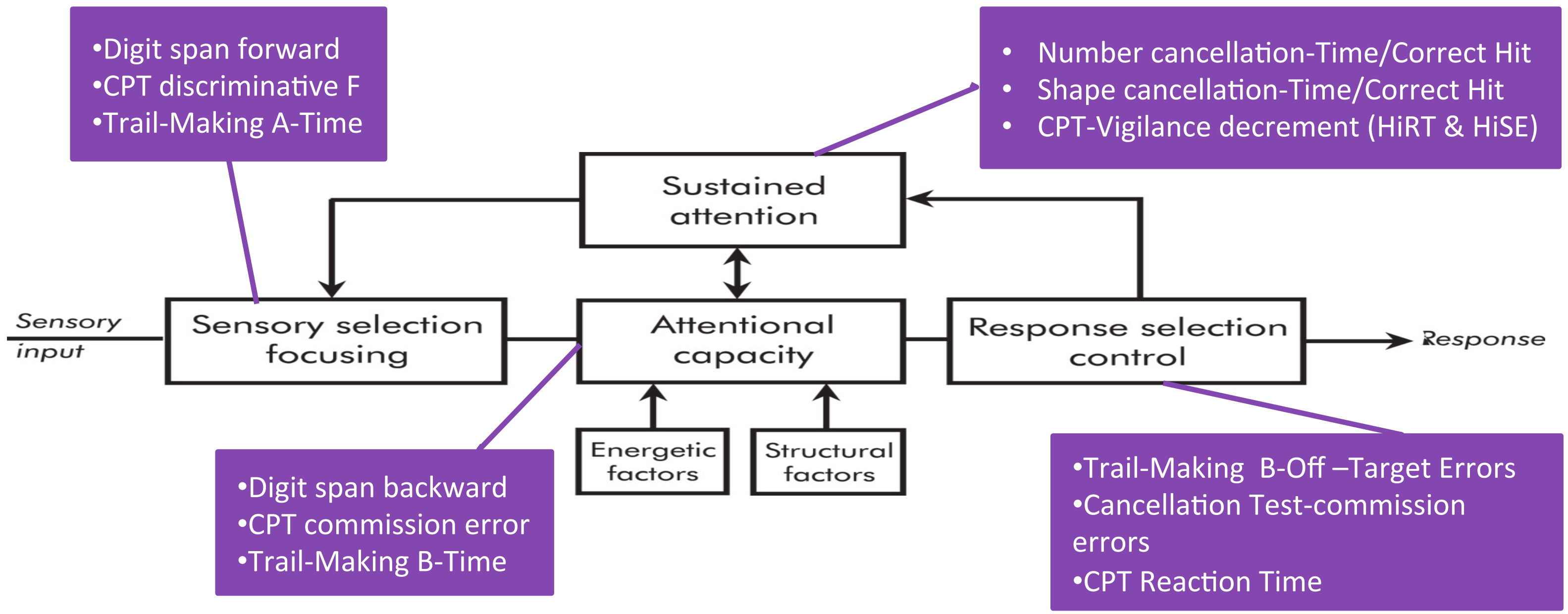
- Executive functions (Roth et al., 2004) :
  - Initiation, response inhibition and execution
  - Working memory and updating
  - Set-shifting and task-switching
  - Interference control
  - Self monitoring, planning /organization
- The inhibitory control theory is supported by increased CPT commission 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).
- Working memory (WM): larger deficit in spatial WM than in verbal WM (Martinussen, 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).

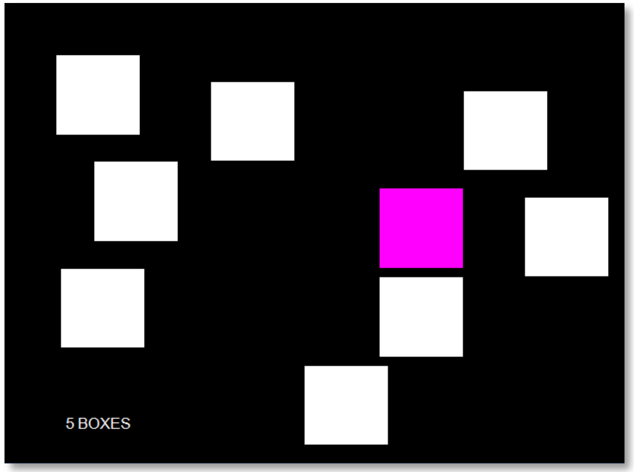
Neuropsychological Validity of ADHD Subtypes

- 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)

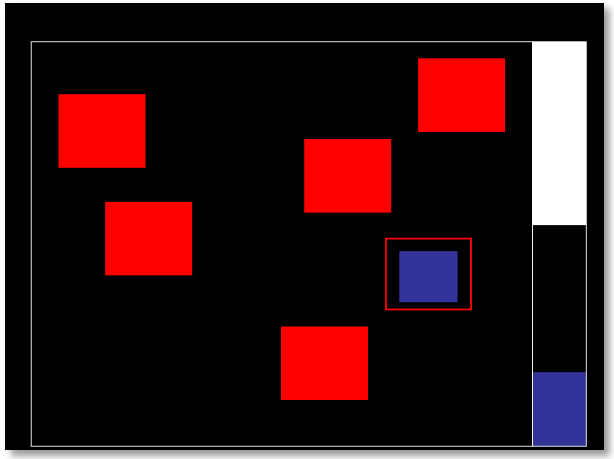


Executive Functions (CANTAB)

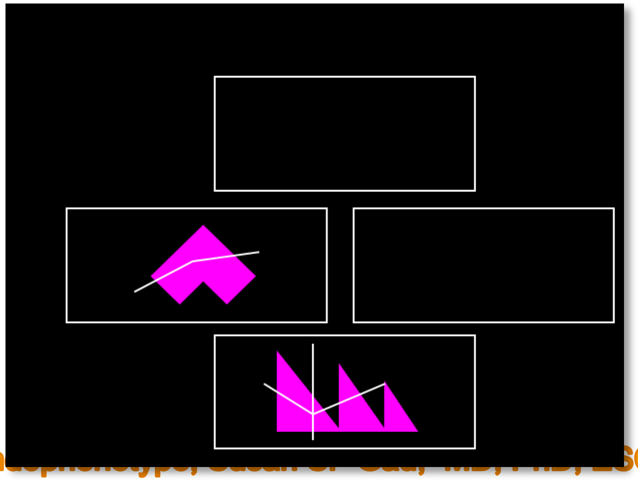
Spatial Span (SSP)



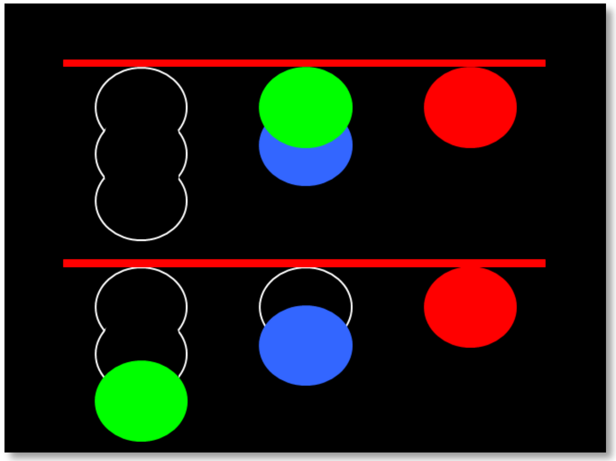
Spatial Working Memory (SWM)



Intradimension/Extradimension Shift (IED)

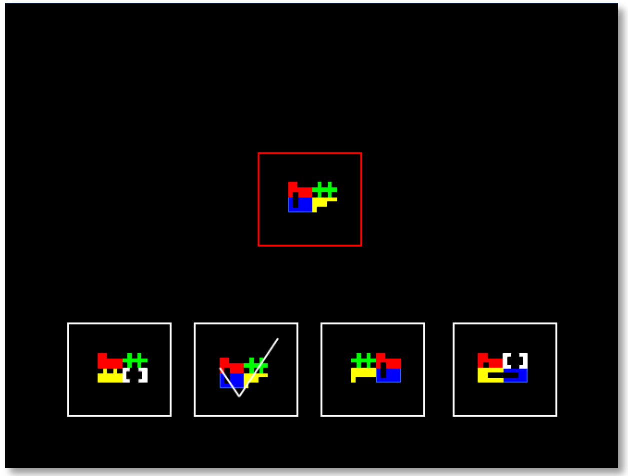


Stockings of Cambridge (SOC)

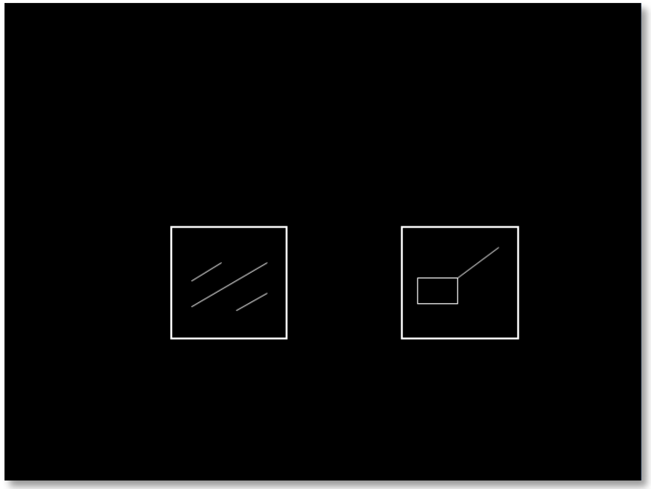


Visual Memory (CANTAB)

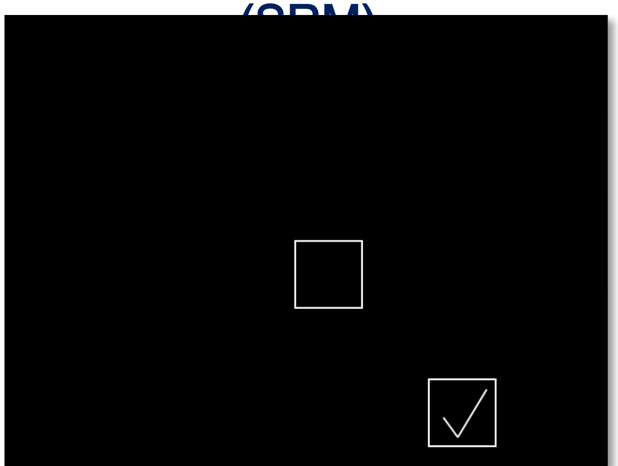
Delayed Matching to Sample (DMS)



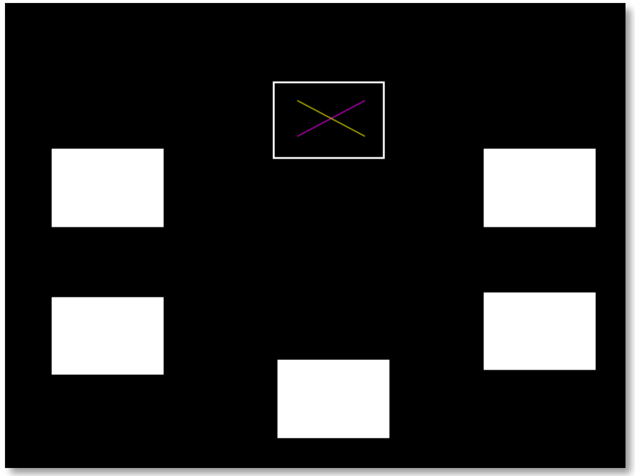
Pattern Recognition Memory (PRM)



Spatial Recognition Memory (SRM)

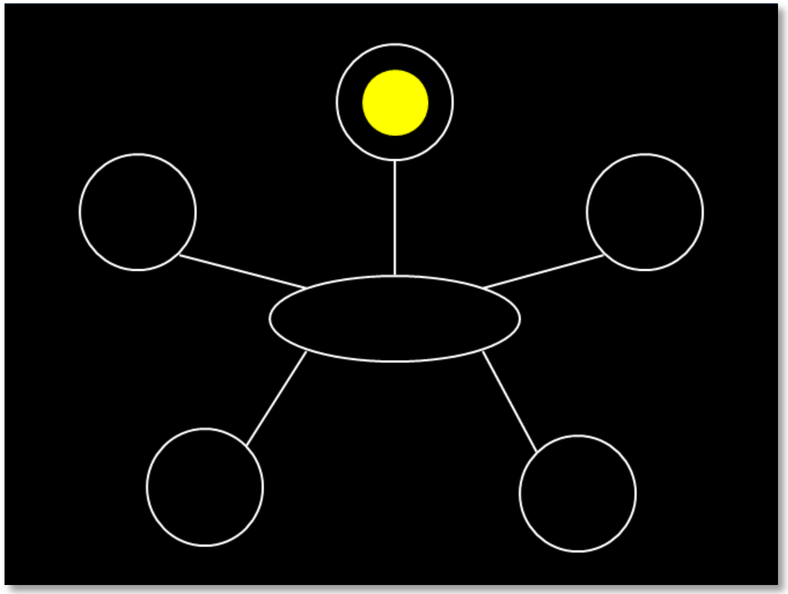


Paired Associates Learning (PAL)



Reaction Time and Attention

Reaction Time (RT)

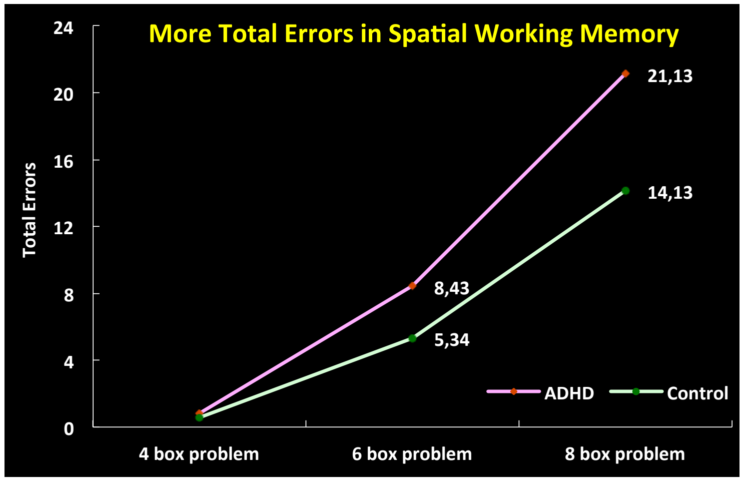


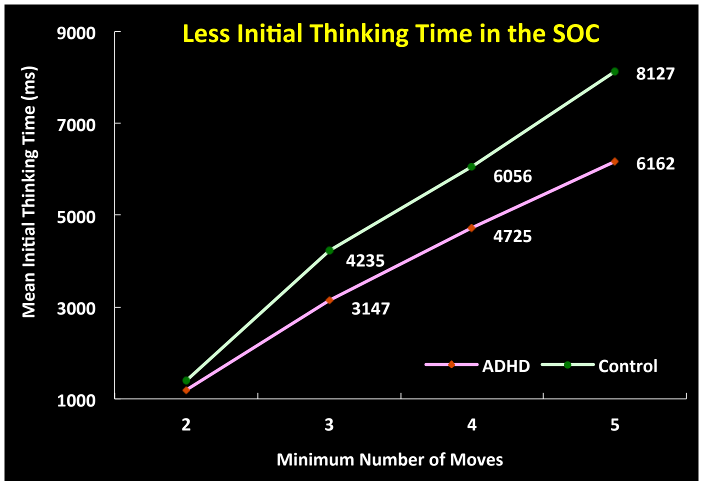
Rapid Visual Information Processing (RVP)

Executive Dysfunction in ADHD

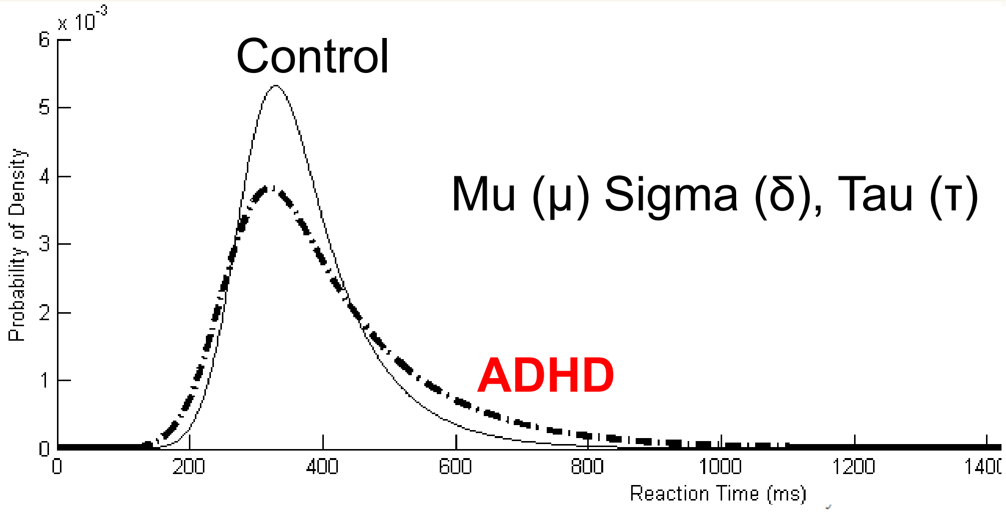
(Gau et al., 2010)

- 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

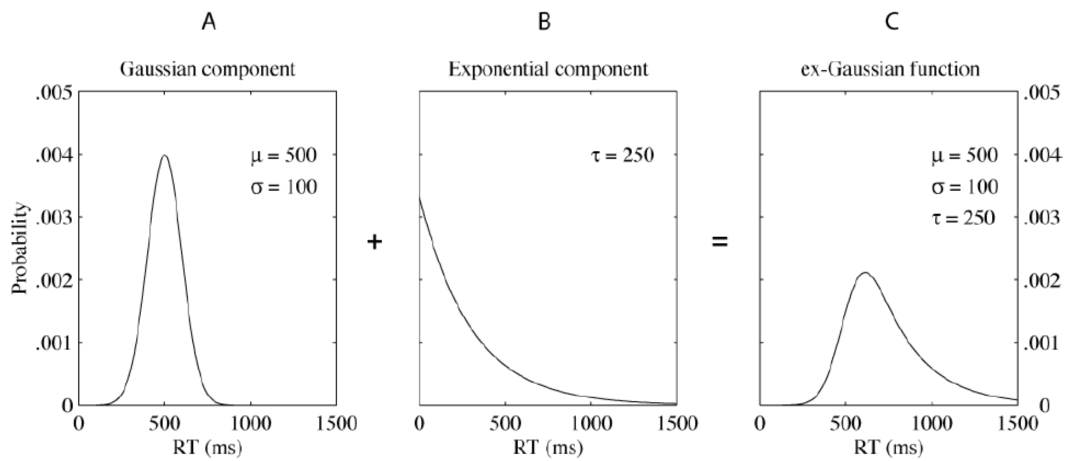
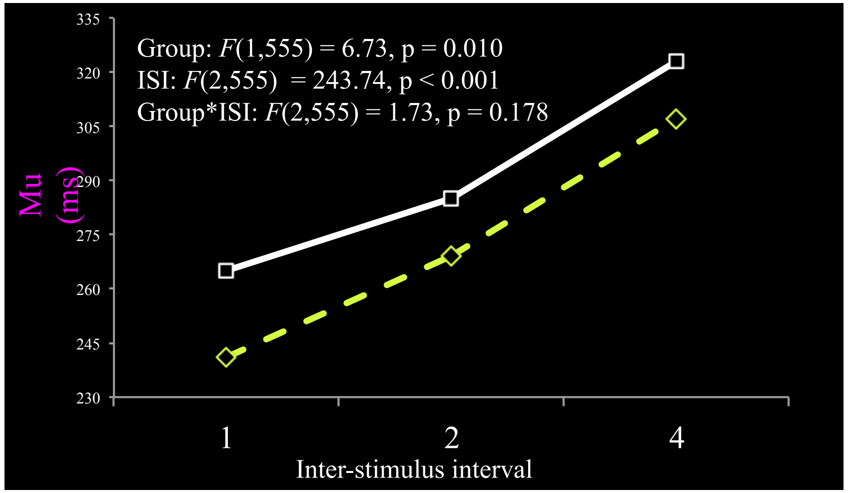
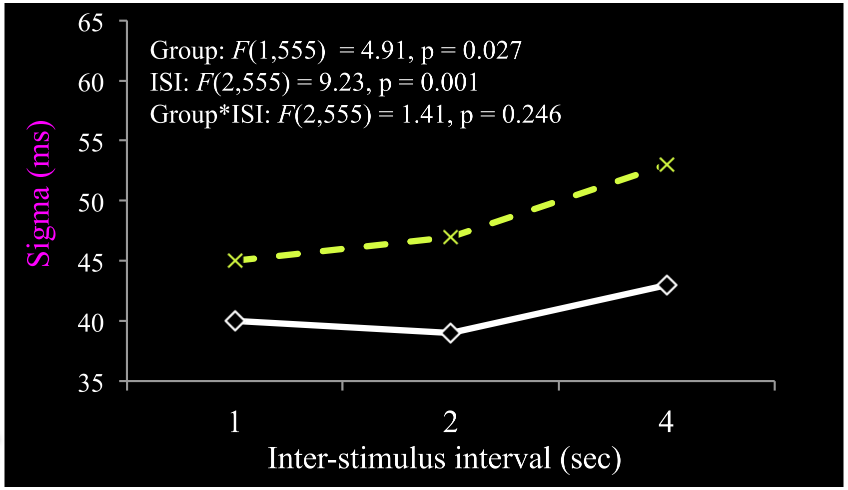


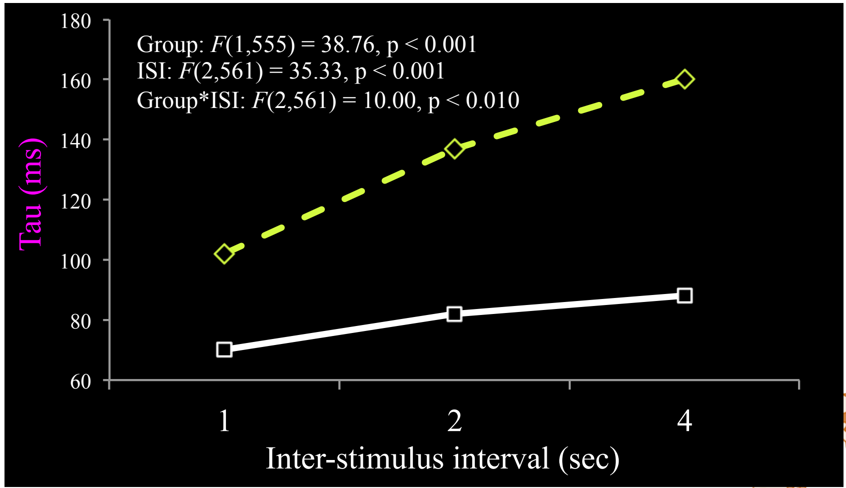
Figure 4. The ex-Gaussian probability function with parameters μ = 500, σ = 100, and τ = 250 (Panel c) resulting from the convolution a Gaussian probability function (Panel A) with an exponential function (Panel B).

A smaller μ, larger σ and larger τ in ADHD; Greater τ in ADHD increased with increased ISI

Means of the three ex-Gaussian parameters [Mu (μ), Sigma (δ), Tau (τ)] plotted across the 1-, 2-, 4-second ISIs for the ADHD and control groups.

