

**Varieties of Clinical Trajectories in ADHD:  
Significance of Neuropsychology.**

**Joseph A. Sergeant  
Emeritus Professor of Clinical Neuropsychology  
Vrije Universiteit Amsterdam.**

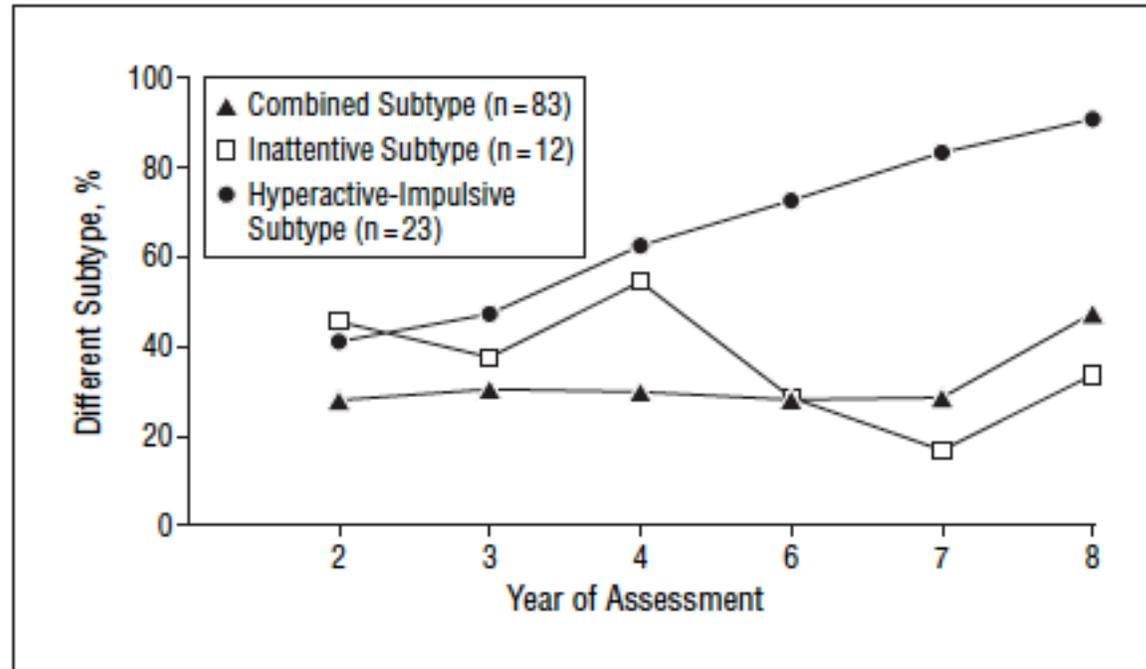
***ADHD is not a stable condition:***

- **Fluctuations in symptomatology occur during childhood, adolescence, persist or remit in adulthood and can emerge de novo in adulthood.**
- **Research differentiates:  
normal development, subthreshold, syndromatic and persistent ADHD.**
- **Longitudinal follow-up indicates that some childhood ADHD individuals have reduced (subthreshold) ADHD symptomatology. This is often referred to as “remission”.**
- **Subthreshold ADHD is not benign.**

# Instability of the *DSM-IV* Subtypes of ADHD From Preschool Through Elementary School

*Arch Gen Psychiatry.* 2005;62:896-902

Benjamin B. Lahey, PhD; William E. Pelham, PhD; Jan Loney, PhD; Steve S. Lee, PhD; Erik Willcutt, PhD



**Figure 2.** Percentage of children who met criteria for each subtype of attention-deficit/hyperactivity disorder in year 1 who met criteria for a different subtype in each of years 2 through 8.