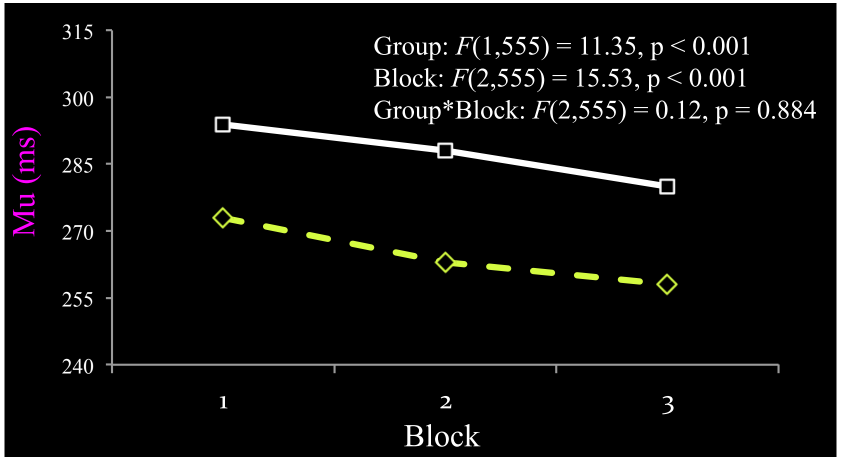


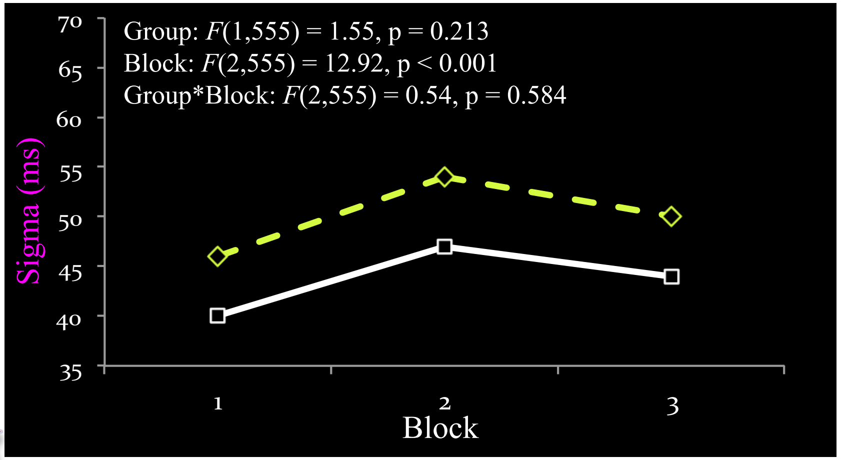


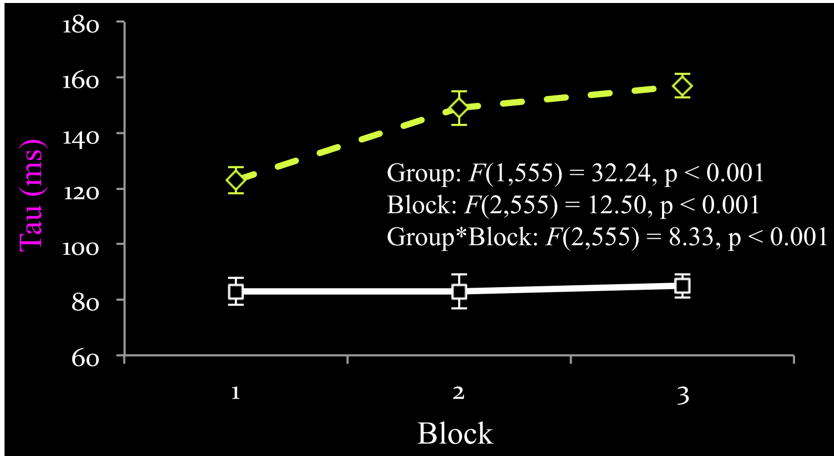


The moderating effects of ISIs and blocks on τ support difficulty in effort allocation in ADHD.

- Mu (μ), Sigma (δ), Tau (τ) plotted across the Blocks 1-3
- τ with inattentive symptoms and omission errors
- μ correlated with commission errors



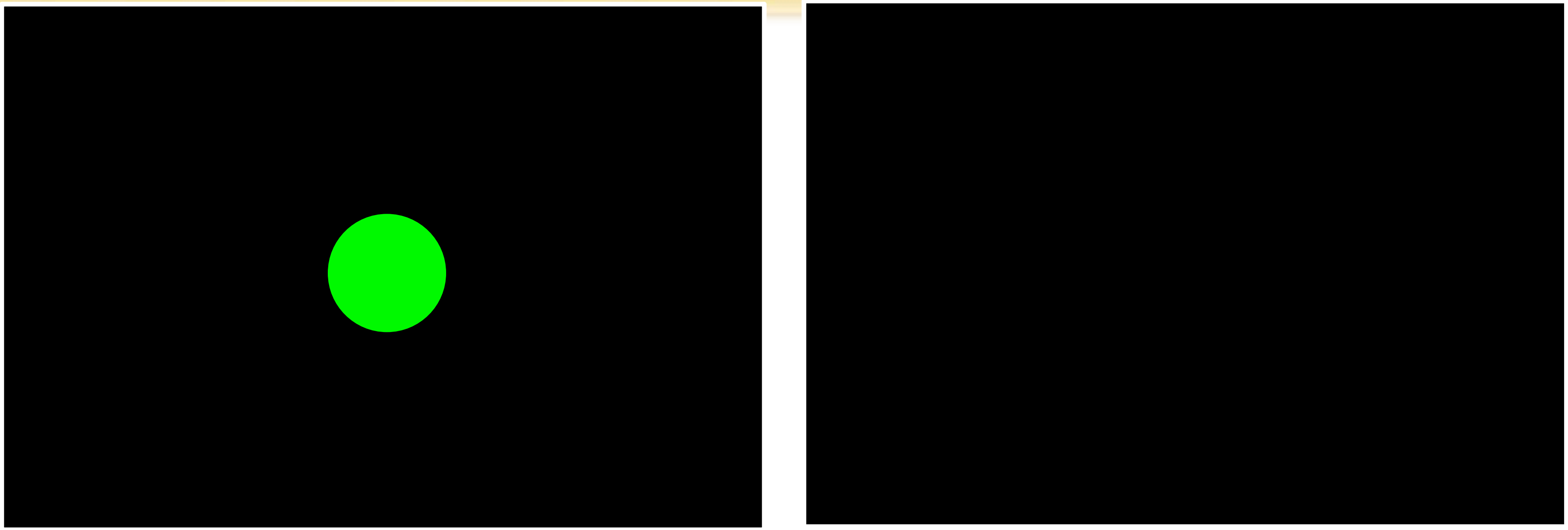




Conclusion of ex-Gaussian Distribution

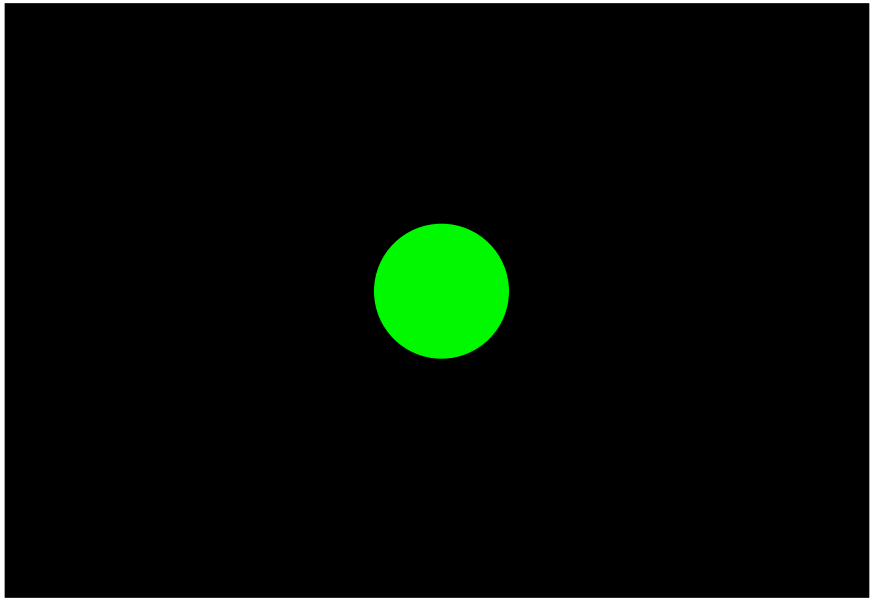
- tau would be related to the attention lapses due to the problems of effort regulation, proposed by the cognitive-energetic model
- mu would be related to the impulsive response style.
- The ex-Gaussian decomposition of RT variability suggests ADHD as an impulsive response style with attentional lapses rather than a cautious response style in CCPT.

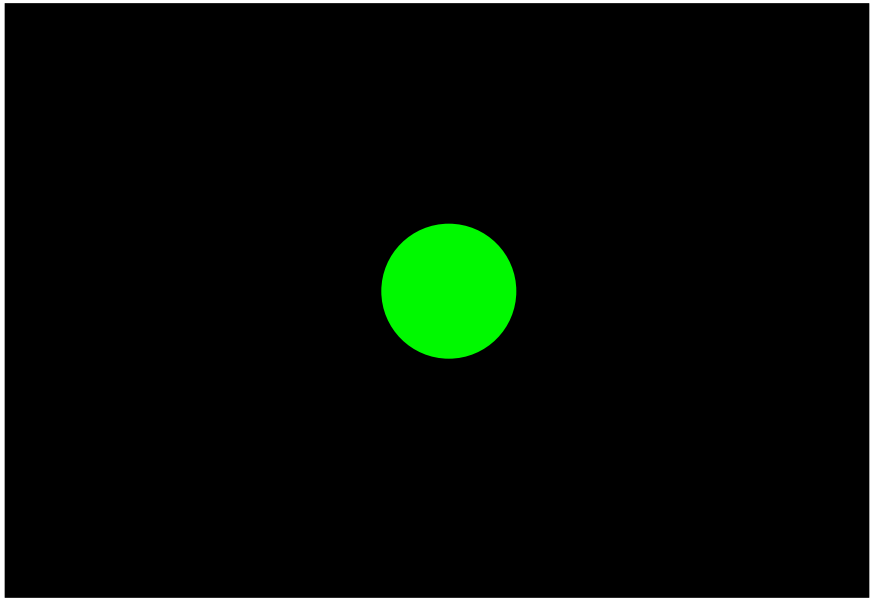
Time Estimation Task



- 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.

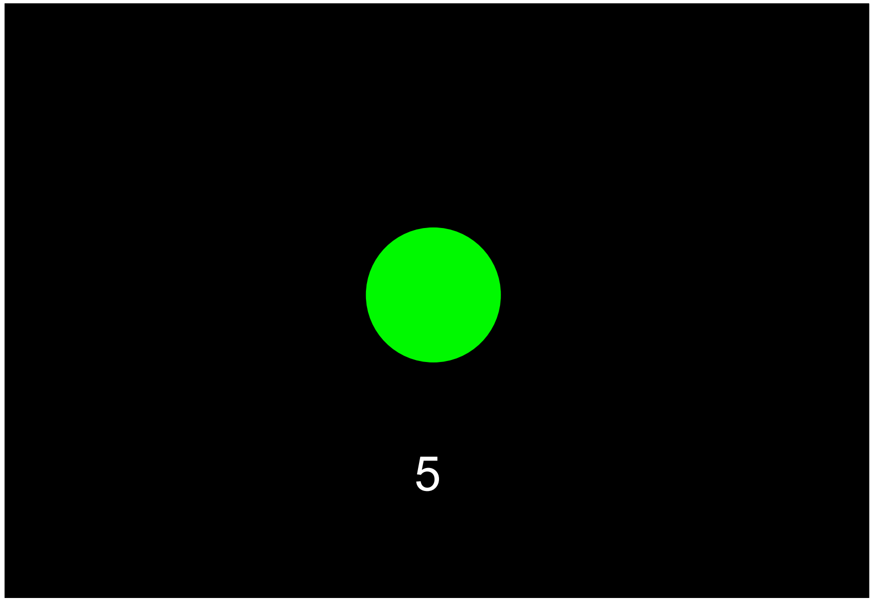
Time Reproduction Single Version

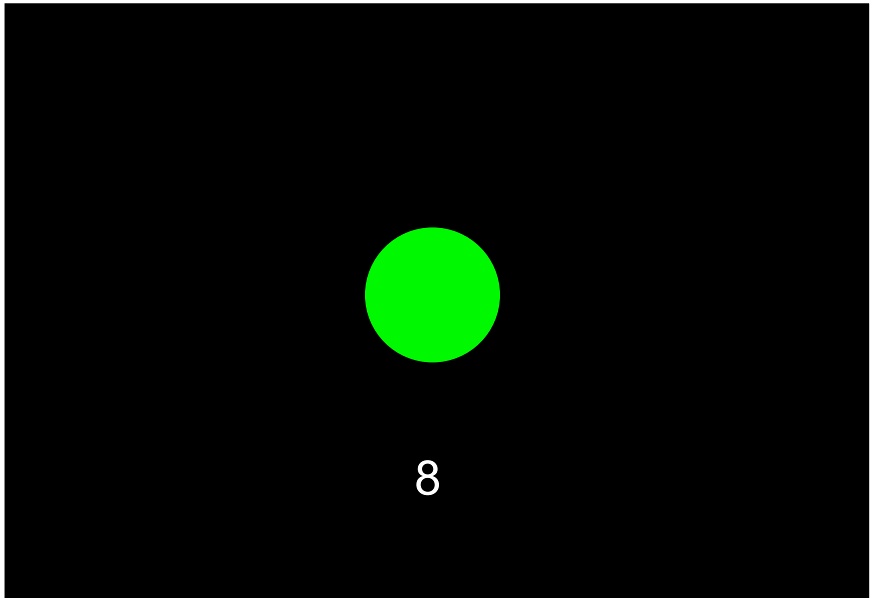




- The stimuli and the duration are same with the time estimation (5,12,17 sec).
- After the screen went blank, participants were instructed "Press the joystick key and let the circle appear and last again, and raise the key when you think the same duration of time has elapsed."

Time Reproduction Dual Tasks
Simple and Difficult Versions





- 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.

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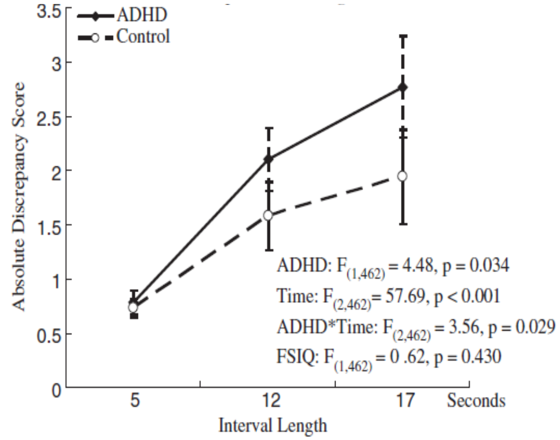
Journal of Child Psychology and Psychiatry 51:3 (2010), pp 223–232 doi:10.1111/j.1469-7610.2009.02163.x

Deficits in interval timing measured by the dual-task paradigm among children and adolescents with attention-deficit/ hyperactivity disorder

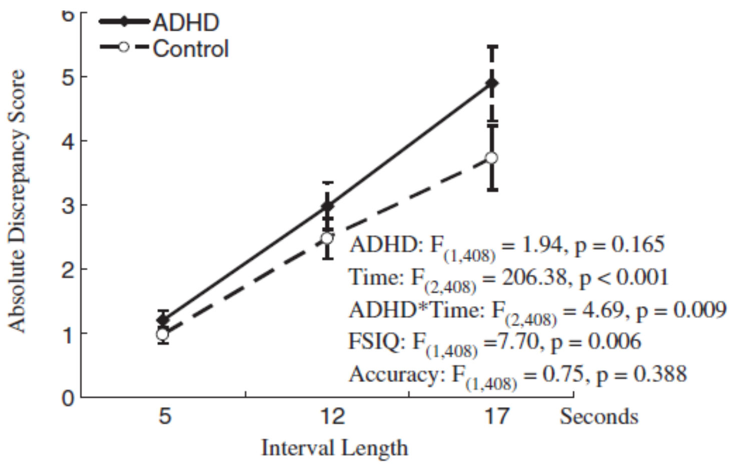
Shoou-Lian Hwang,[1,2] Susan Shur-Fen Gau,[3,4] Wen-Yau Hsu,[1,5] and Yu-Yu Wu[6]

Single Task

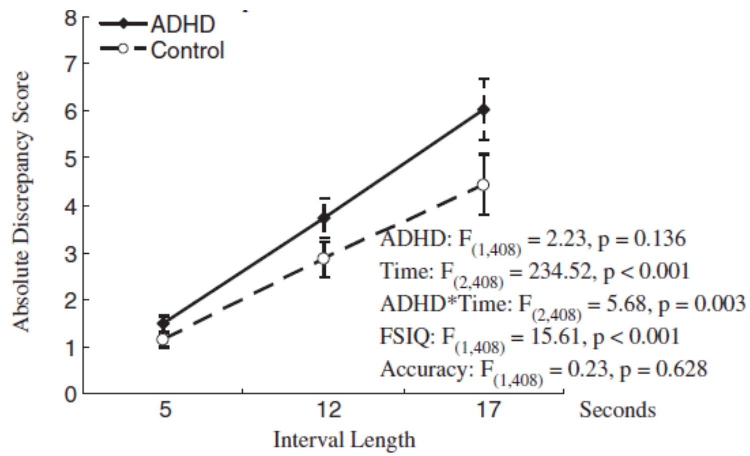


Using the time reproduction dual task to explore the role of the attentional resource in time perception deficits in ADHD, our findings suggest that impaired timing processing in ADHD during long time intervals may be explained by the limited attentional capacity rather than a primary problem in timing per se.

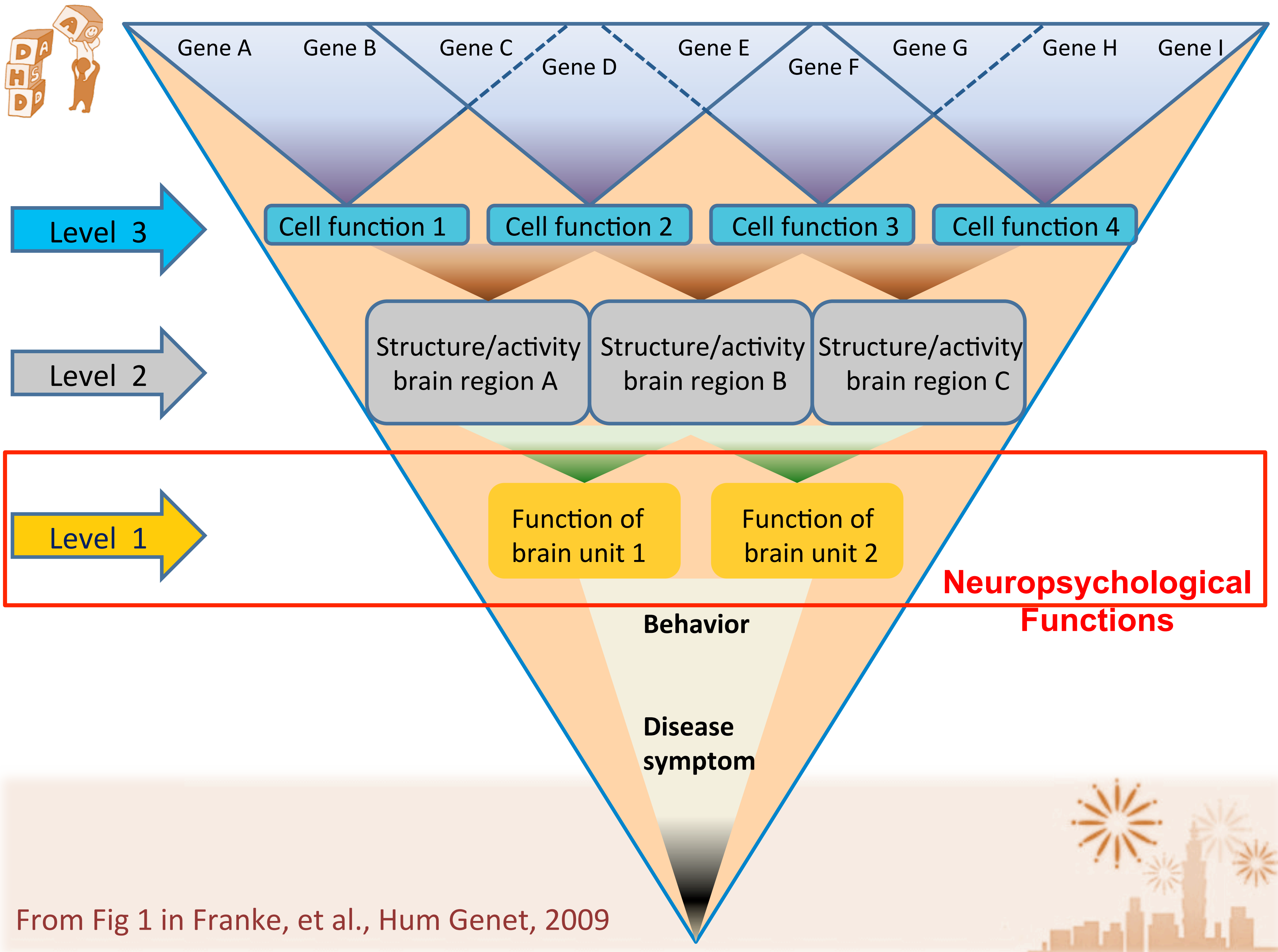
Dual Task-Simple Version



Dual Task-Difficult Version



Which Neuropsychological Functions are Potential Endophenotypes for ADHD



From Fig 1 in Franke, et al., Hum Genet, 2009

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Journal of Child Psychology and Psychiatry 51:7 (2010), pp 838–849 doi:10.1111/j.1469-7610.2010.02215.x

Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB)