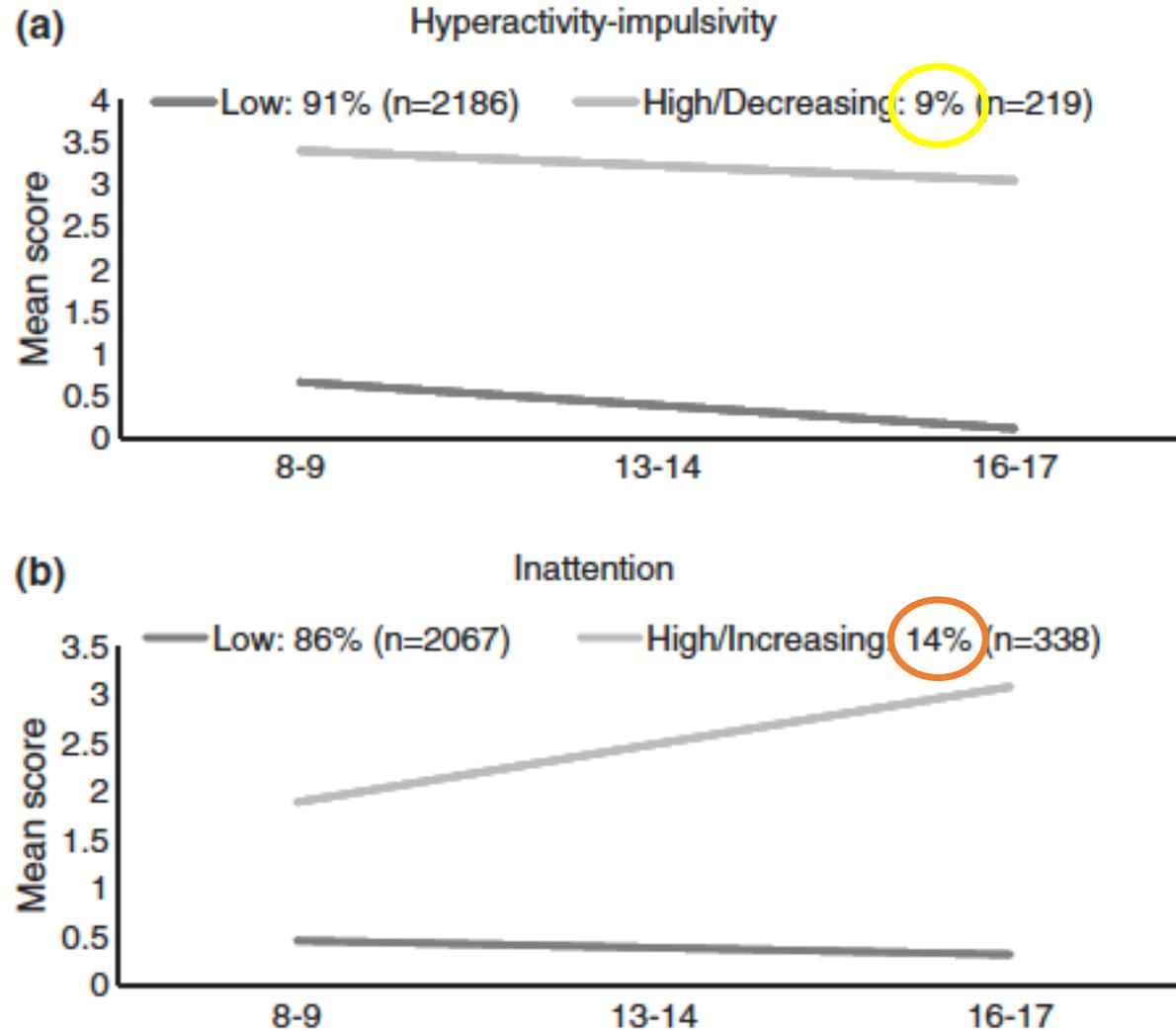
**This indicates that there is considerable instability in ADHD expression with the greatest variability in the subtype Hyperactivity-Impulsivity.**

# Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology

Henrik Larsson,<sup>1,2</sup> Rezin Dilshad,<sup>1</sup> Paul Lichtenstein,<sup>1</sup> and Edward D. Barker<sup>1</sup>

Trajectories of hyperactivity impulsivity and inattention between 8–9 to 16–17 years.

1,450 twin pairs participating in a population-based, longitudinal twin study. Developmental trajectories were defined using parent-ratings of hyperactivity-impulsivity and inattention symptoms.



Those on a high trajectory, hyperactivity decreased whereas inattention increased.

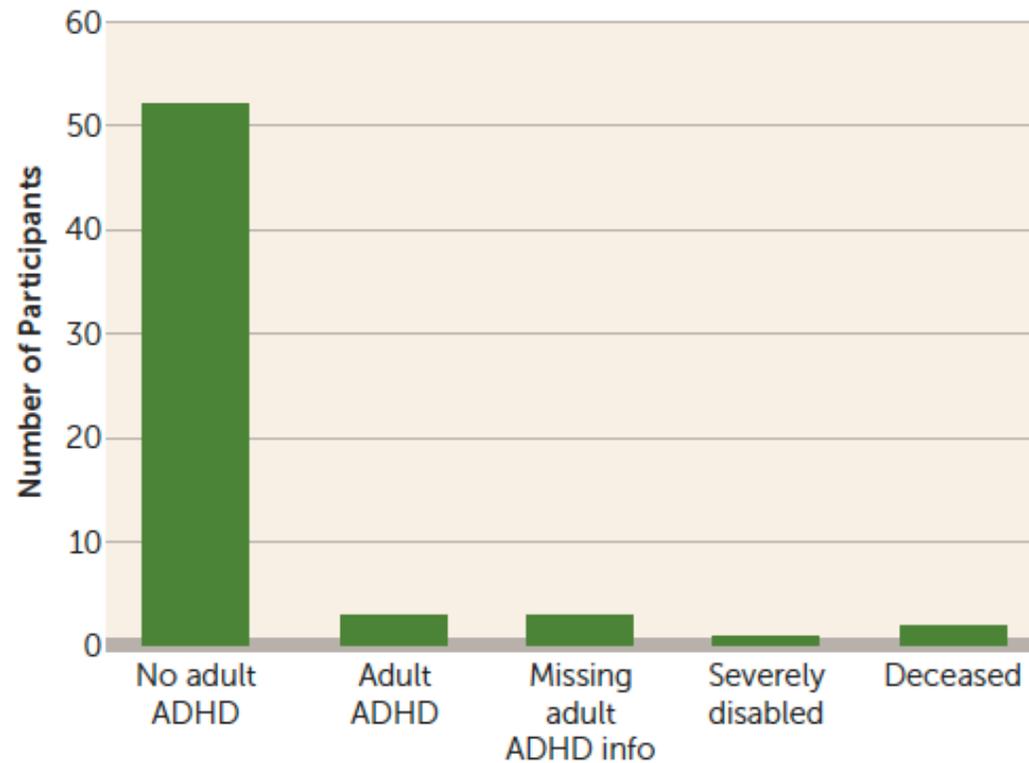
This study suggests that ADHD subtypes cannot be viewed as discrete and *stable* categories.

# Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study

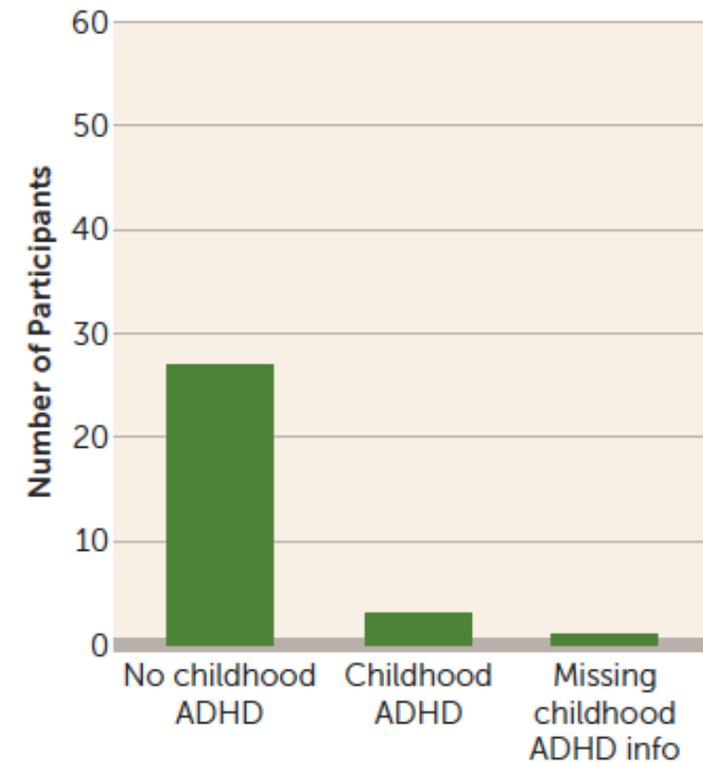
*AJP in Advance* (doi: 10.1176/appi.ajp.2015.14101266)