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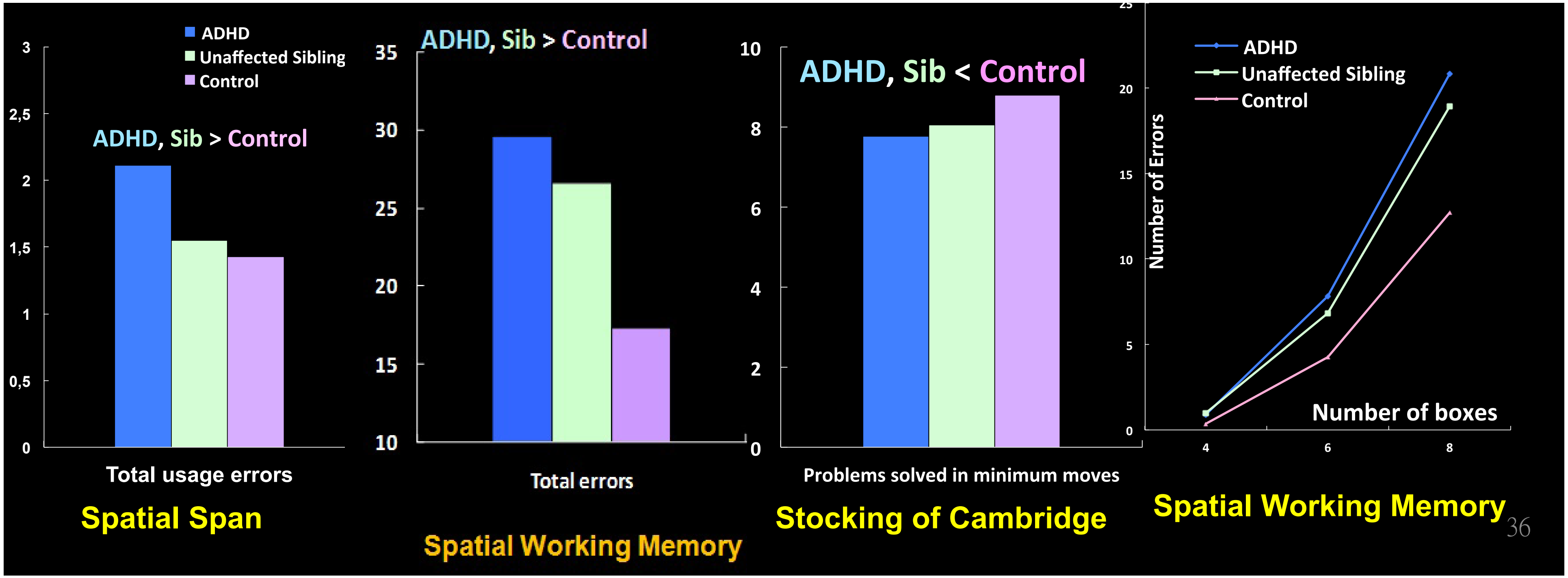
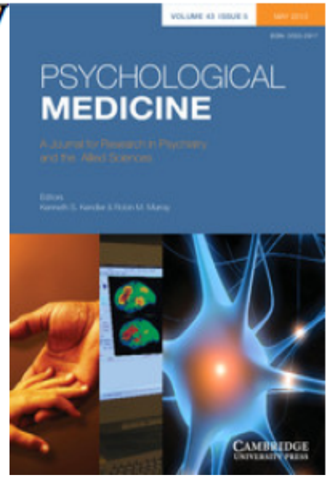


Psychological Medicine (2011), **41**, 2603–2614. © Cambridge University Press 2011
doi:10.1017/S0033291711000857

ORIGINAL ARTICLE

Visual memory as a potential cognitive endophenotype of attention deficit hyperactivity disorder



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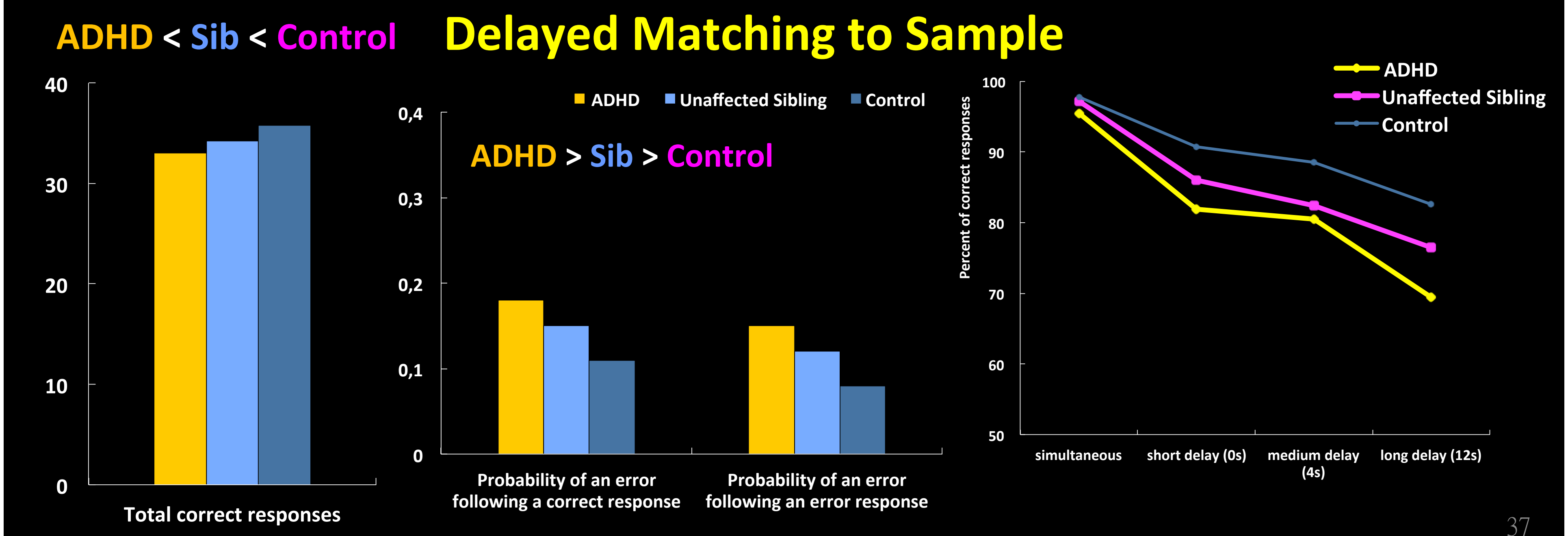

Psychological Medicine, Page 1 of 12.
doi:10.1017/S0033291713000640

ORIGINAL ARTICLE

Rapid visual information processing as a cognitive endophenotype of attention deficit hyperactivity disorder

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Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan
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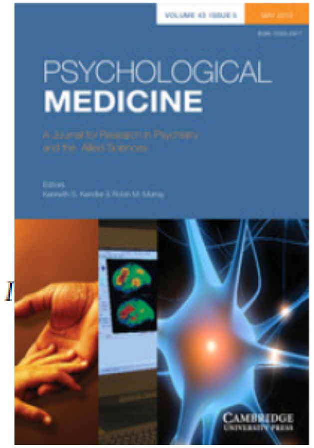
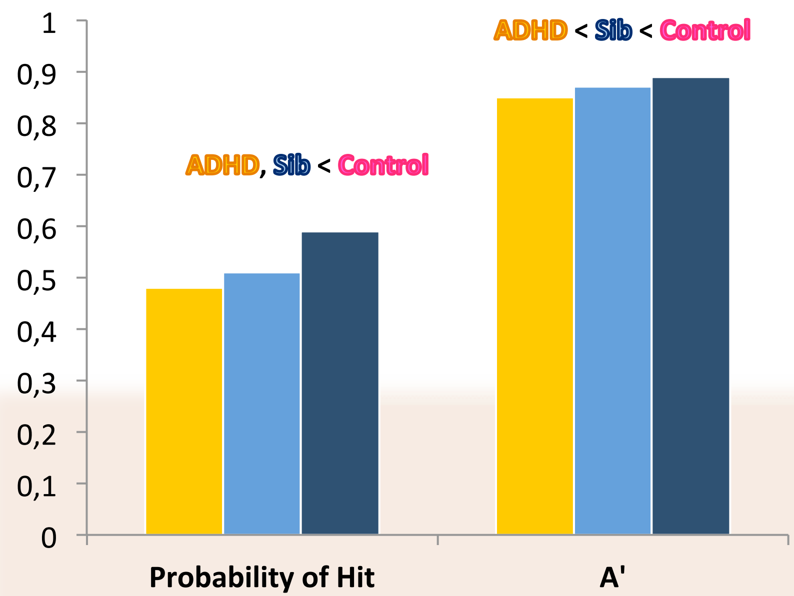
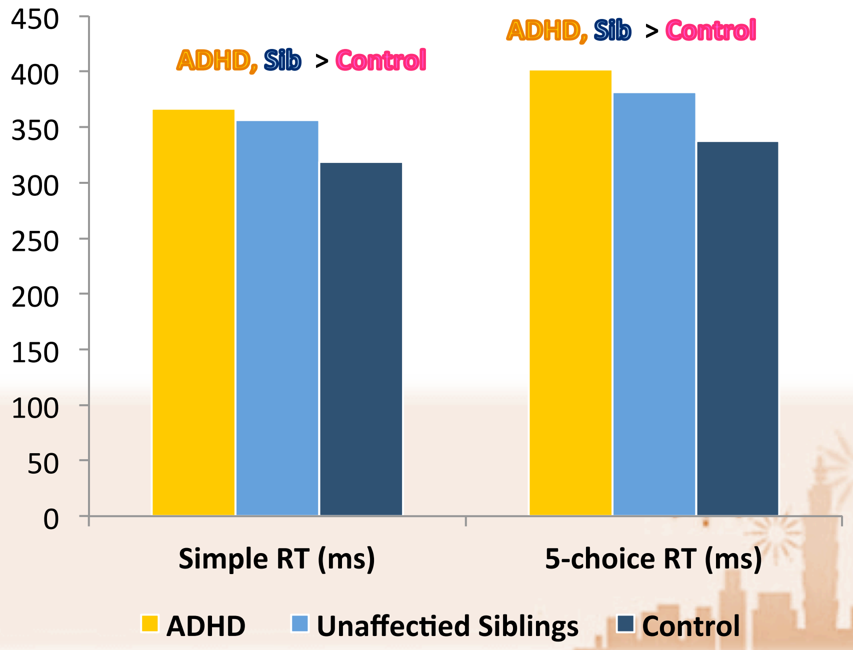


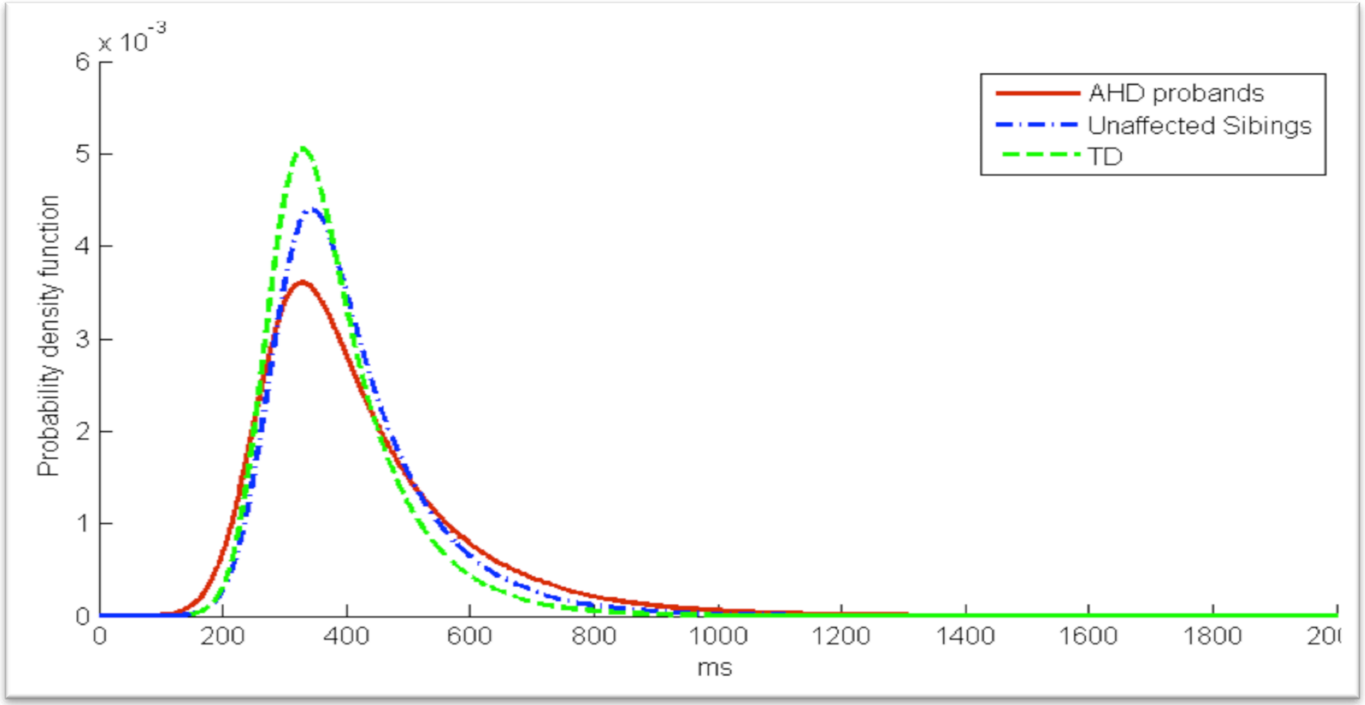
Rapid Visual Information Processing



Reaction Time



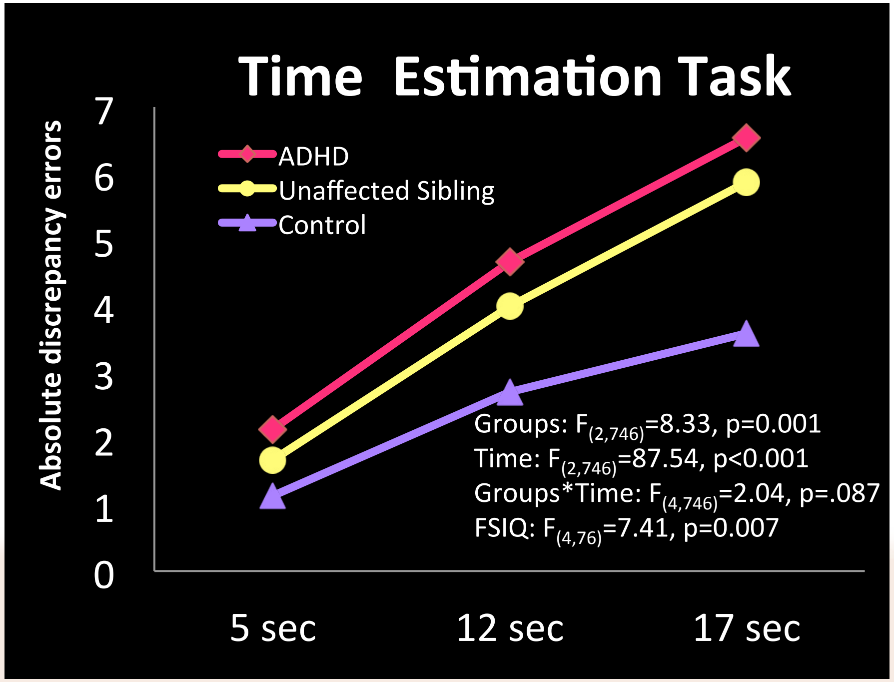
Intraindividual Variability as a Candidate Endophenotype for ADHD ?



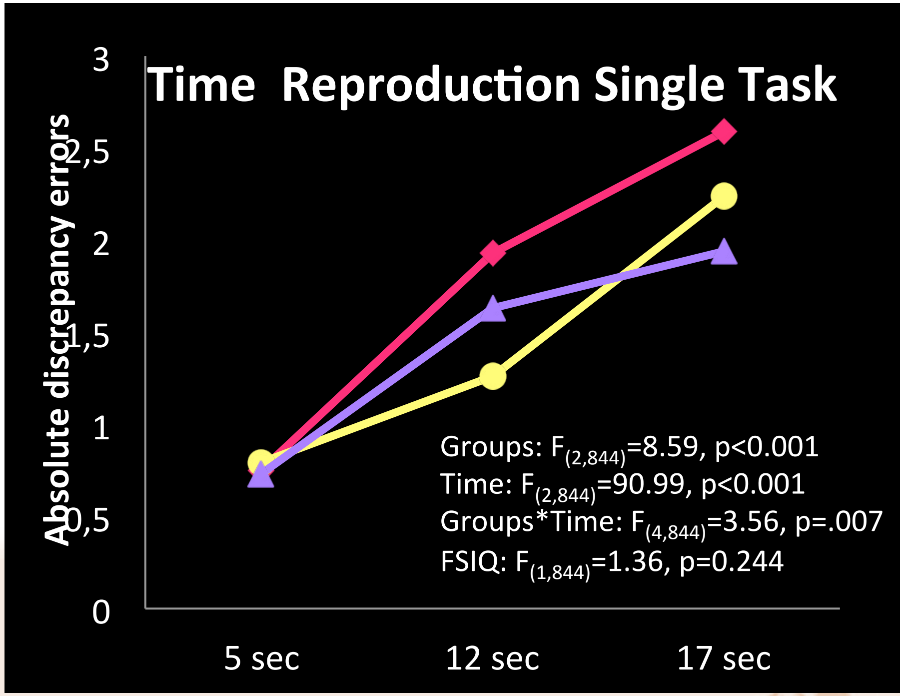
- **ADHD had faster mu (μ) and larger sigma (σ) than the other two groups. Both ADHD and unaffected sibling groups had larger tau (τ) than TD across the 3 ISIs and 3 Blocks.**
- **The attention lapse in tau could be a candidate endophenotype for ADHD.**

Deficit in Interval Timing May be a Candidate Endophenotype for ADHD (1/2)

Both ADHD and unaff Sib had more discrepancy errors than controls

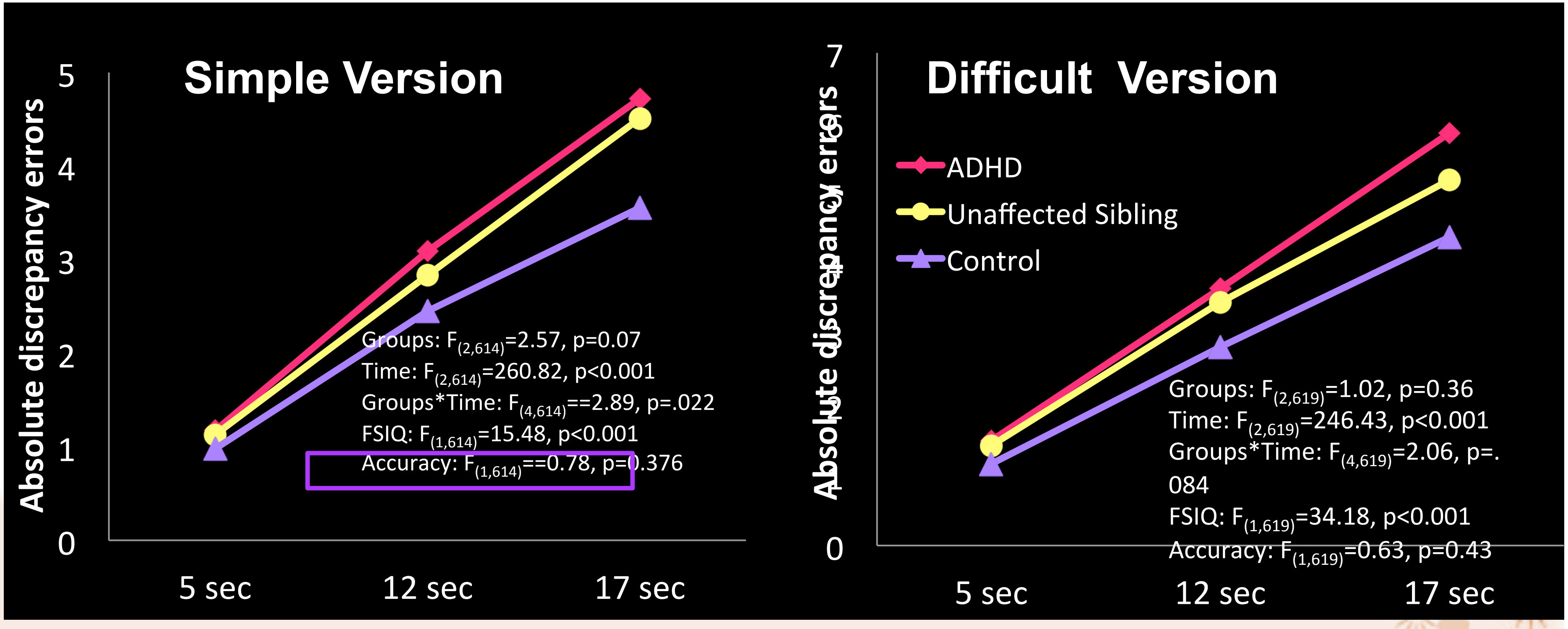


More discrepancy errors in ADHD



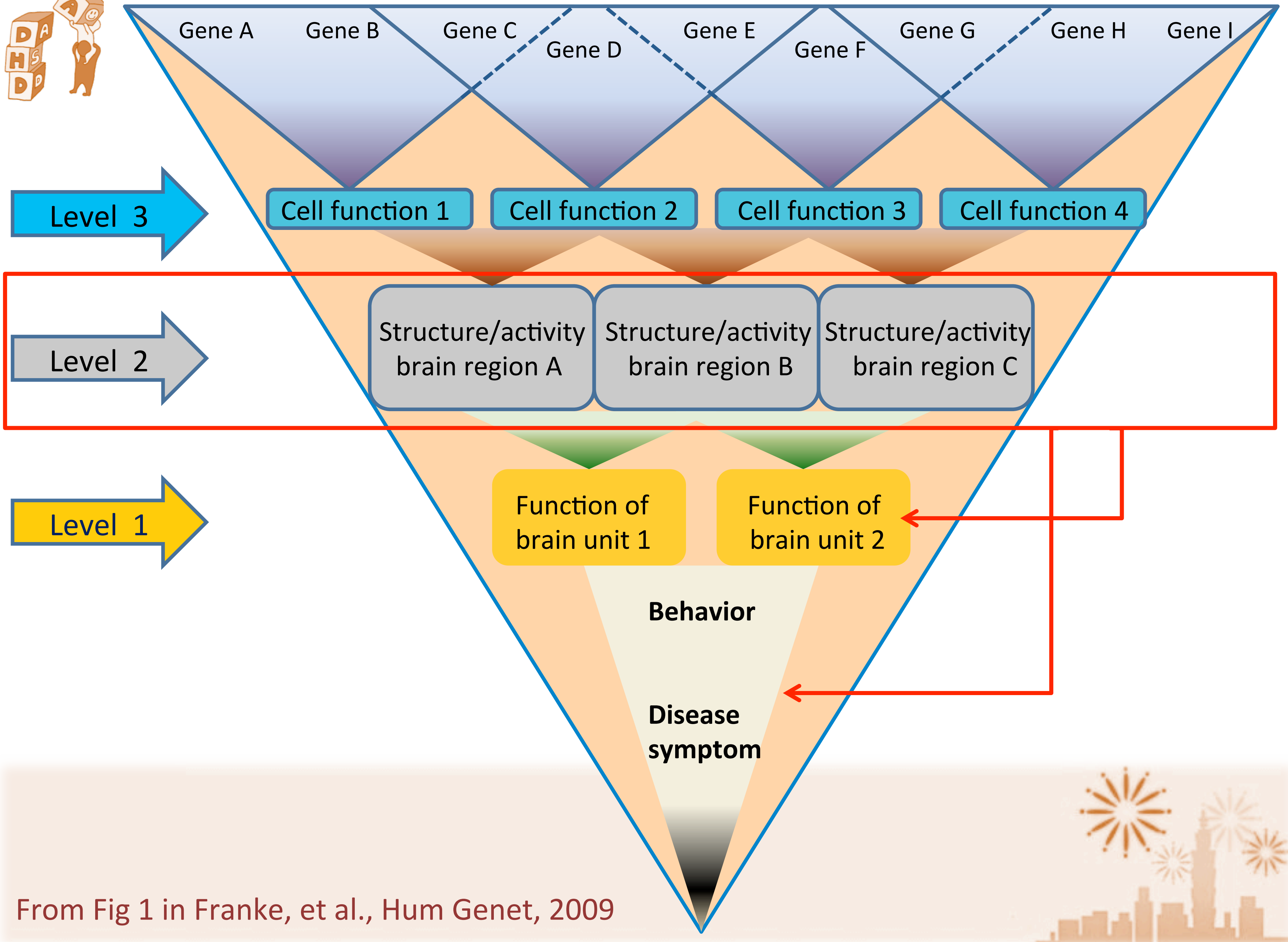
Deficit in Interval Timing May be a Candidate Endophenotype for ADHD (2/2)

More discrepancy errors in **ADHD** and **unaff- 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 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.