Terrie E. Moffitt, Ph.D., Renate Houts, Ph.D., Philip Asherson, M.D., Daniel W. Belsky, Ph.D., David L. Corcoran, Ph.D., Maggie Hammerle, B.A., HonaLee Harrington, B.A., Sean Hogan, M.S.W., Madeline H. Meier, Ph.D., Guilherme V. Polanczyk, M.D., Richie Poulton, Ph.D., Sandhya Ramrakha, Ph.D., Karen Sugden, Ph.D., Benjamin Williams, B.A., Luis Augusto Rohde, M.D., Avshalom Caspi, Ph.D.

**A. Follow-Forward: Did Those With Childhood ADHD (N=61) Continue to Have Adult ADHD?**



**B. Follow-Back: Did Those With Adult ADHD (N=31) Have Childhood ADHD?**



**Most of the participants who had childhood ADHD did not have adult ADHD.  
Most of those with adult ADHD did not have childhood ADHD, (Dunedin birth cohort).  
Hence, predictive validity of ADHD ratings for life-time ADHD uncertain.**

## Life Span Studies of ADHD—Conceptual Challenges and Predictors of Persistence and Outcome

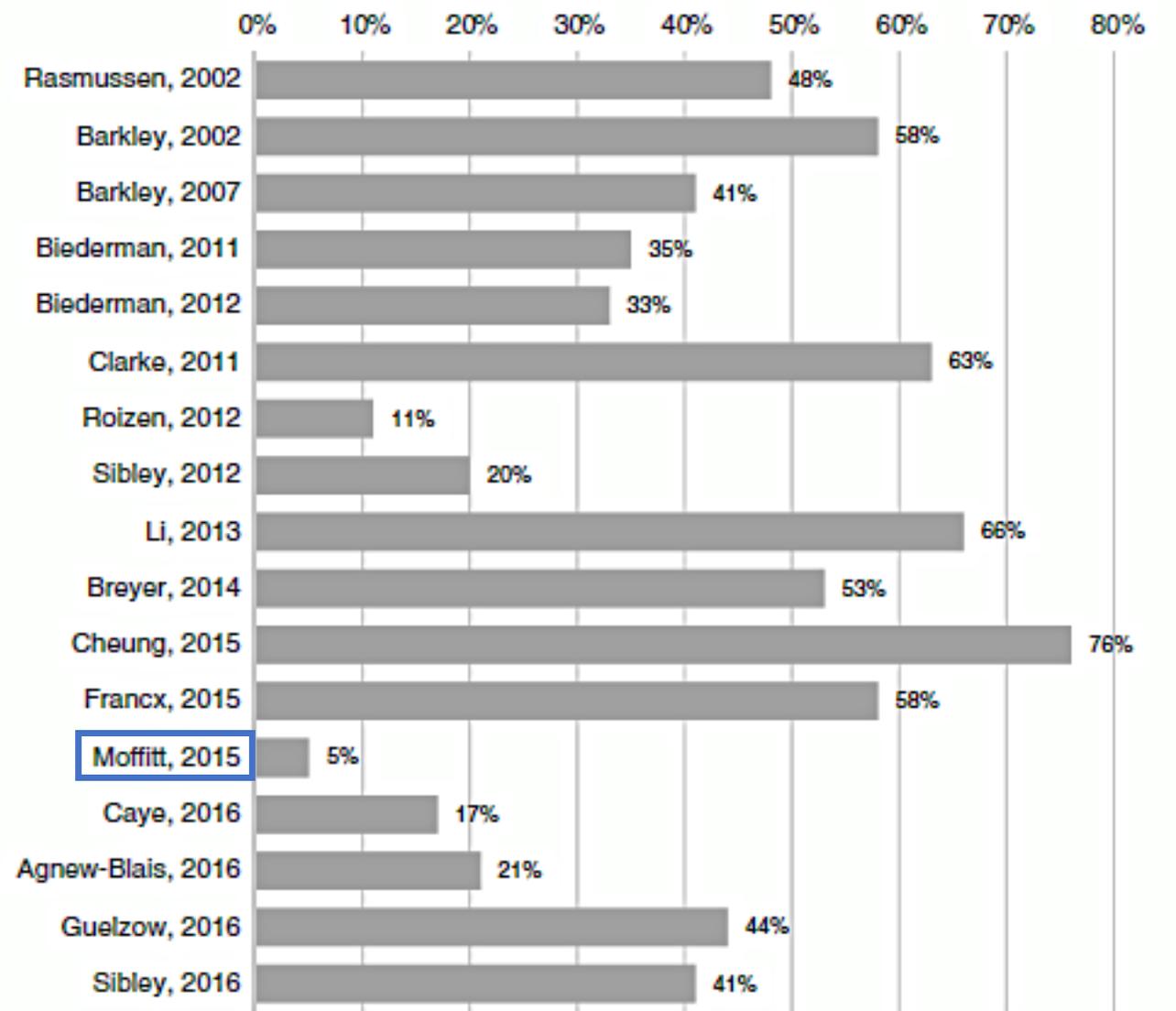
Arthur Caye<sup>1</sup> · James Swanson<sup>2</sup> · Anita Thapar<sup>3</sup> · Margaret Sibley<sup>4</sup> · Louise Arseneault<sup>5</sup> · Lily Hechtman<sup>6</sup> · L. Eugene Arnold<sup>7</sup> · Janni Niclasen<sup>8,9</sup> · Terrie Moffitt<sup>10</sup> · Luis Augusto Rohde<sup>1,11,12</sup>

Estimates of ADHD persistence rates into adulthood in longitudinal studies.

Mean age at follow-up of *at least 18 years old* and a full diagnosis (syndromatic) definition of persistence.

This study indicates that there is a very large *variation* between studies in the long-term persistence of ADHD.

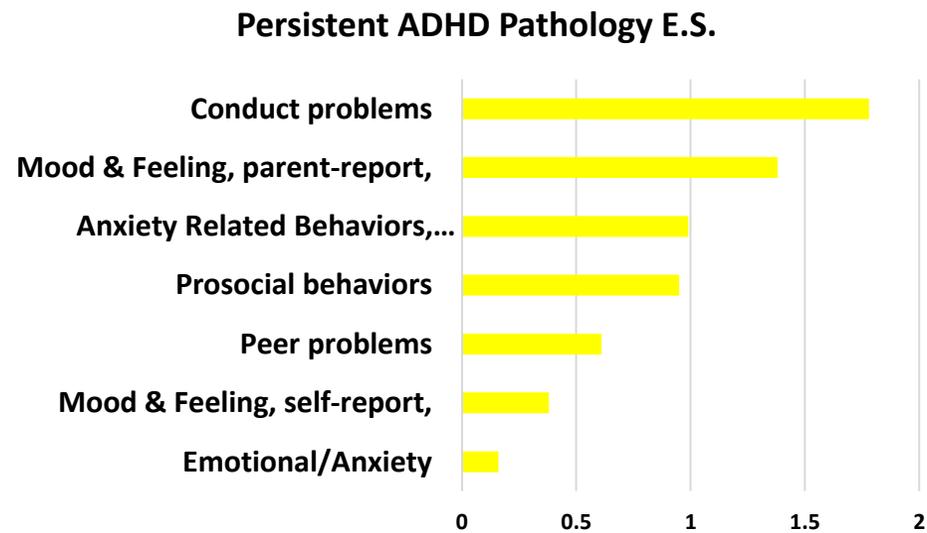
This raises the issue of whether tests (of whatever type) with high test-retest reliability can psychometrically account for the change in clinical status.