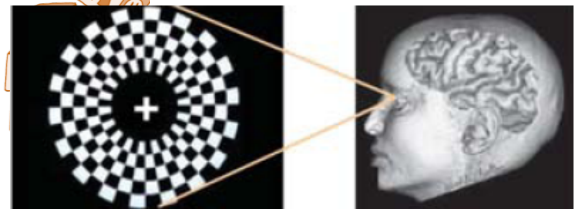


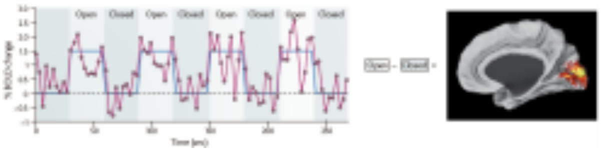
From Fig 1 in Franke, et al., Hum Genet, 2009

Brain Image Studies

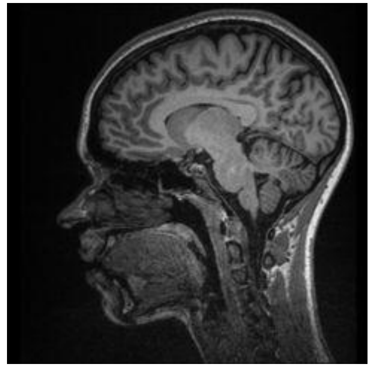
--Structural and Functional Connectivity

Magnetic Resonance Imaging

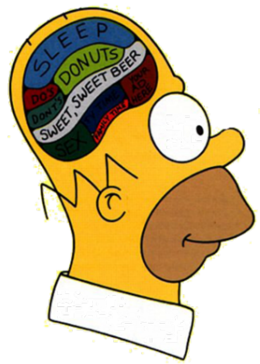




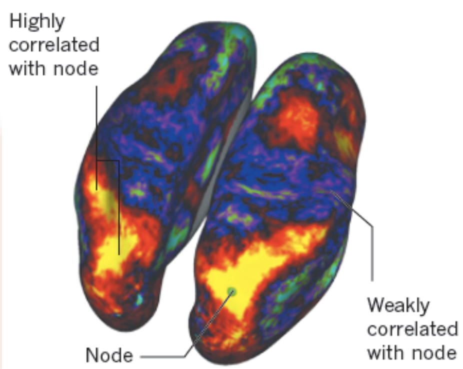
Task fMRI
Mapping function



Mapping structure
Voxel-based morphometry, cortical thickness, cortical surface area, cortical gyrification

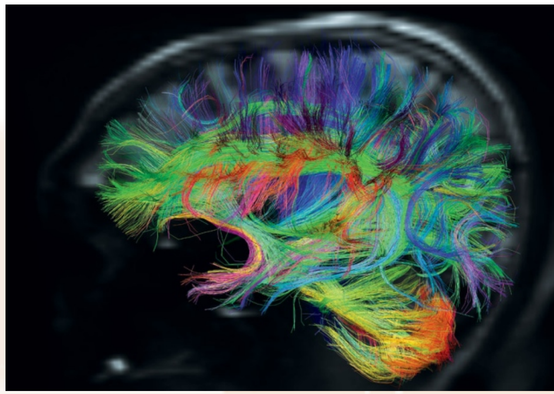


Resting fMRI
Mapping functional link (connectivity)

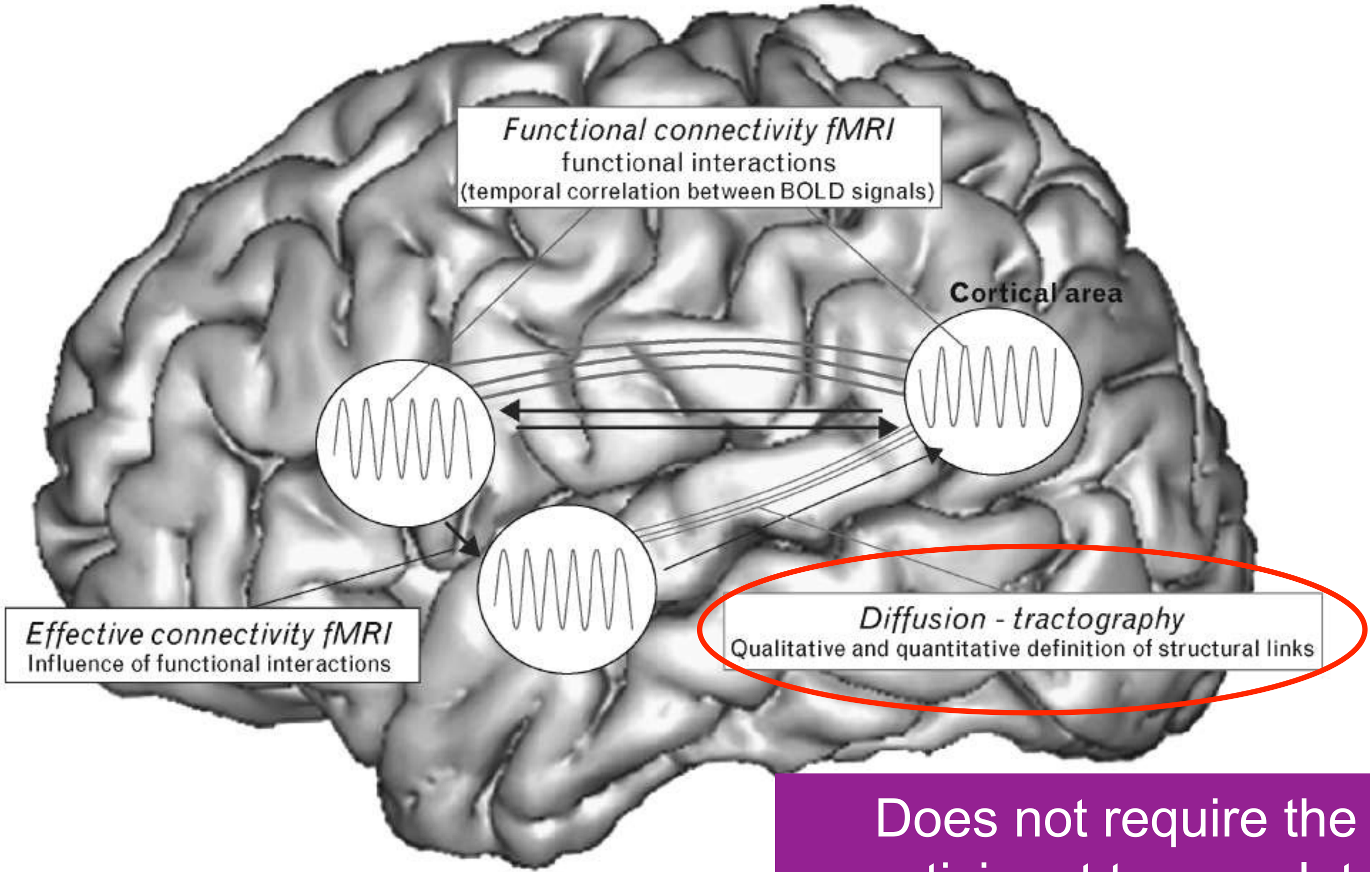


And magnetic resonance spectroscopy (MRS), arterial spin labeling, etc…

Diffusion tractography
Mapping wiring (DTI, DSI)

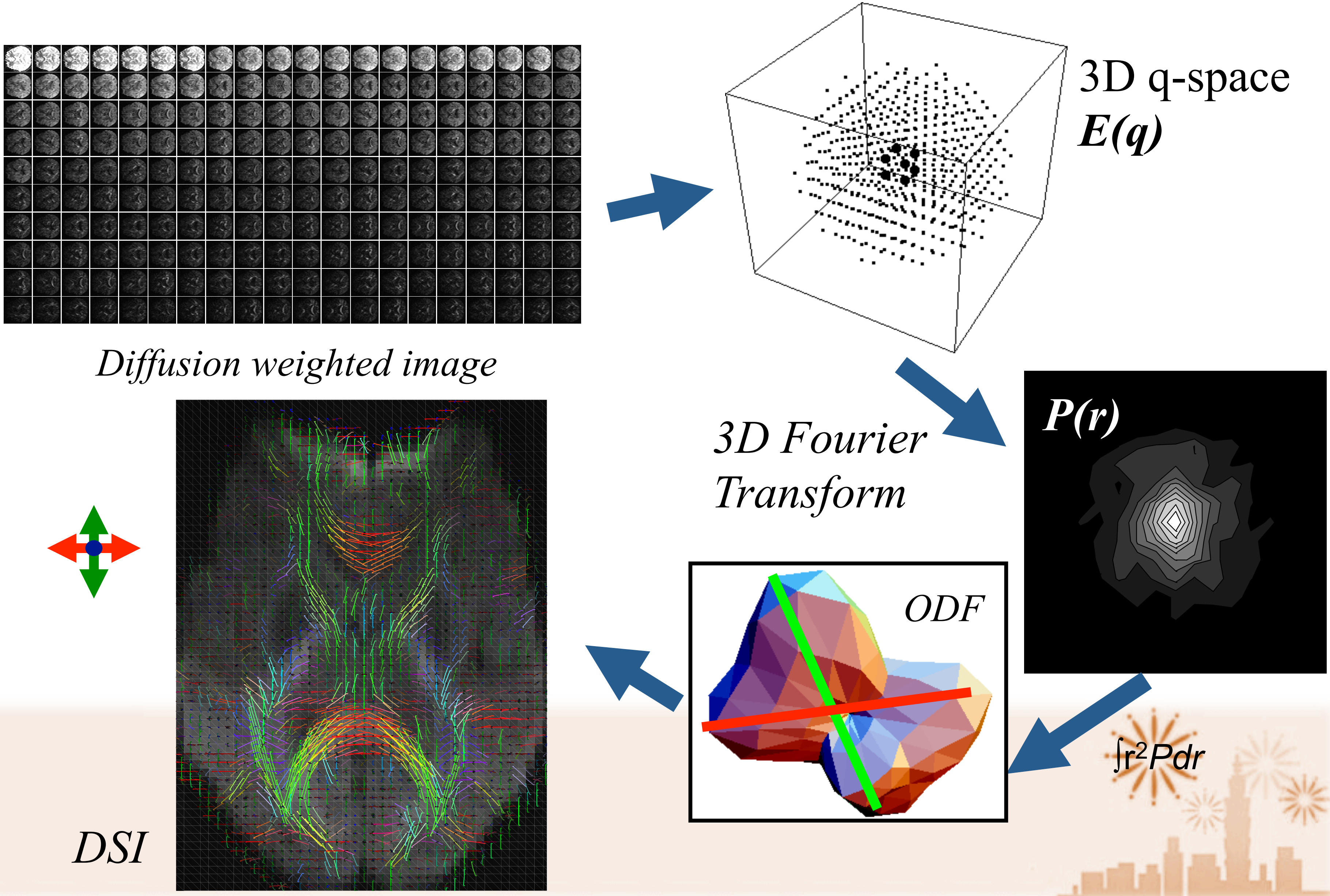


Using MRI, We Can Investigate…

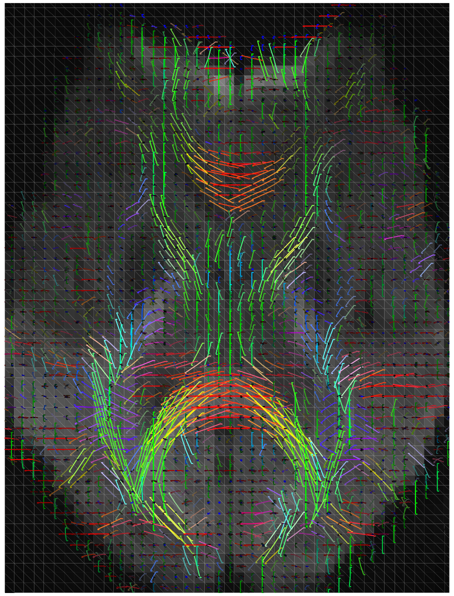


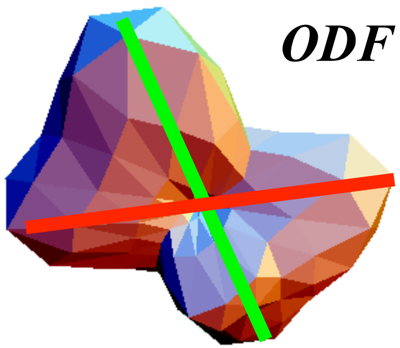
Does not require the participant to complete functional tasks

DSI Acquisition Scheme

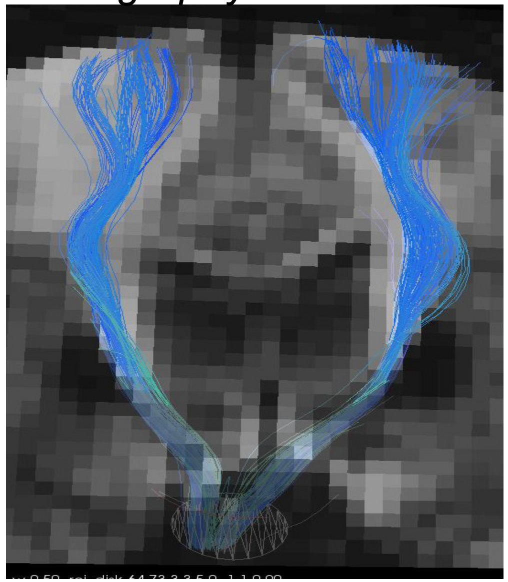


Reconstruct fiber tracts and quantify integrity

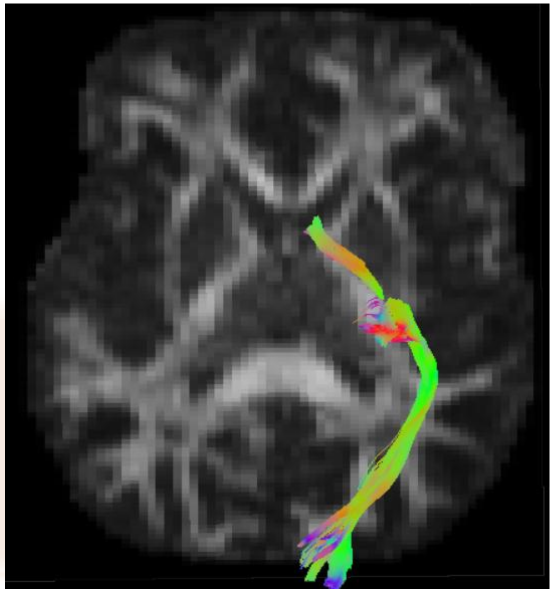




tractography



GFA mapping



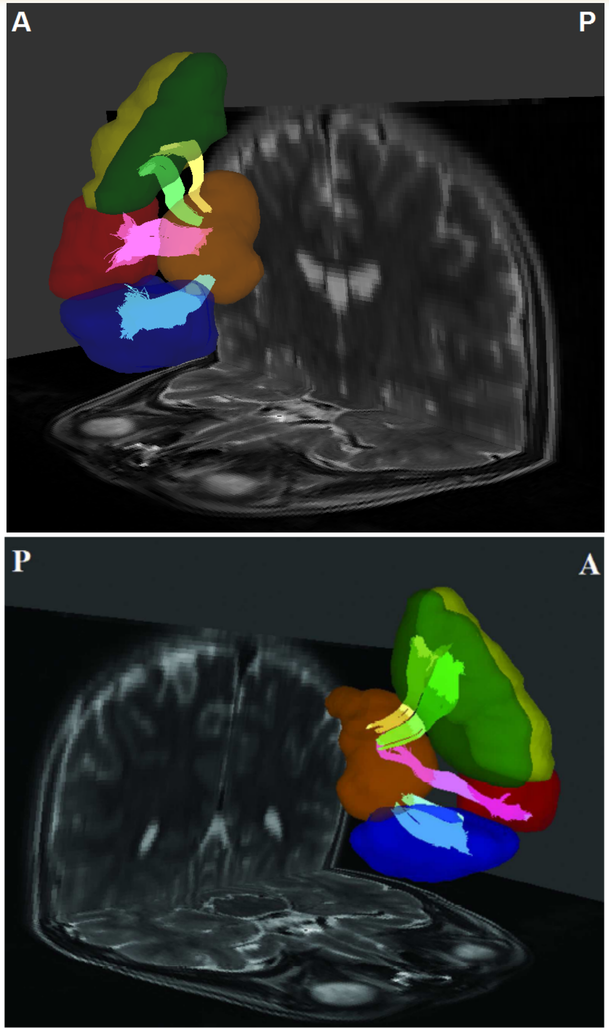
Generalized fractional anisotropy

$$\mathrm{GFA} = \frac{\mathrm{std}(\psi)}{\mathrm{rms}(\psi)} = \sqrt{\frac{n \sum_{i=1}^{n} (\psi(\mathbf{u}_i) - \langle\psi\rangle)^2}{(n-1) \sum_{i=1}^{n} \psi(\mathbf{u}_i)^2}}$$

- **Fiber Integrity**
  - *myelination*
  - *directional coherence*
  - *axonal density*

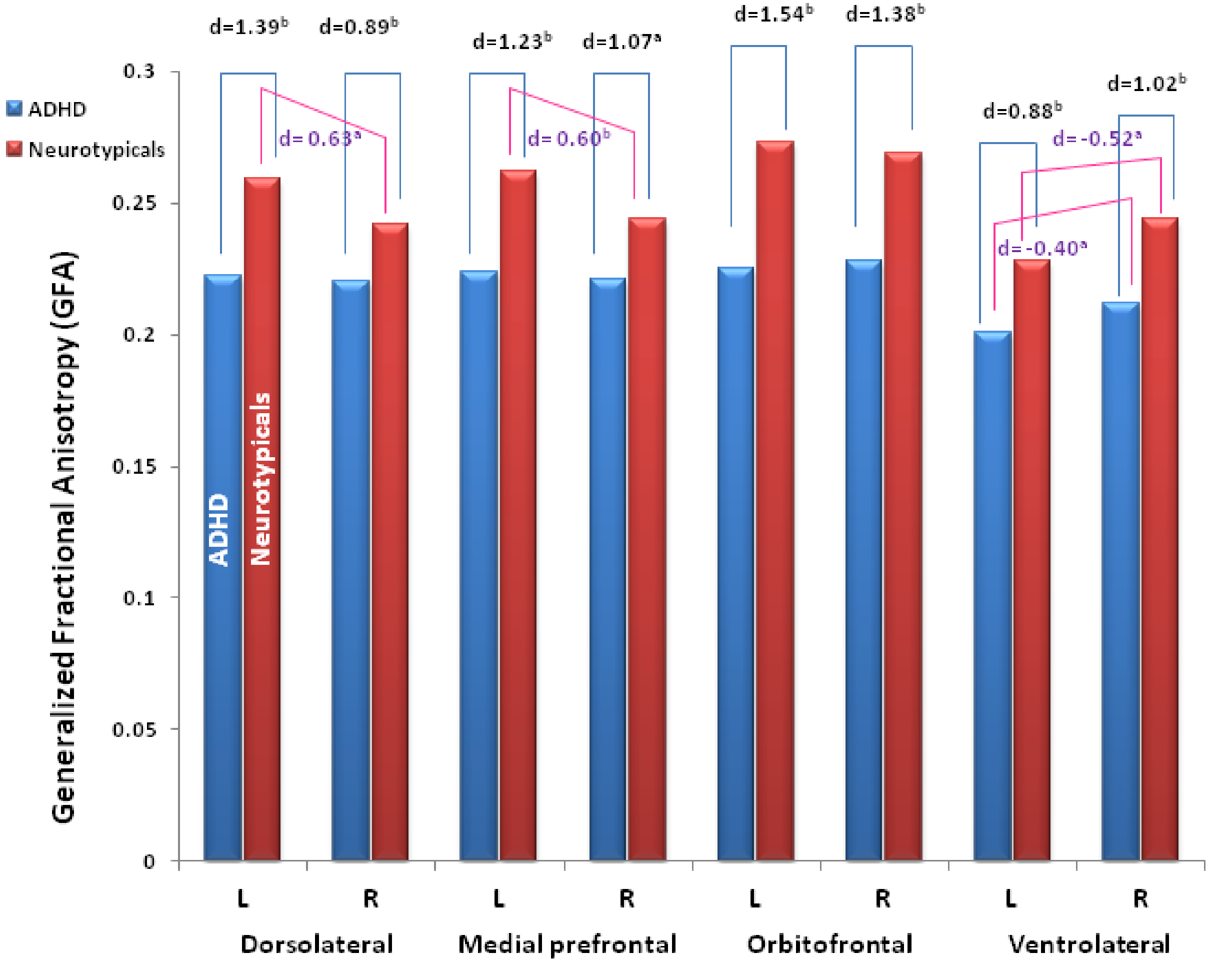
Hypothesis

- *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



Expert Rev Neurother. 2007 Oct;7(10):1337-56
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

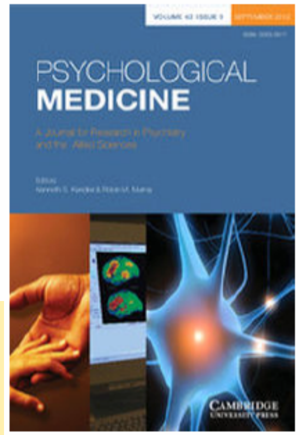
Yi-Huan Wu,[1] Susan Shur-Fen Gau,[2,3,4*] Yu-Chun Lo,[5]
and Wen-Yih Isaac Tseng[3,5,6*]

Human Brain Mapping 2012 Aug 30. doi: 10.1002/hbm.22169.

[Epub ahead of print]

Psychological Medicine, Page 1 of 15.
doi:10.1017/S0033291712001869

Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder



C. Y. Shang[1], Y. H. Wu[2], S. S. Gau[1,3]* and W. Y. Tseng[3,4,5]*

Psychological Medicine 2012 Aug 15:1-15.