# Early Predictors of De Novo and Subthreshold Late-Onset ADHD in a Child and Adolescent Cohort

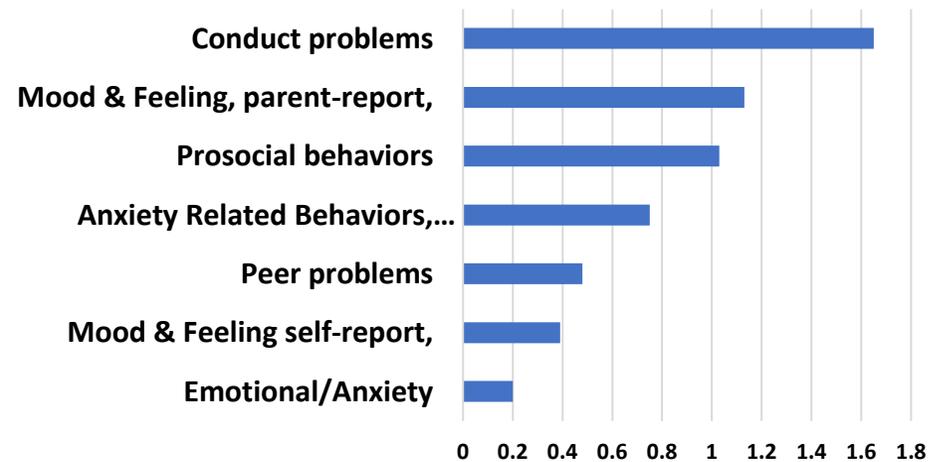
Chao-Yu Liu<sup>1,2</sup> , Philip Asherson<sup>3</sup>, Essi Viding<sup>1</sup>, Corina U. Greven and Jean-Baptiste Pingault<sup>1,3</sup>

Journal of Attention Disorders  
1-11  
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DOI: 10.1177/1087054719892888



ADHD symptoms were assessed in 9,875 participants: Twins Early Development Study

### Subthreshold ADHD Pathology E.S.



The three ADHD groups: developed similar levels of behavioural and emotional problems in adolescence.

Subthreshold ADHD is not benign.

### De Novo ADHD Pathology E.S.



# Investigating late-onset ADHD: a population cohort investigation

Miriam Cooper,<sup>1</sup> Gemma Hammerton,<sup>2</sup> Stephan Collishaw,<sup>1</sup> Kate Langley,<sup>1,3</sup>  
 Ajay Thapar,<sup>1</sup> Søren Dalsgaard,<sup>4,5,6</sup> Evie Stergiakouli,<sup>7</sup> Kate Tilling,<sup>2,7</sup>  
 George Davey Smith,<sup>2,7</sup> Barbara Maughan,<sup>8</sup> Michael O'Donovan,<sup>1</sup> Anita Thapar,<sup>1</sup> and  
 Lucy Riglin<sup>1</sup>