[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)

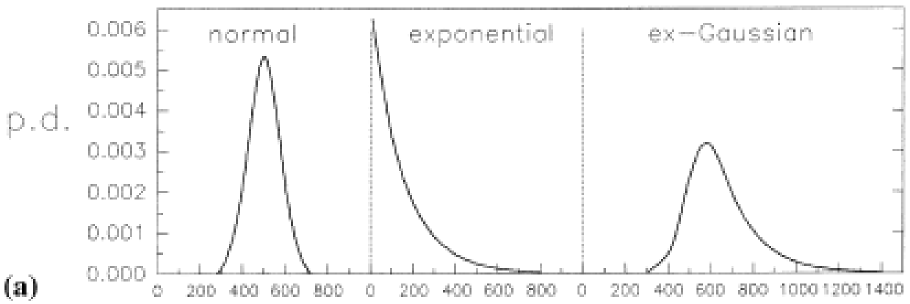
Intraindividual variability (IIV) and ex-Gaussian distribution

- **Increased IIV in ADHD**

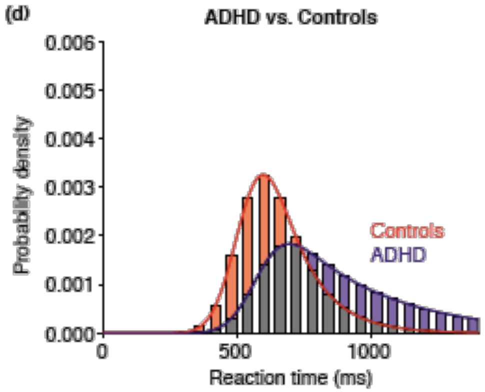
"One ubiquitous finding in ADHD research across a variety of speeded-reaction-time tasks, laboratories and cultures", Castellanos and Tannock, NRN, 2002

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

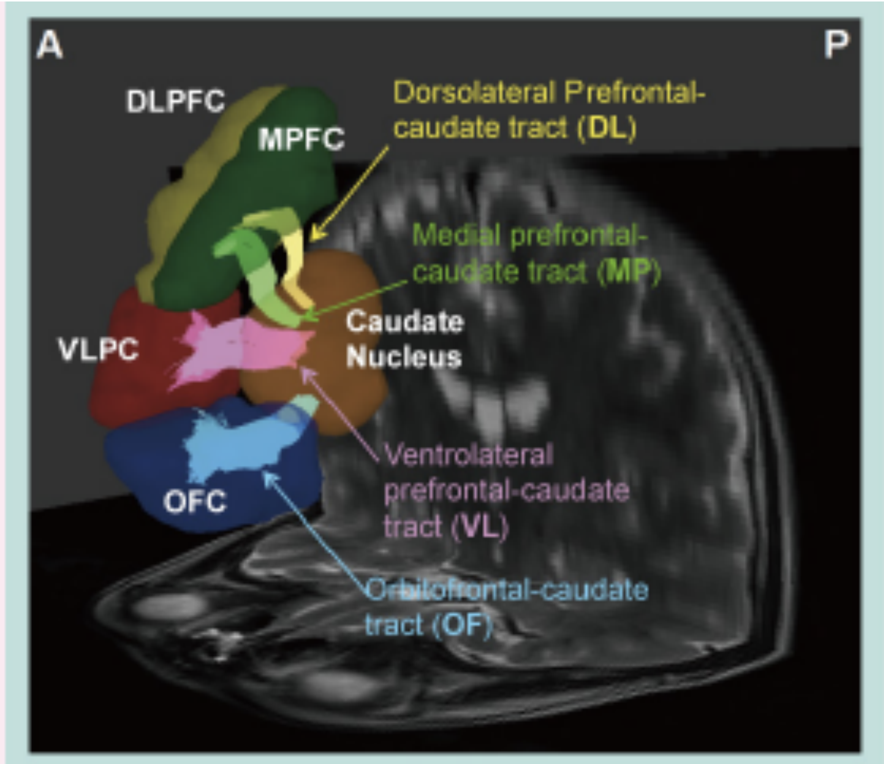
- **Larger τ in ADHD, across choice RT task** (Leth-Steensen et al. 2000), **Conner's continuous performance test** (Hervey et al. 2006, Gu-Huang & Gau et al. 2012), **and working memory task** (Buzy et al. 2009)

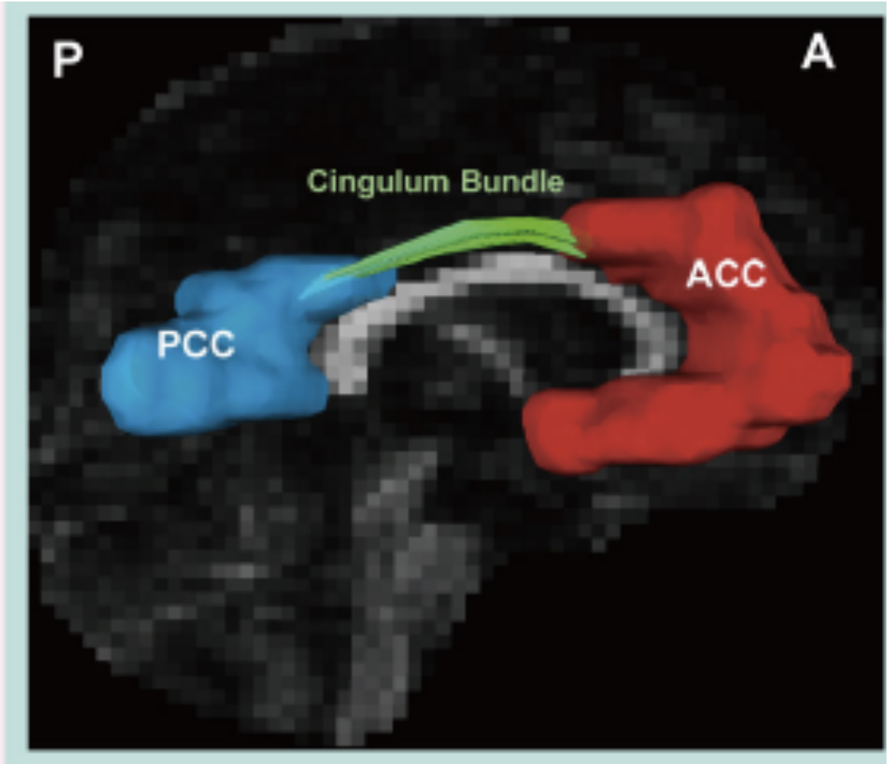


Leth-Steeson et al. 2000



Microstructural integrity of frontostriatal tracts and cingulum bundle

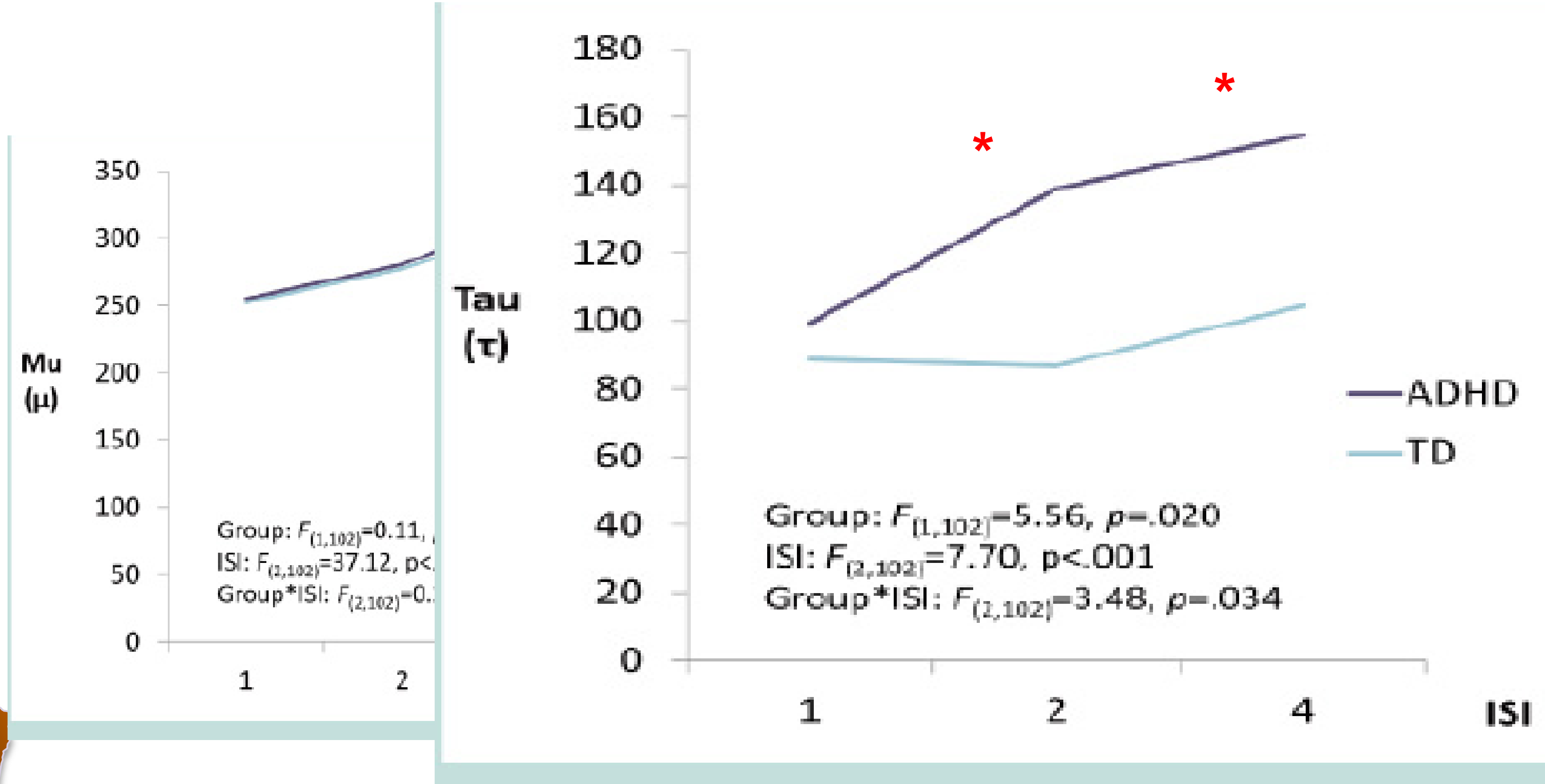




- **Based on top-down control and DMN interference model accounting for IIV in ADHD**

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 frontostriatal circuitry integrity may mediate RT variability in TD children.

		Mu (μ)†		Sigma (σ)†		Tau (τ)†	
		β	*p*	*β*	*p*	*β*	*p*
ADHD							
Medial prefrontal	L't	-2521.40	.039			-	-
Orbitofrontal	L't	3605.18	.020			-	-
Ventrolateral	L't			-	-	2685.16	.045
Cingulum	L't			-527.35	.004	-1482.21	.014
	R't	-1195.27	.026	-341.18	.077		
F values		$F_{(3,22)}$= 4.68	p =.011	$F_{(2,21)}$= 8.72	p = .002	$F_{(2,23)}$= 4.57	p = .021
R-square		0.39		0.45		0.28	
Typically Developing Children							
Dorsalateral	R't	-	-	-	-	-2195.92	.062
Orbitofrontal	L't	-	-	-	-	1973.91	.030
	R't	-1846.37	.065	-	-	-	-
Ventrolateral	L't	2695.73	.006	-	-	-1935.69	.029
	R't	2156.81	.059	-	-	-	-
Cingulum	L't			-73.46	.444		
F values		$F_{(3,22)}$= 5.26	p = .007	$F_{(1,22)}$= 0.61	p = .444	$F_{(3,22)}$= 2.97	p = .054
R-square		0.42		0.03		0.29	

†Sum of ISI-1S, ISI-2S and ISI-4S.

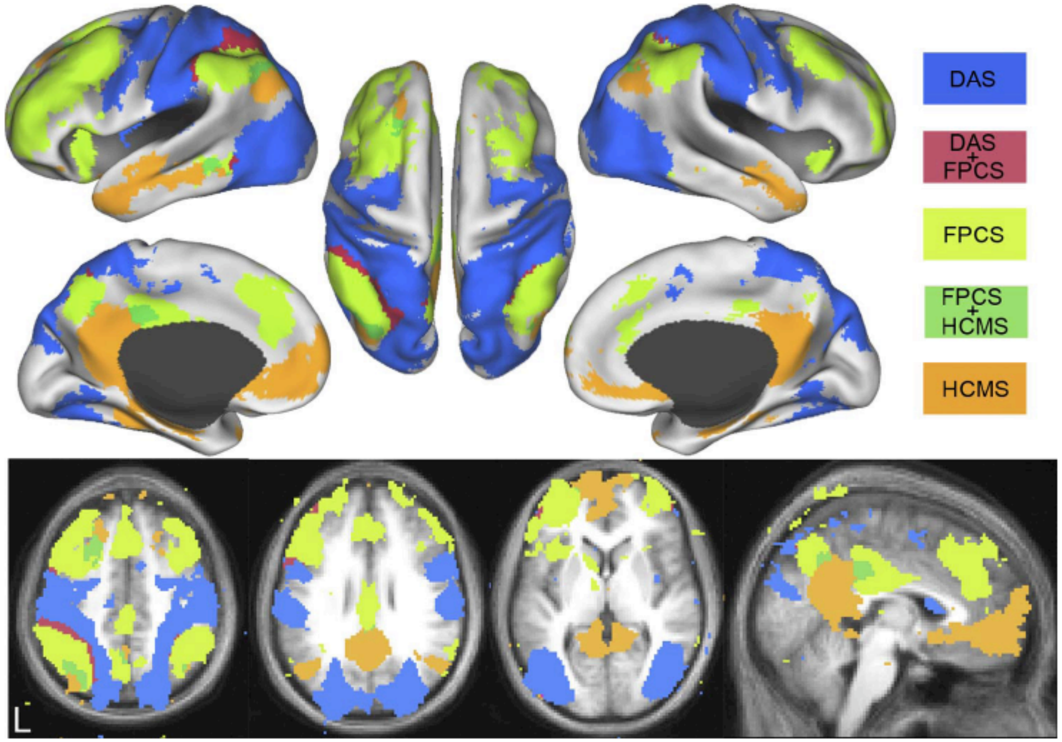
ADHD Cognitive Endophenotype

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

Frontoparietal control network (FPCN)



Vincent et al. 2008

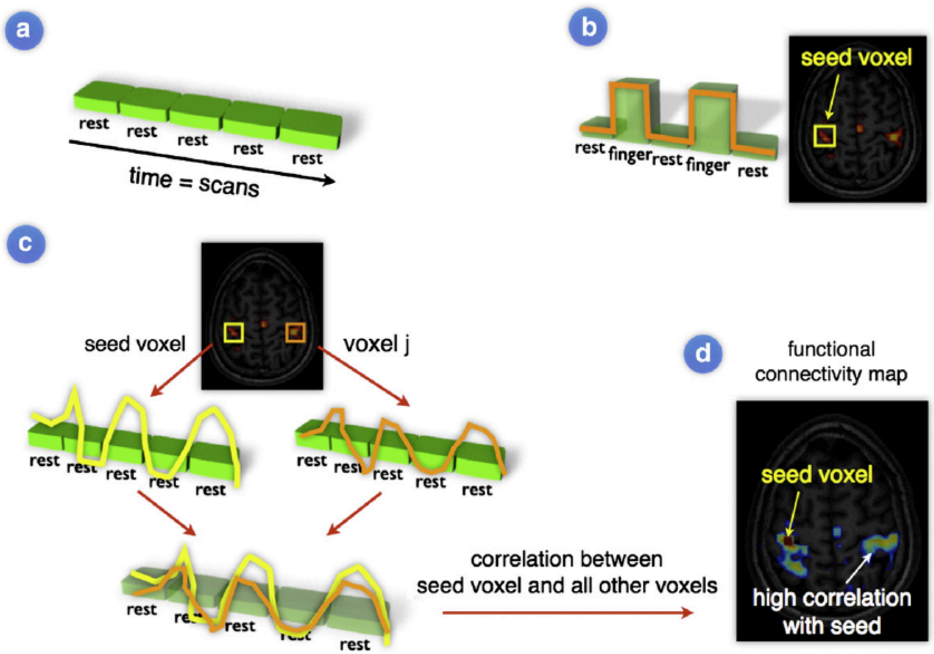
- Anatomically interposed between the default and dorsal attention networks
- Cognitive control & goal-directed integration of information (Spreng et al. 2010)

- 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

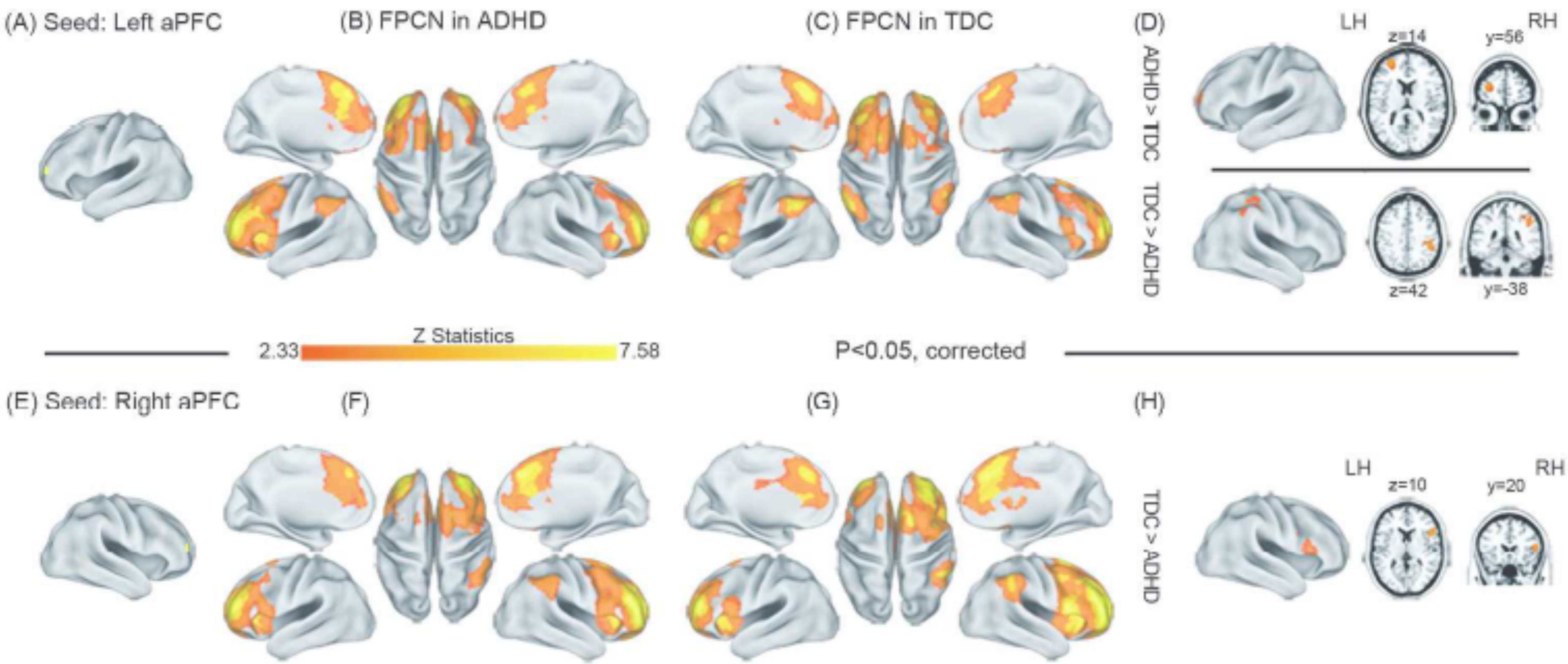
Sample and rfMRI connectivity analysis

- 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



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

	laPFC-raIPL		laPFC-lDLPFC		raPFC-rVLPFC	
	r	B	r	B	r	B
ADHD(n=25)						
Inattention	-0.09	.43	-0.01	.31	-0.20	.74
Hyperactivity	-0.23	.89	-0.02	.32	-0.06	.38
Impulsivity	-0.41*	3.93	-0.01	.31	-0.11	.47
Oppositional	0.11	.47	-0.13	.52	-0.50*	12.24

	laPFC-raIPL		laPFC-lDLPFC		raPFC-rVLPFC	
	r	B	r	B	r	B
Sustained attention						
Omissions	-0.08	0.45	-0.07	0.26	0.37	0.12
Hit RT SE	-0.54*	23.67	0.24	1.03	-0.03	0.37
Variability	-0.47*	8.41	0.36	2.55	0.03	0.30
Detectability (d')	0.34	2.14	-0.55*	28.01	0.01	0.34
Response inhibition						
Commissions	-0.33	1.97	0.48*	9.61	-0.07	0.43
Perseverations	-0.45*	6.56	0.30	1.56	-0.31	1.68

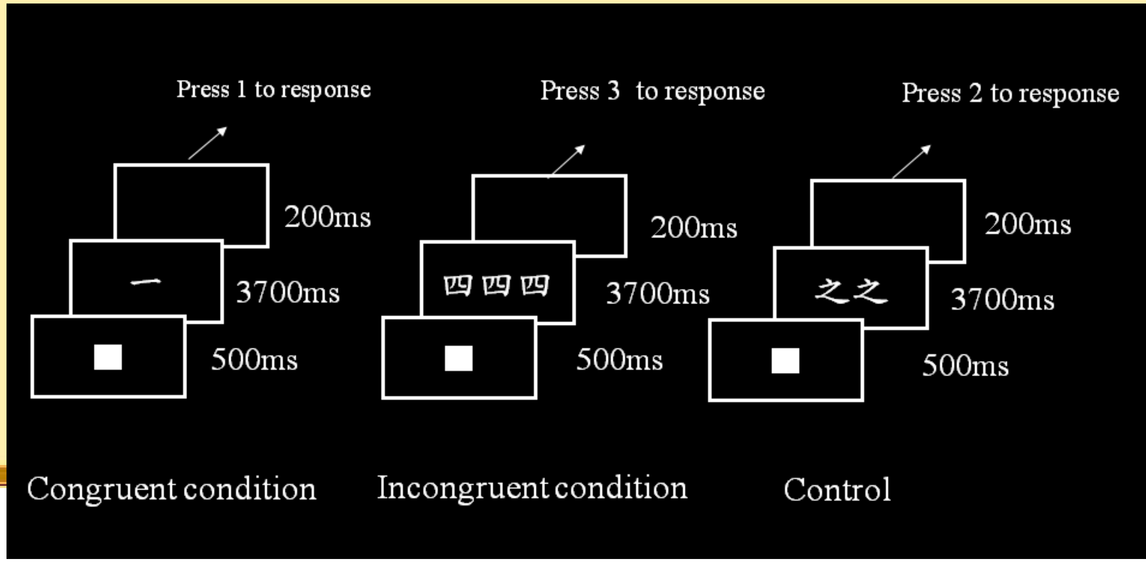
Key Points of the Study

- 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

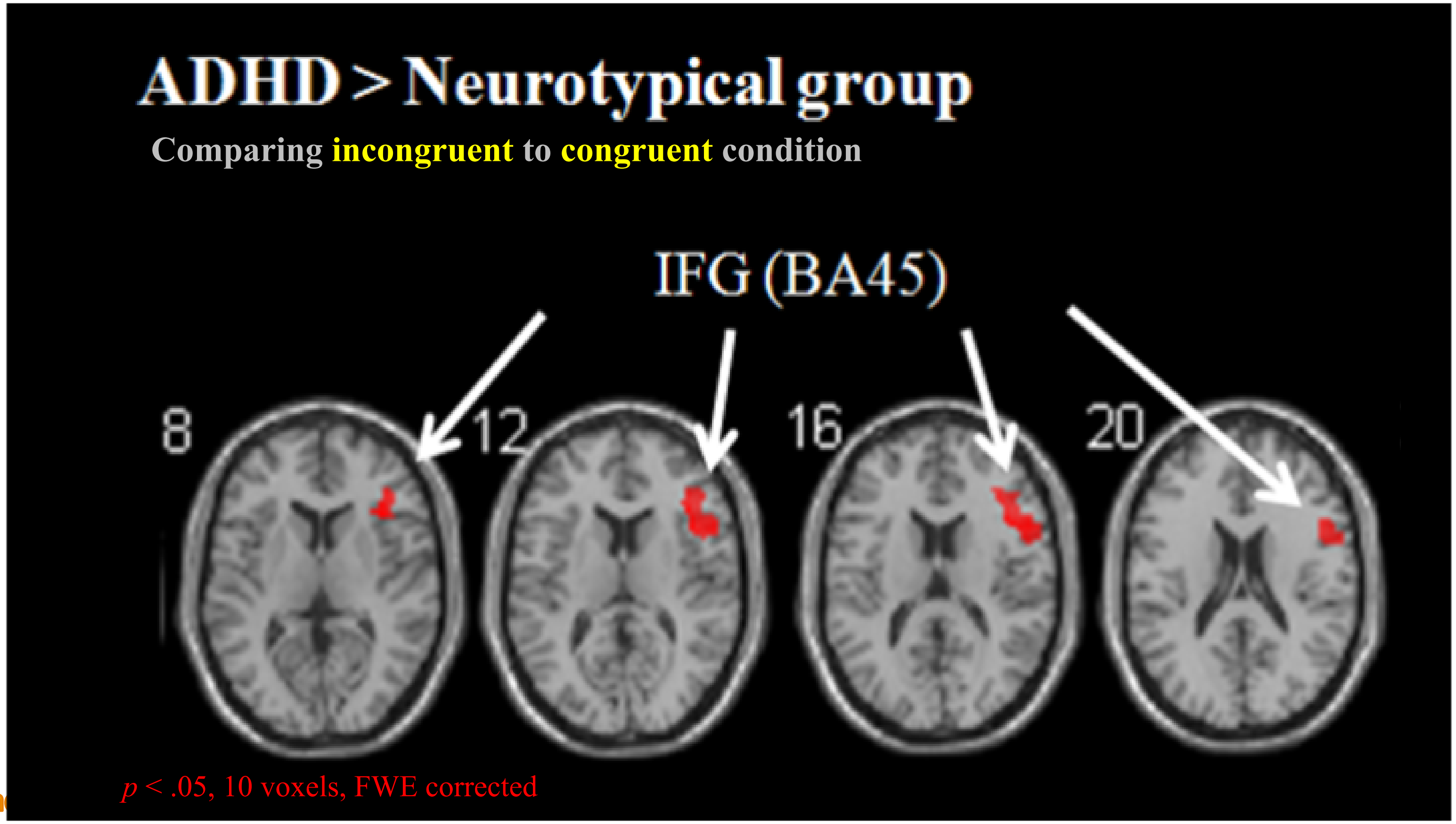
Fan LY, Gau SS, Chou TL (under review)

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



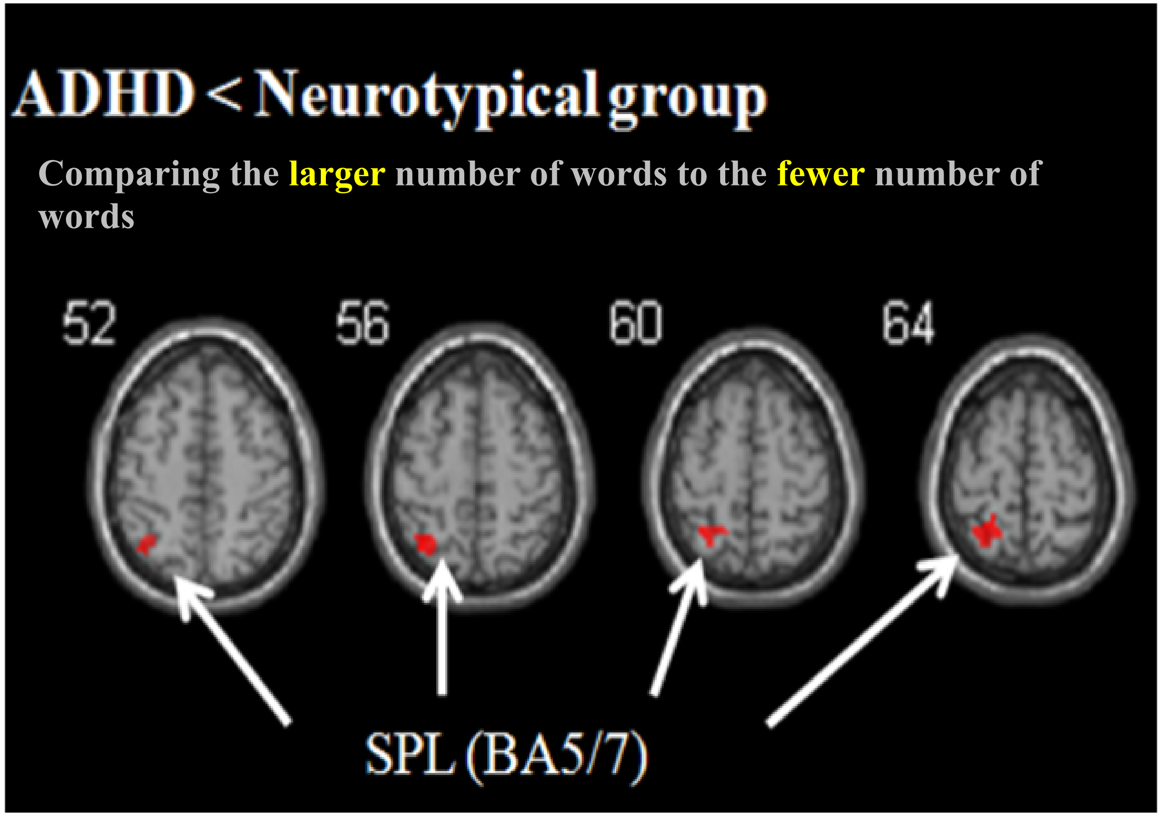
Sustained attention and inhibitory control

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



Results: Visuo-spatial memory

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).



$p < .05$, 10 voxels, FWE corrected

Key Point

- 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

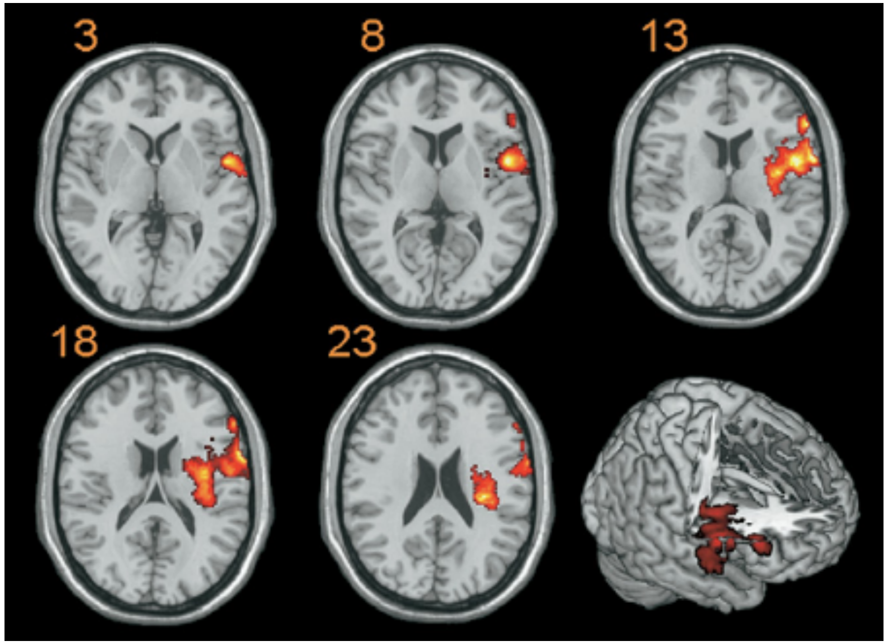
Cognitive effects of Atomoxetine (ATX) (1/2)

- **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)

Cognitive effects of ATX (2/2)

- **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)

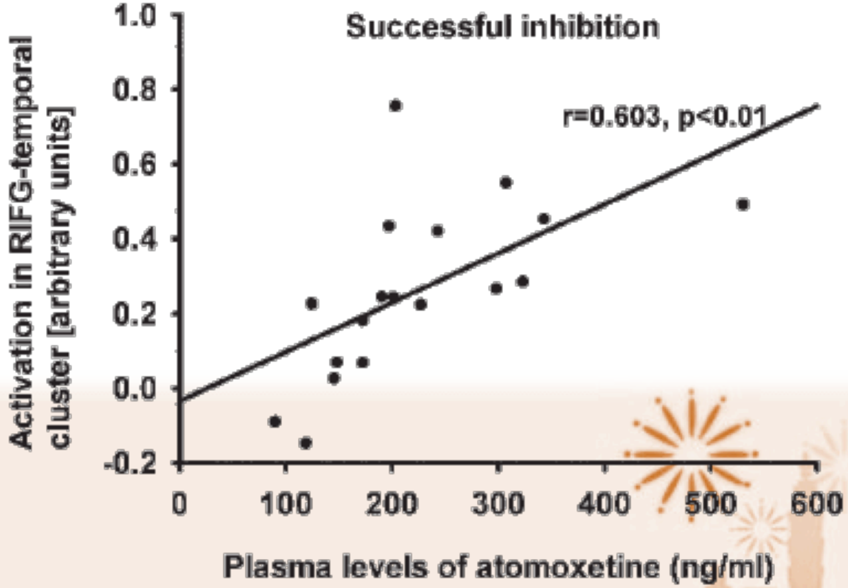
ATX modulates right inferior frontal gyrus during inhibitory control in adults



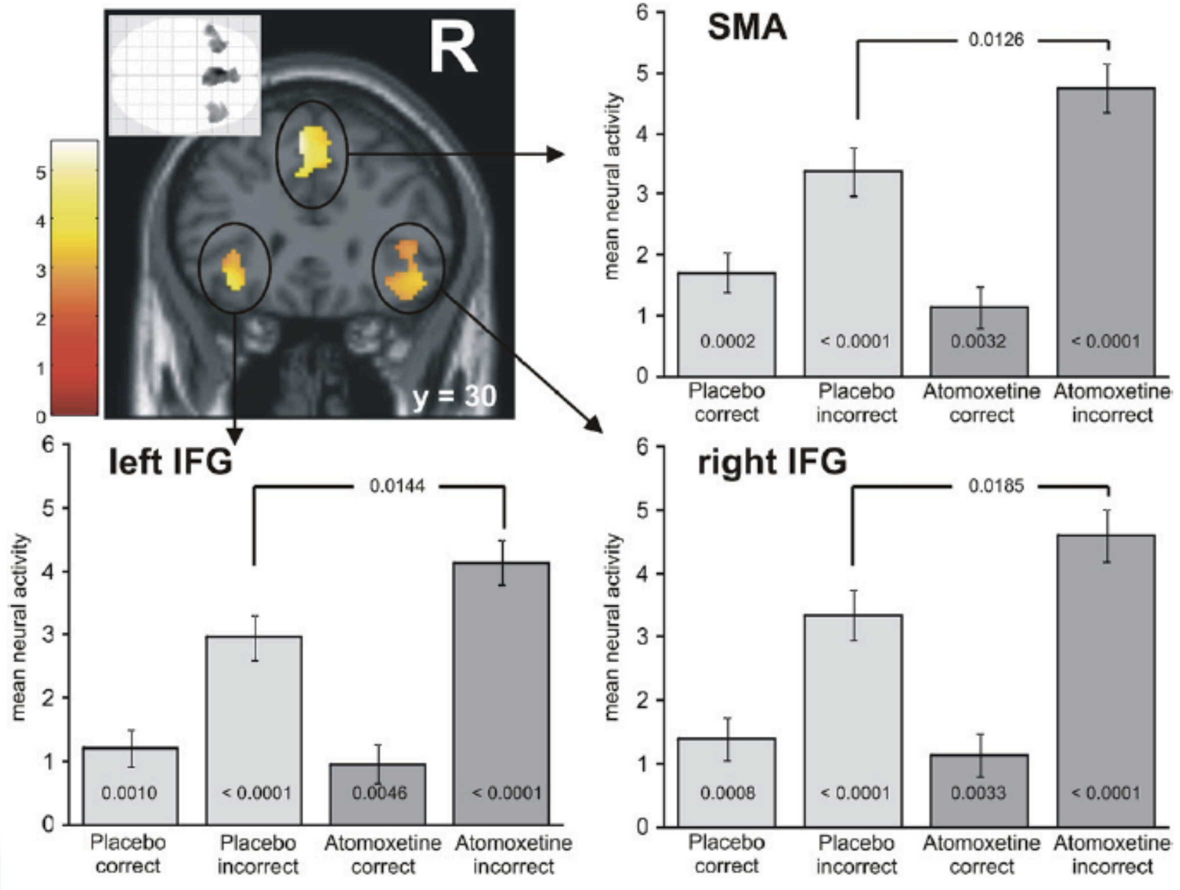
Chamberlain et al. 2009

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

Stop-signal task fMRI



ATX modulates bilateral inferior frontal gyrus and supplementary motor area during error monitoring

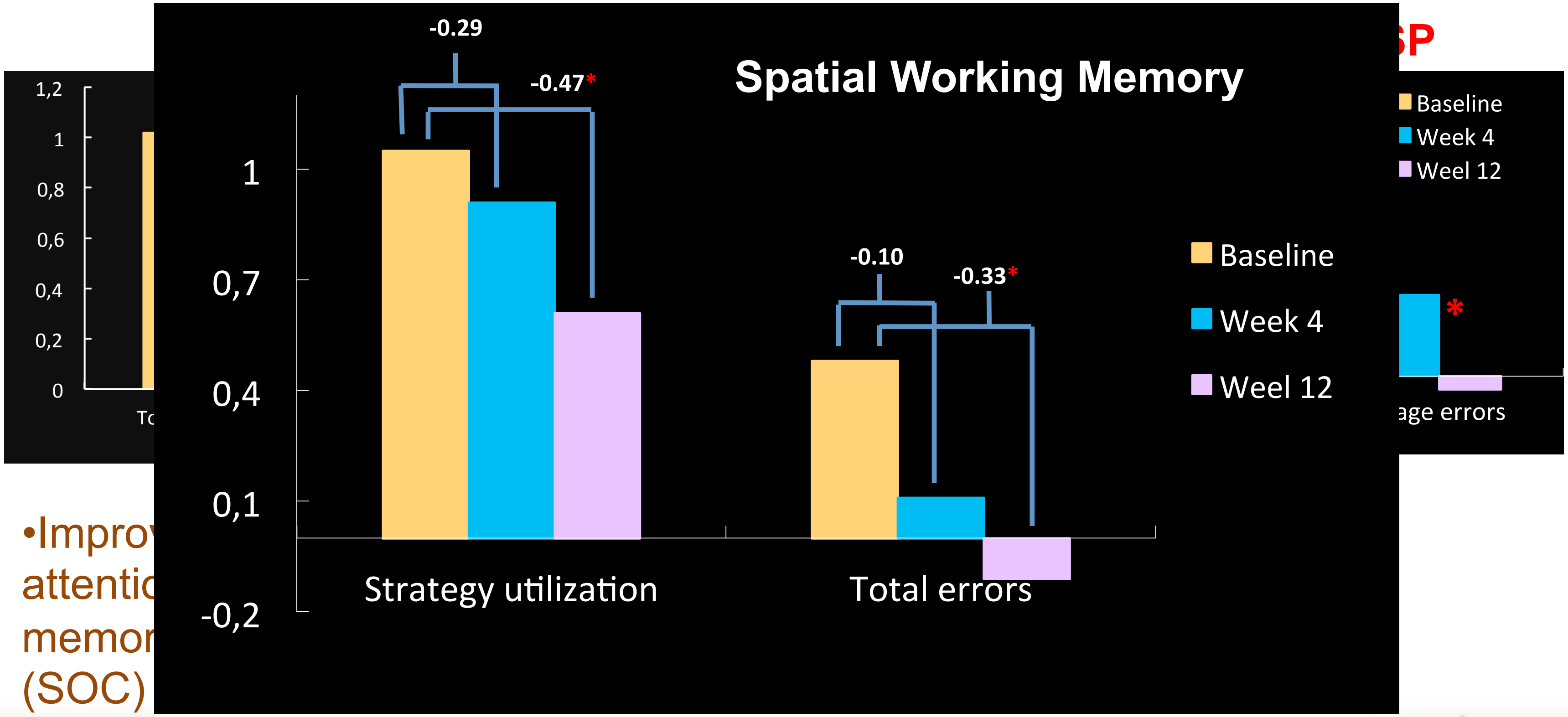


- Within-subject, double-blind, placebo-controlled design; 12 healthy adults; single dose of 80mg ATX
- Eriksen flanker-Go/NoGo task fMRI

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[1,2] and Chi-Yung Shang[1,2]

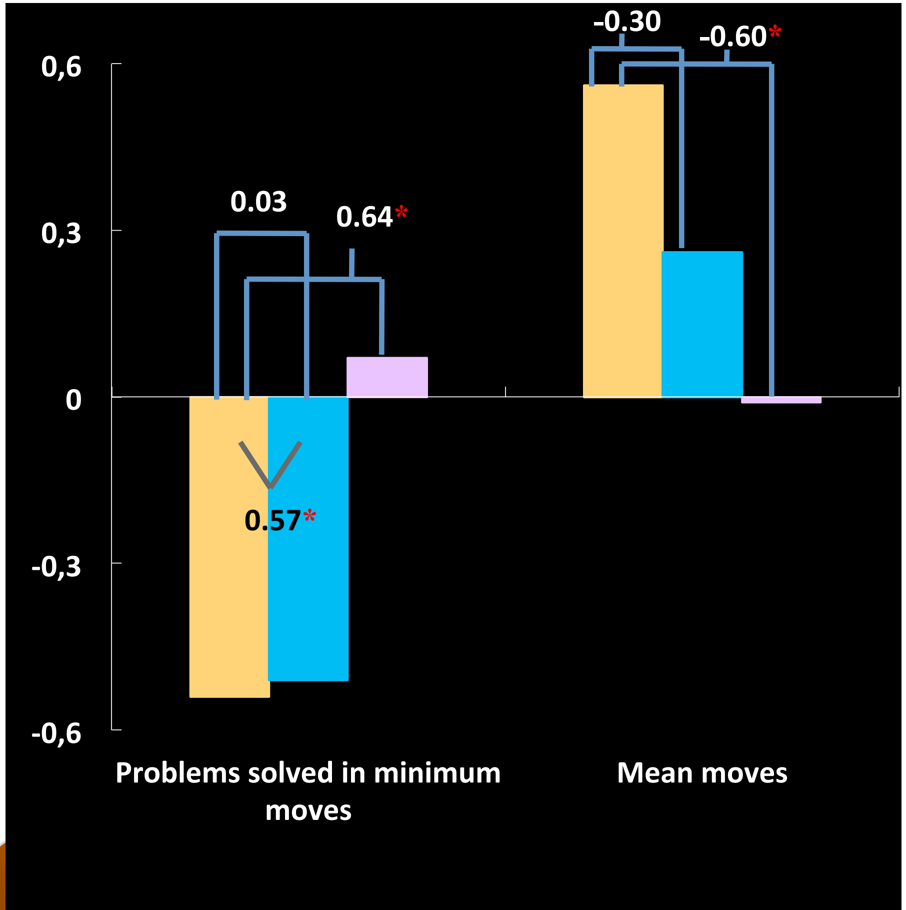


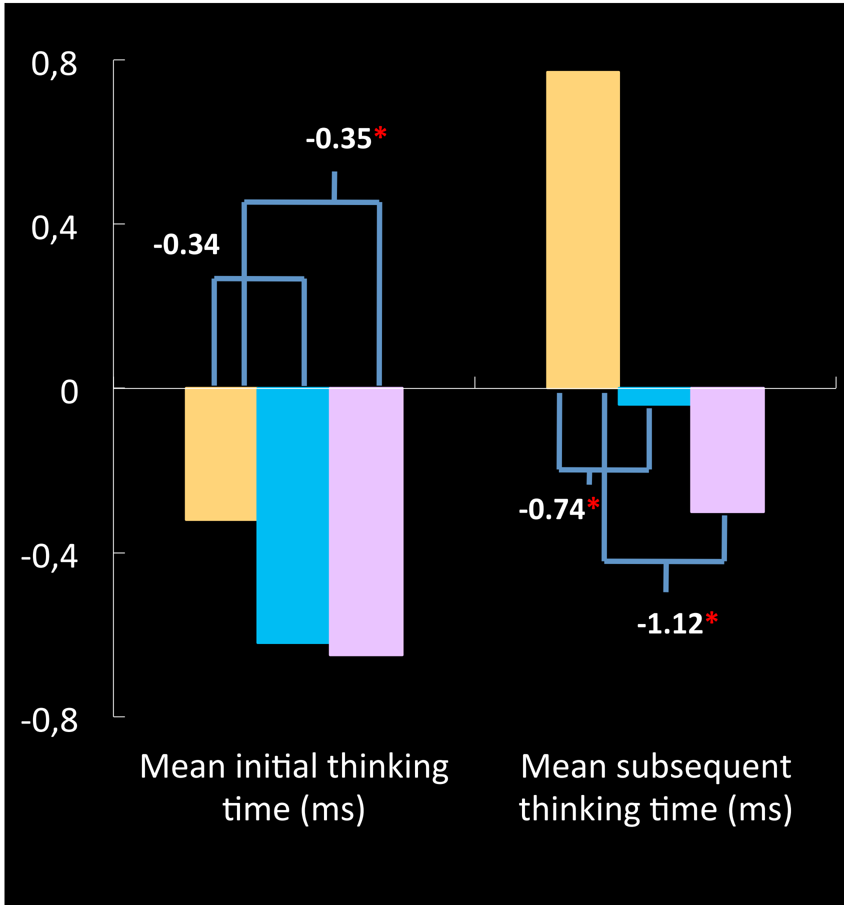
•Impro
attentic
memor
(SOC)

•Moreover, the magnitude of improvement in **spatial planning** and **problem solving** was a function of treatment duration of atomoxetine and task difficulties.

Improving Spatial Planning and Problem Solving at Week 12

Stockings of Cambridge (Cohen's *d*, * *p* <.05)



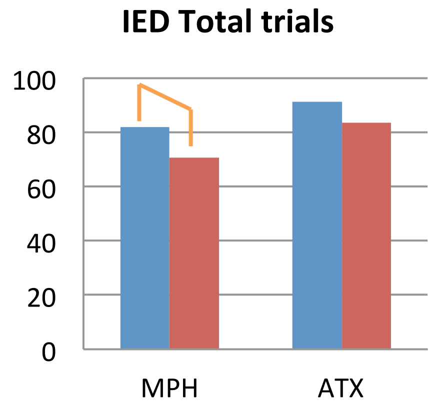


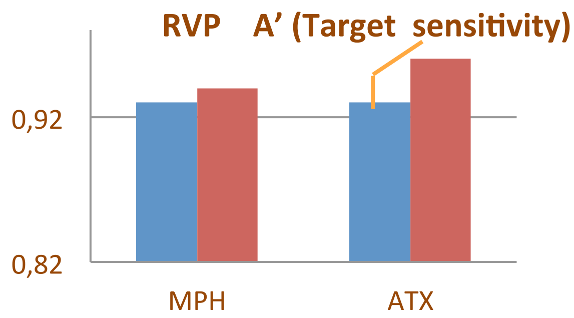
International Journal of Neuropsychopharmacology, Page 1 of 15.
doi:10.1017/S1461145713000357

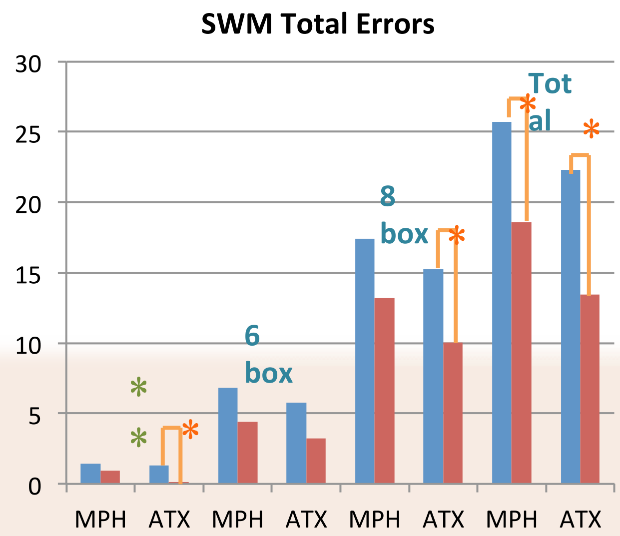
ARTICLE

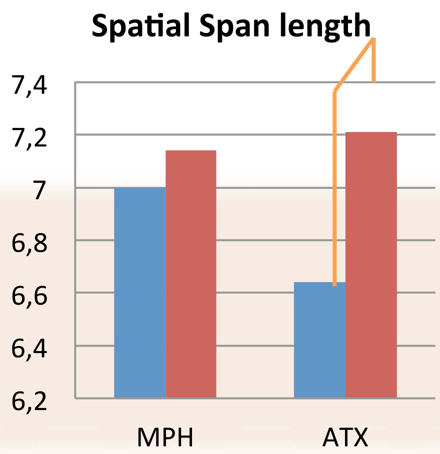
A head-to-head randomized clinical trial of methylphenidate and atomoxetine treatment for executive function in adults with attention-deficit hyperactivity disorder

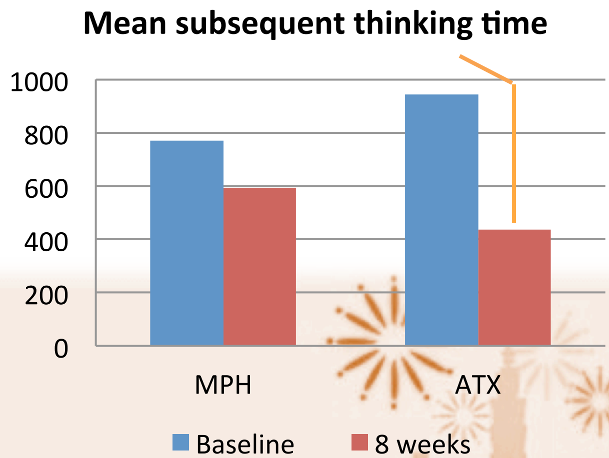
Hsing-Chang Ni[1,2,3], Chi-Yung Shang[1,4], Susan Shur-Fen Gau[1,4,5], Yu-Ju Lin[1,6], Hui-Chun Huang[7] and Li-Kuang Yang[1,8]











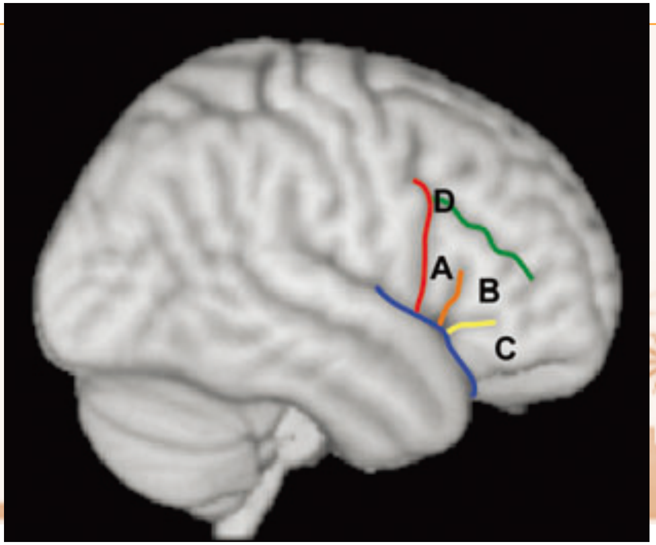
Key Findings

- 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-tem 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)**

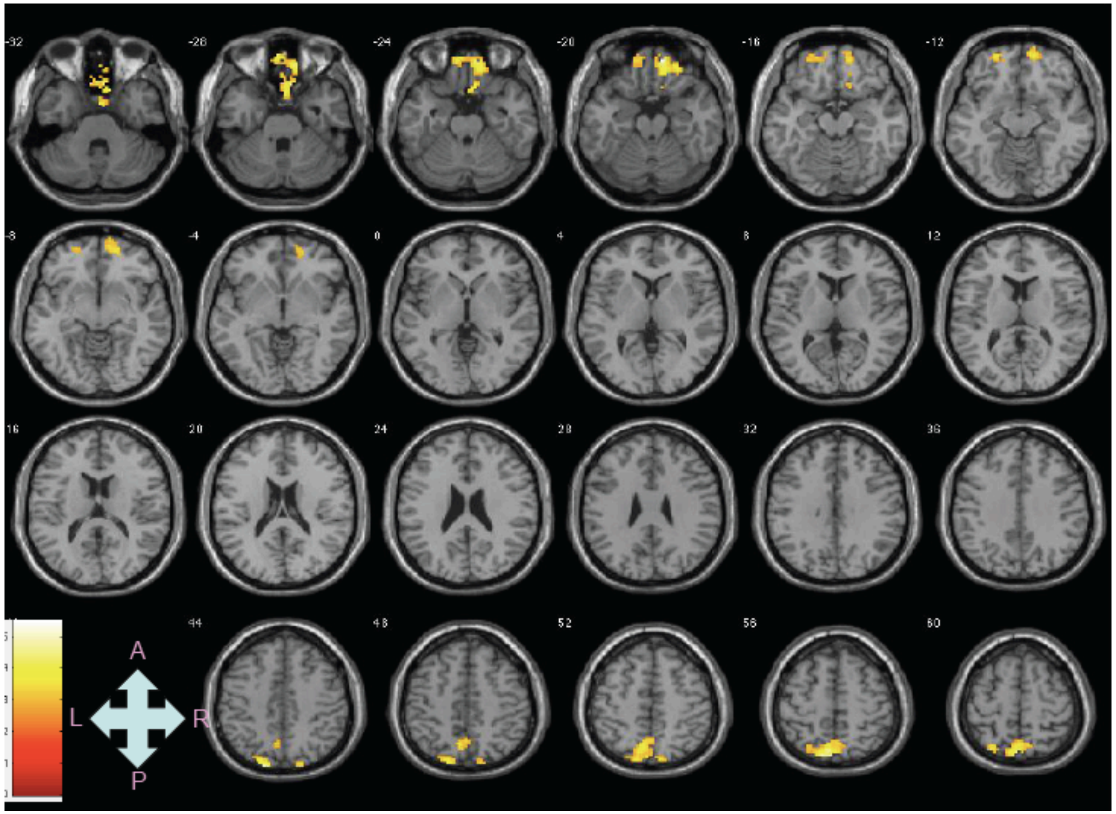


Objectives

- 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

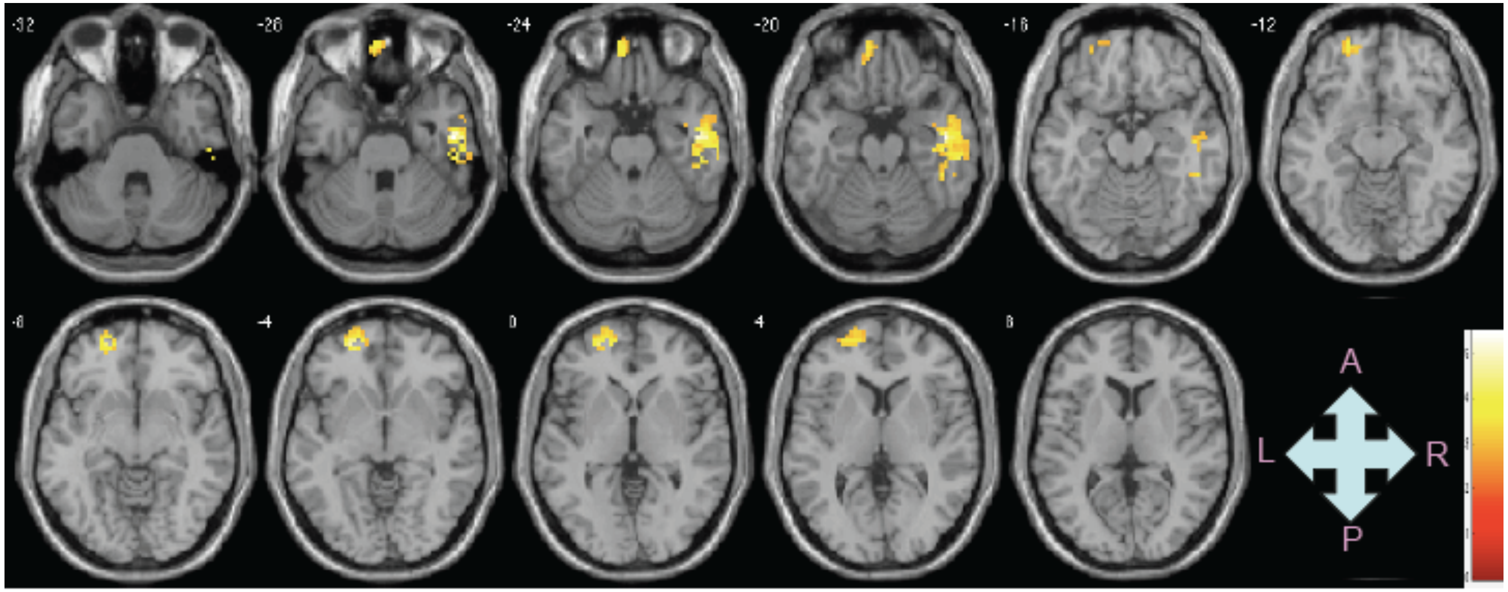
- We hypothesized ATX would modulate intrinsic functional connectivity of right VLPFC seeds, especially mid- and posterior VLPFC (mainly involved in inhibitory control), but not in left VLPFC seeds, in adults with ADHD

ATX effects on right post-VLPFC seed (group by time interaction)



	MNI coordinate	Cluster size	Interaction term	Treatment period	Connection strength, mean (SD)	
					Atomoxetine	Placebo
Left precuneus (BA 7)	-6, -72, 57	136	F=17.30 P<0.001	Post	**0.281 (0.2229)**	**0.118 (0.1743)**
				Pre	**0.124 (0.2221)**	**0.282 (0.1555)**
Right orbitofrontal cortex (BA 11)	12, 51, -21	121	F=23.38 P<0.001	Post	**0.301 (0.1905)**	**0.12 (0.1433)**
				Pre	**0.086 (0.1967)**	**0.307 (0.19)**

ATX effects on right mid-VLPFC seed (group by time interaction)



	MNI coordinate	Cluster size	Interaction term	Treatment period	Connection strength, mean (SD)	
					Atomoxetine	Placebo
Right inferior temporal lobe (BA 20)	51, -12, -27	207	F=30.4 P<0.001	Post	0.469 (0.1504)	0.304 (0.2162)
				Pre	0.209 (0.2445)	0.441 (0.1209)
Left orbitofrontal cortex (BA10)	-24. 54,-3	158	F=22.26 P<0.001	Post	0.303 (0.2034)	0.158 (0.2389)
				Pre	0.137 (0.1644)	0.349 (0.247)

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

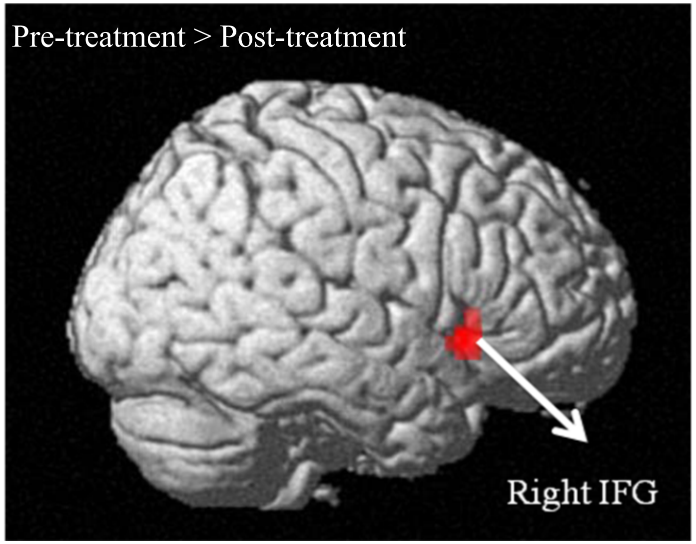
- Based on previous fMRI studies in ADHD (Cortese et al., 2012), we hypothesized that pre-treatment group may show greater activation relative to post-treatment group in right prefrontal cortex (PFC).
- Based on previous fMRI findings of atomoxetine in adults with ADHD (Bush et al., 2013), we hypothesized that post-treatment with atomoxetine may enhance parietal activation.

Results-
Executive functions

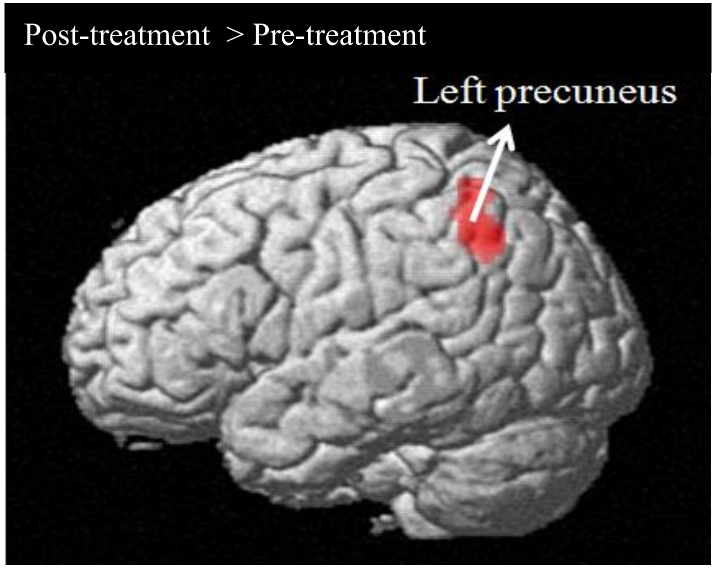
- Increasing right inferior frontal gyrus (IFG) with thinking time of SOC and errors in IED

Results-
visuo-spatial memory

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



$p < .05$, 10 voxels, FWE corrected



Taken together, 8-week treatment with atomoxetine might improve executive functions and visuo-spatial memory in adults with ADHD.

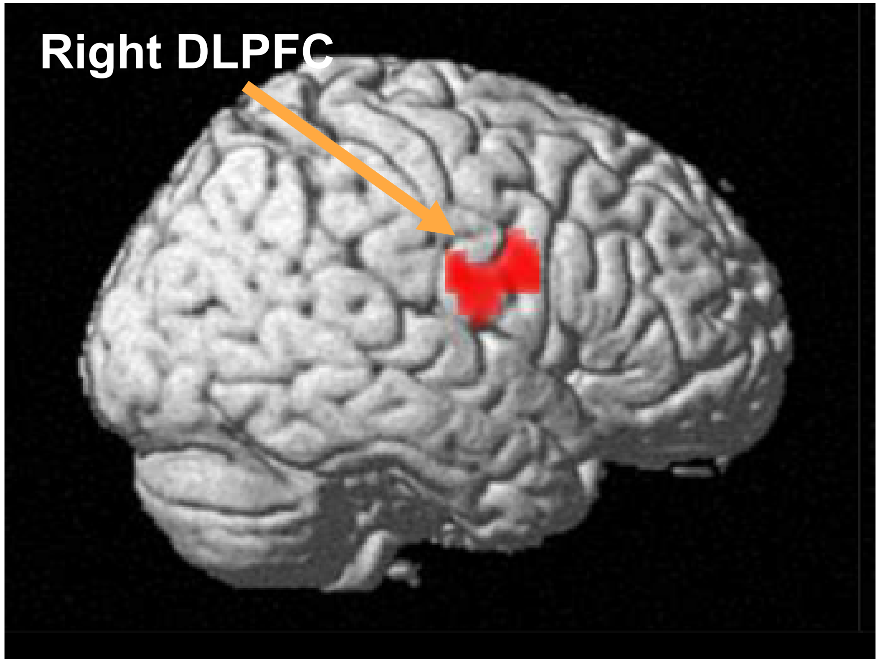
Neural correlates of **atomoxetine** and **methylphenidate** improving executive functions and visuo–spatial memory in chidren with ADHD
(in preparation)

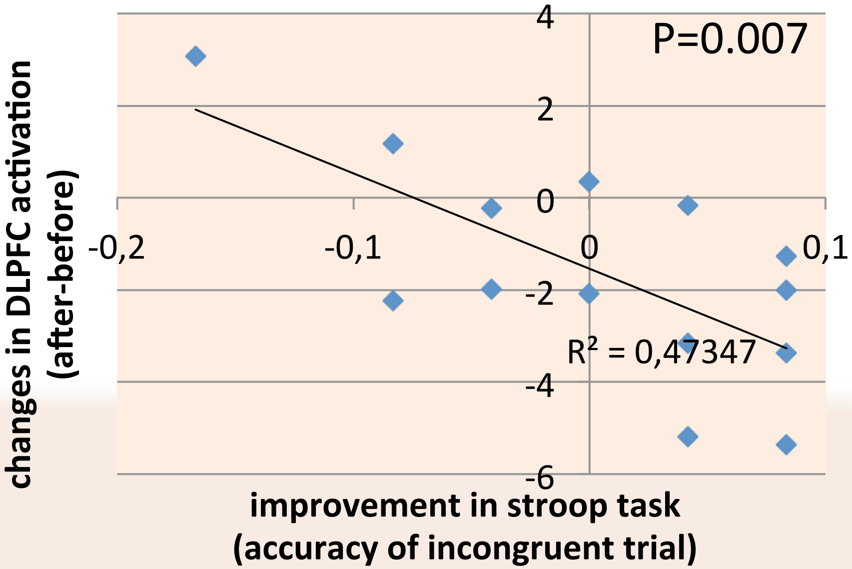
- **Study Design:** 12-week head-to-head ATX vs MPH RCT
- **Participants:** 28 drug-naïve ADHD adults
- **Treatment Arms:** Atomoxetine (n=14) vs Methylphenidate (n=14)
- **Neuropsychological Assessments:**
  - **IED and SOC**
    - **executive function**
  - **SSP and DMS**
    - **visual spatial memory**
- **Counting Stroop - fMRI Assessment**

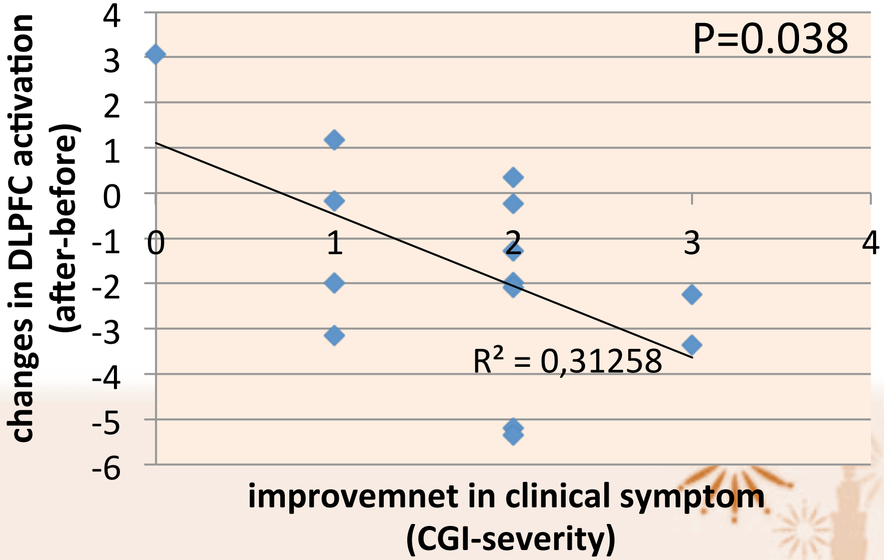
Incongruent vs. Congruent

Pre-ATX > Post -ATX

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



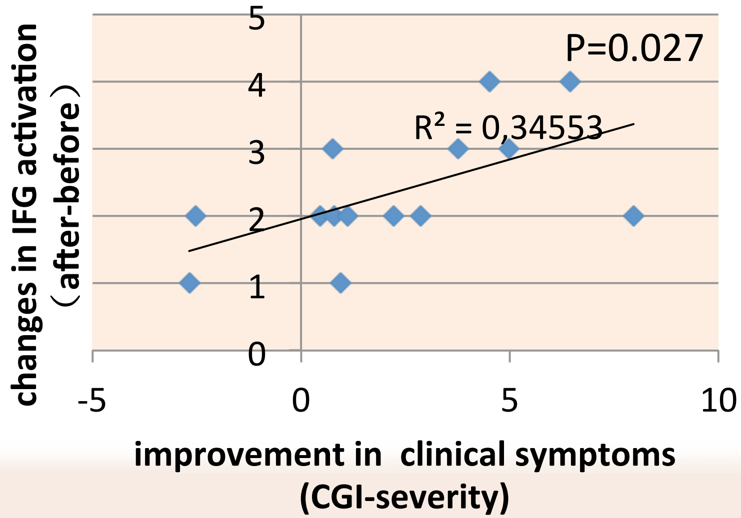


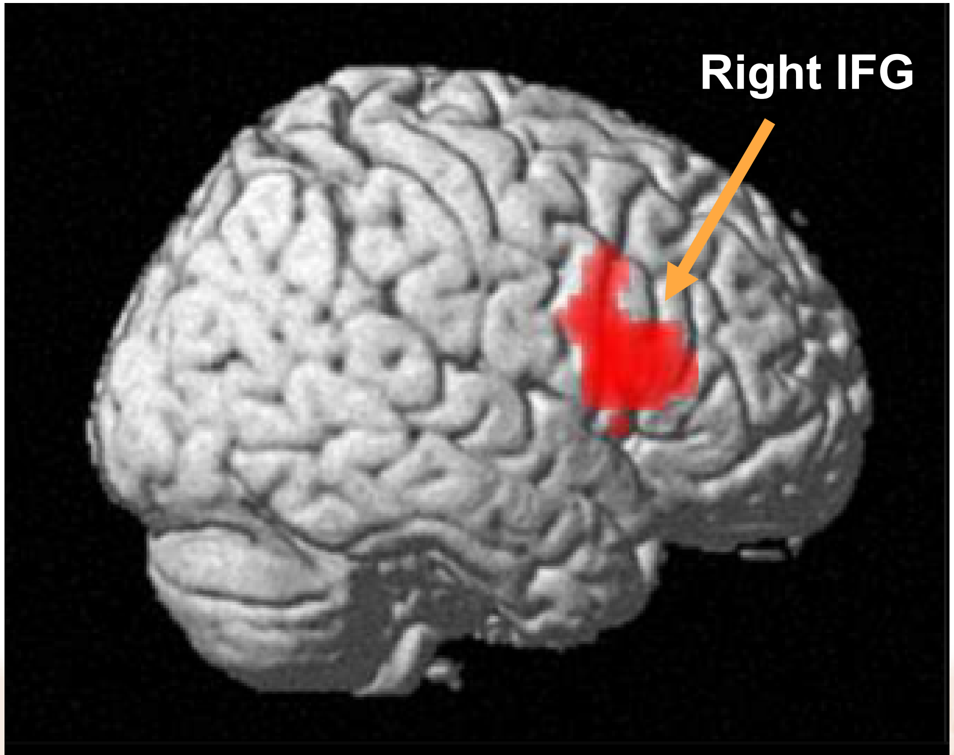


Upregulation of activation in rIFG after MPH treatment is correlated with performance in clinical symptoms

Incongruent vs. Congruent

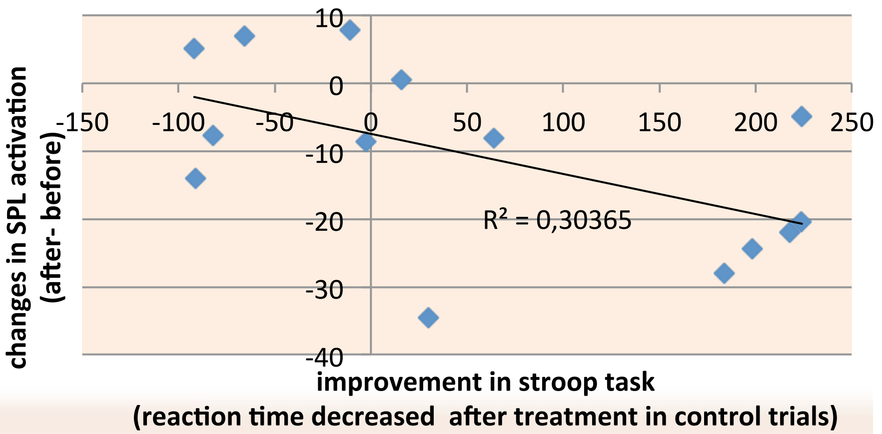
Post-MPH > Pre-MPH

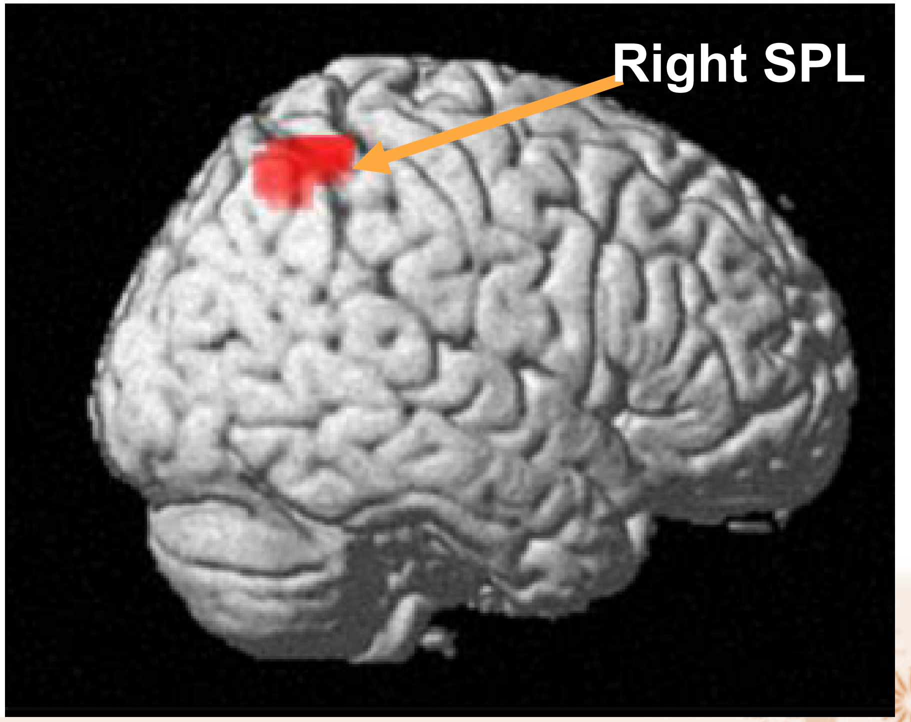




Digits (3&4)>Digits(1&2)
Pre-MPH > Post-MPH

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



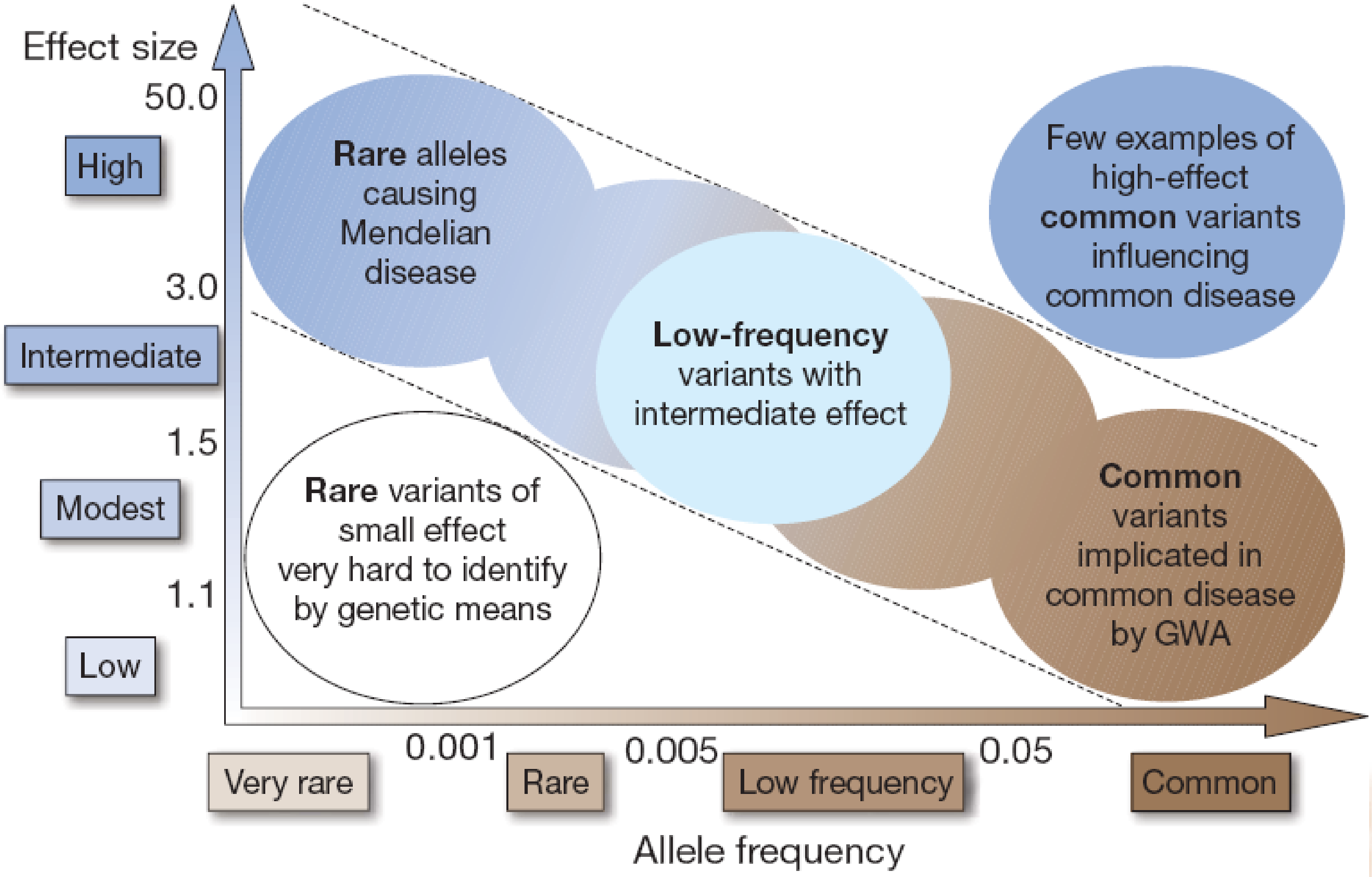


Summary of results

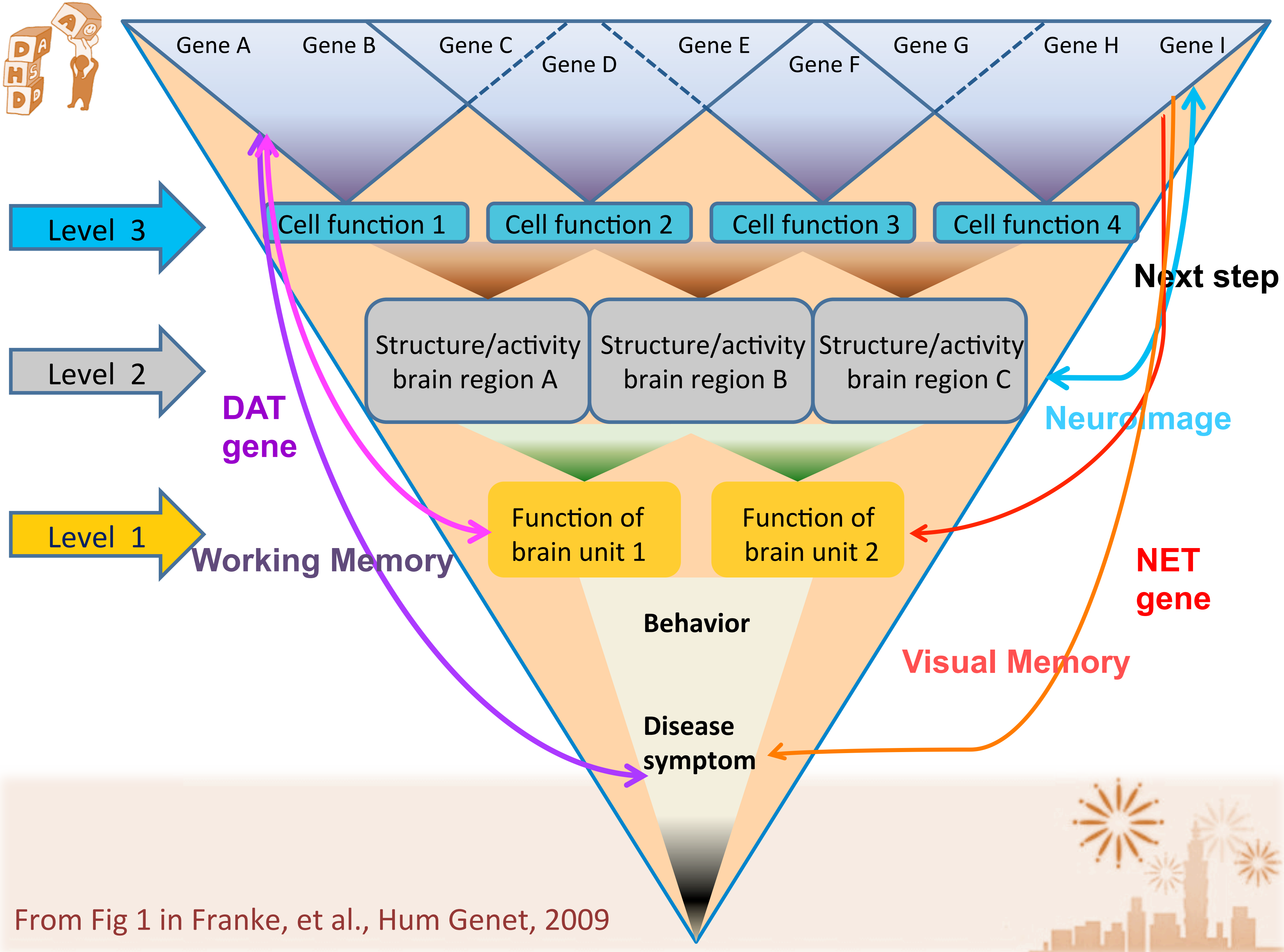
- **Behavioral result showed only main effect of time and condition.**
- **Inhibitory control:**
  - ATX decreased activation in DLPFC significantly (correlated with both Stroop performance & clinical symptoms-severity).
  - MPH increased activation in IFG significantly (correlated with clinical symptoms-severity).
- **Visuospatial:**
  - MPH decreased activation in SPL significantly (correlated with Stroop performance)

Summary

- 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 neurocogntive 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



From Fig 1 in Franke, et al., Hum Genet, 2009

Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 421–428

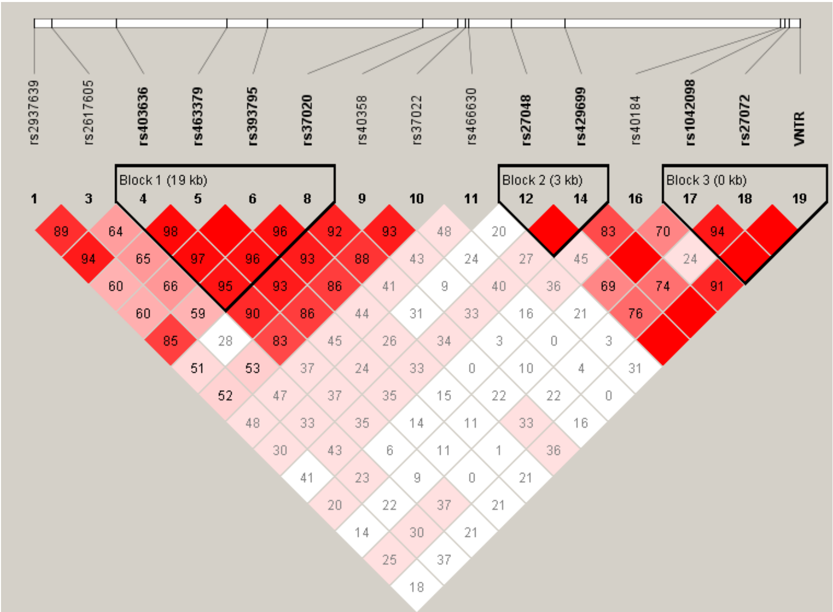
Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Association between the dopamine transporter gene and the inattentive subtype of attention deficit hyperactivity disorder in Taiwan

Chi-Yung Shang [a,b], Susan Shur-Fen Gau [a,b,c,d,*], Chih-Min Liu [a,b,e], Hai-Gwo Hwu [a,b,c]



Linkage Disequilibrium of the 15 Variants in the *DAT1* gene

***DAT1* gene was significantly associated with the inattentive subtype of ADHD and the severity of inattentive symptoms.**

Association between Spatial Working Memory and *DAT1* Gene in ADHD

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

SNP ID	Allele	Allele Frequency	N	Z	P
rs2937639	G	0.145	49	1.94	0.052345
rs2617605	G	0.172	55	3.053	0.002265**
rs403636	G	0.697	84	2.258	0.023953*
rs463379	C	0.464	88	0.761	0.446692
rs393795	C	0.462	86	0.847	0.396898
rs37020	G	0.675	86	2.858	0.00426*
rs40358	T	0.656	90	1.242	0.214112
rs37022	T	0.502	85	0.438	0.661139
rs466630	C	0.488	63	0.159	0.874054
rs27048	T	0.175	64	0.768	0.44235
rs429699	C	0.756	71	1.325	0.185058
rs40184	G	0.731	75	1.015	0.310136
rs1042098	C	0.103	52	0	1
rs27072	T	0.271	59	0.606	0.544618
3VNTR	10	0.918	35	1.042	0.297555

SNP, haplotype	Haplotype frequency	Number of Informative Families	Z	*P*	*P*_2 side, by haplotype permutation test	Minimal *P*
rs403636, rs463379, rs393795, and rs37020						
G/G/A/G	0.521	90	-0.784	0.432779	0.43314	
T/C/C/T	0.3	91	-1.869	0.061641	0.06031	
G/C/C/G	**0.137**	**54**	**3.382**	**0.000719***	**0.00042***	
G/C/C/T	0.023	12	-1.265	0.205903	0.2179	
						0.0014*
rs27048 and rs429699						
C/C	0.58	100	0.383	0.70201	0.710977	
C/T	0.244	76	-1.235	0.216752	0.201410	
T/C	0.176	68	0.866	0.386571	0.408862	
						0.456697
rs27072, and 3VNTR						
C/10	0.643	77	-0.328	0.742711	0.760067	
T/10	0.273	64	1.042	0.297393	0.348993	
C/9	0.061	30	-0.386	0.699722	0.738255	
						0.918624

2 SNPs (rs2937639, and rs2617605) and Haplotype Block 1 were Significantly Associated with SWM within Errors.

SNP ID	Allele	Allele Frequency	N	Z	P
rs2937639	G	0.145	68	1.968	0.049043*
rs2617605	G	0.172	76	2.847	0.00441*
rs403636	G	0.697	104	1.106	0.268513
rs463379	C	0.464	103	1.577	0.114767
rs393795	C	0.462	101	1.702	0.088769
rs37020	G	0.675	106	1.708	0.08763
rs40358	T	0.656	109	0.669	0.503773
rs37022	T	0.502	100	0.985	0.324646
rs466630	C	0.488	81	0.631	0.52814
rs27048	T	0.175	78	0.649	0.516265
rs429699	C	0.756	83	0.873	0.382577
rs40184	G	0.731	91	1.233	0.217597
rs1042098	T	0.897	65	0.377	0.706289
rs27072	T	0.271	79	0.51	0.609932
3VNTR	10	0.918	48	1.684	0.092147

SNP, haplotype	Haplotype frequency	Number of Informative Families	Z	*P*	*P*_2 side, by haplotype permutation test	Minimal *P*
rs403636, rs463379, rs393795, and rs37020						
G/G/A/G	0.521	108	-1.435	0.151157	0.154700	
T/C/C/T	0.3	112	-0.834	0.404339	0.407990	
G/C/C/G	**0.137**	**74**	**3.471**	**0.000519***	**0.000260***	
G/C/C/T	0.023	15	-1.252	0.210506	0.234950	
						0.001000*
rs27048 and rs429699						
C/C	0.58	123	0.149	0.881863	0.941176	
C/T	0.244	91	-0.868	0.385184	0.394118	
T/C	0.176	80	0.753	0.45138	0.458824	
						0.639216
rs27072, and 3VNTR						
C/10	0.643	101	0.095	0.924339	0.904810	
T/10	0.273	84	1.135	0.256169	0.275550	
C/9	0.061	36	-0.509	0.610812	0.629650	
						0.575210

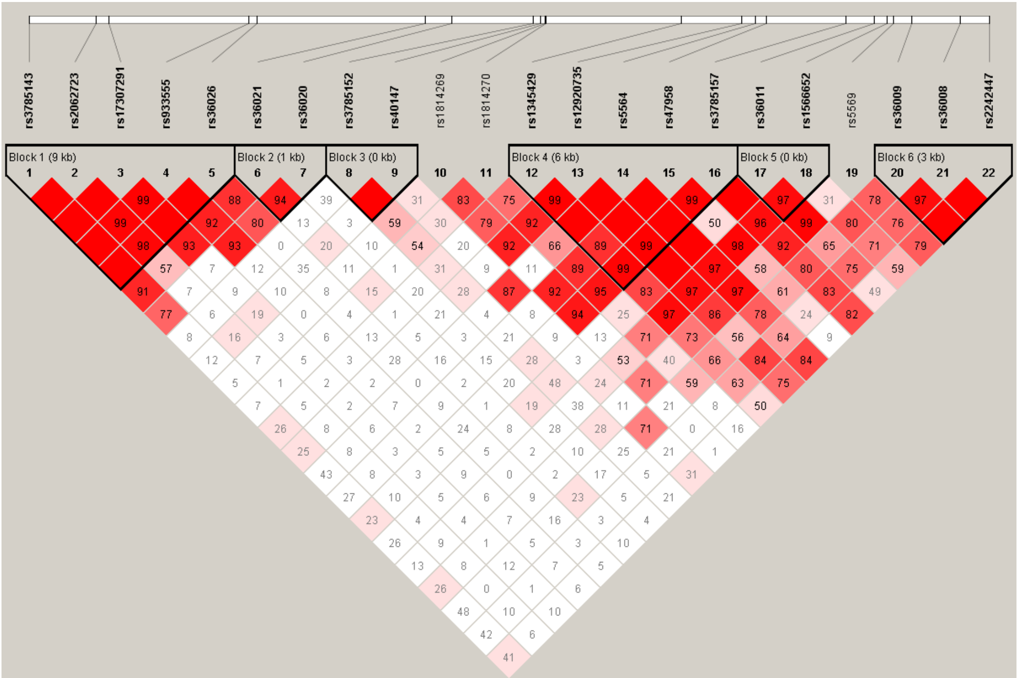
The NET gene and visual memory in the ADHD family genetic study

- **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

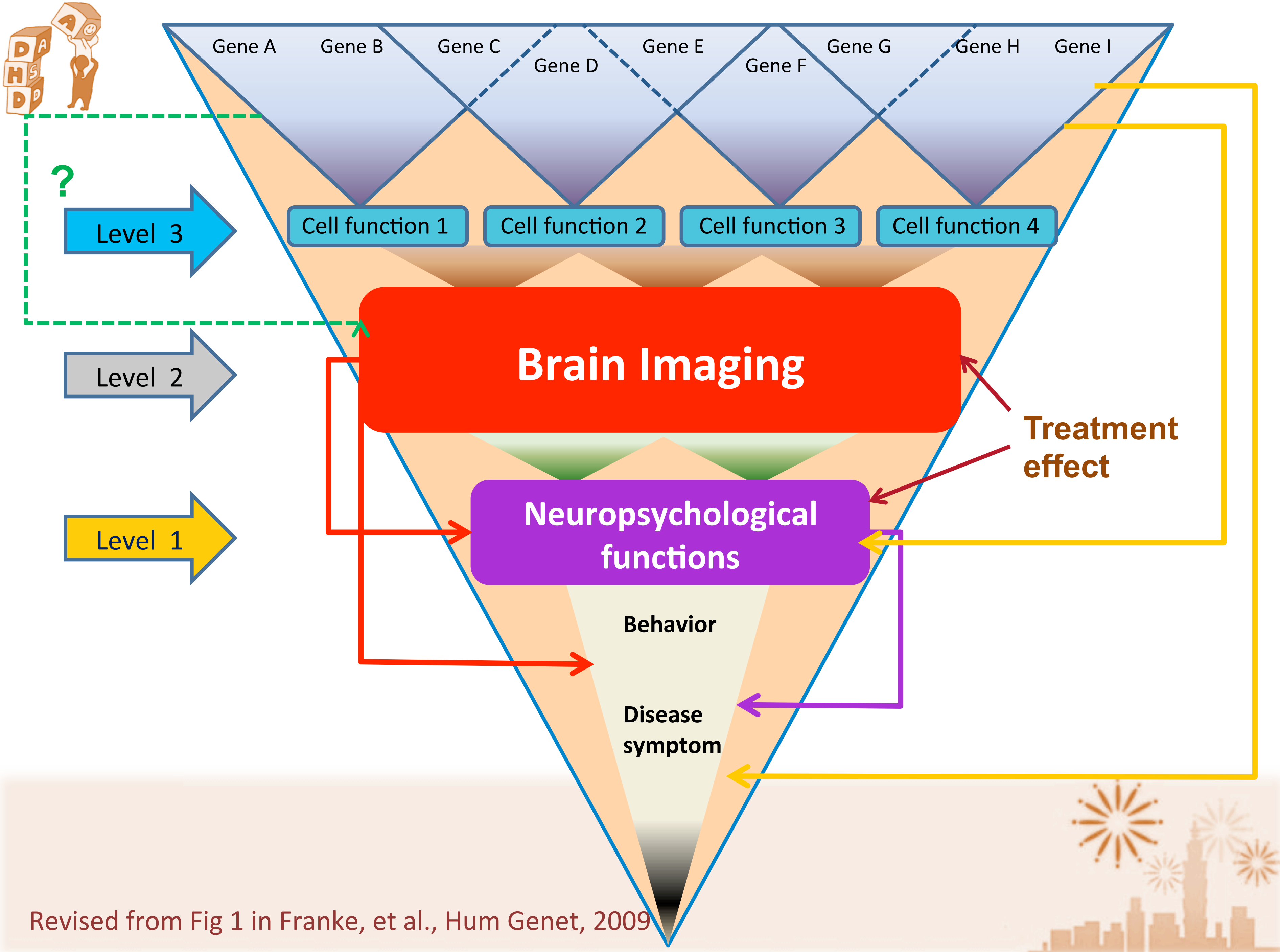


- In the **single marker** analysis, our findings provided evidence for the association between ADHD and rs36011 of the NET gene.

- 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)

Key Findings

- 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

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YL Lin
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