Population, longitudinal, assessed at 12 and 17 years

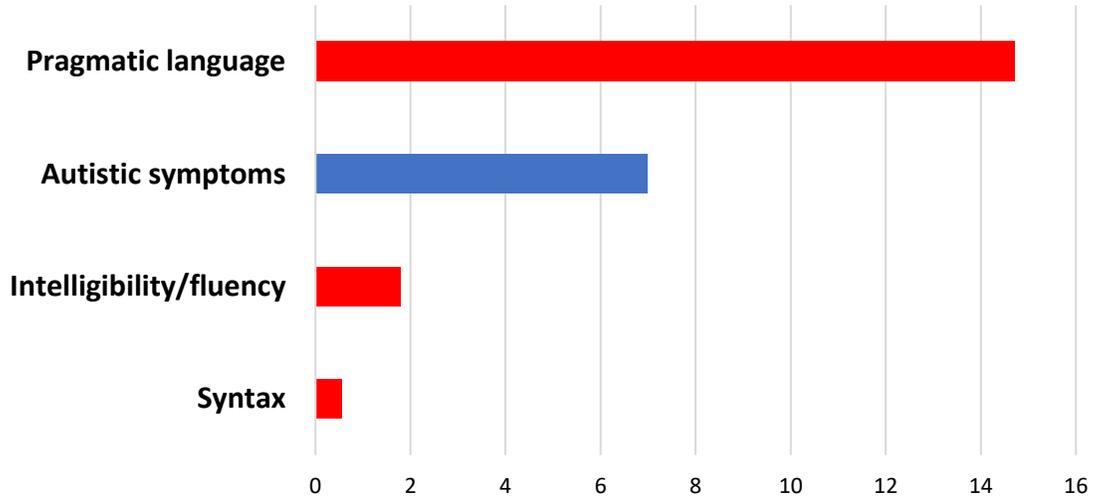
## Definition of ADHD Subgroups

**Genuine late-onset**  
 Close to average score (0–5) SDQ  
 at ages 7, 8, 9 and 12 years

**Childhood-onset Persistent**  
 High or very high (8–10) SDQ at age 12  
 and 17 years

### Genuine Late-Onset v Childhood-onset Persistent

Mean Difference Genuine Late onset v child onset persistent



**Note**  
 Autism Ratings highest for the Childhood-onset persistent.  
 Pragmatic difficulties highest in Genuine Late Onset ADHD group.

Can the *Children's Communication Checklist* differentiate between children with autism, children with ADHD, and normal controls?

Hilde M. Geurts,<sup>1</sup> Sylvie Verté,<sup>2</sup> Jaap Oosterlaan,<sup>1</sup> Herbert Roeyers,<sup>2</sup>  
 Catharina A. Hartman,<sup>3</sup> Erik J. Mulder,<sup>3</sup> Ina A. van Berckelaer-Onnes,<sup>4</sup>  
 and Joseph A. Sergeant<sup>1</sup>

Pragmatic language difficulties present in *both ASD and ADHD* individuals

# Psychiatric problems associated with subthreshold ADHD and disruptive behaviour diagnoses in teenagers *Acta Paediatrica* 2011 **100**, pp. 1468–1475

Kerstin Malmberg (kerstin.malmberg@ki.se)<sup>1,2</sup>, Tobias Edbom<sup>1</sup>, Hanna-Linn Wargelius<sup>3</sup>, Jan-Olov Larsson<sup>1</sup>

## K-SADS-PL ITEMS

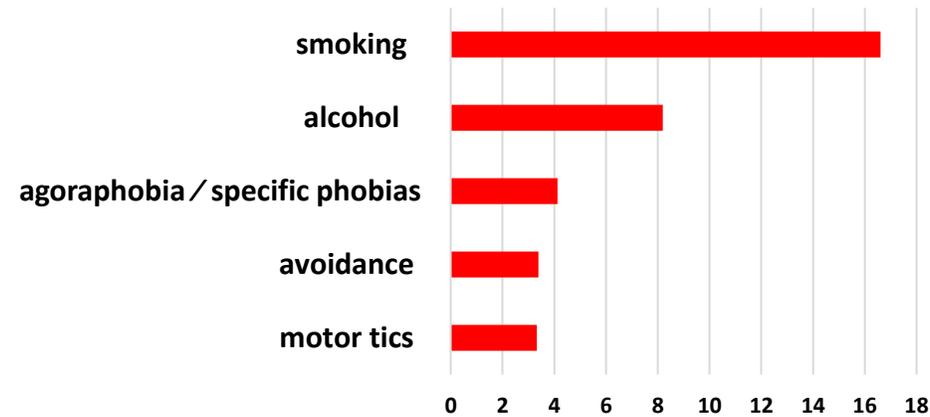
Association with Subthreshold ADHD in a population-based sample of twins including

177 girls and 135 boys.

Note diversity of items between boys and girls.

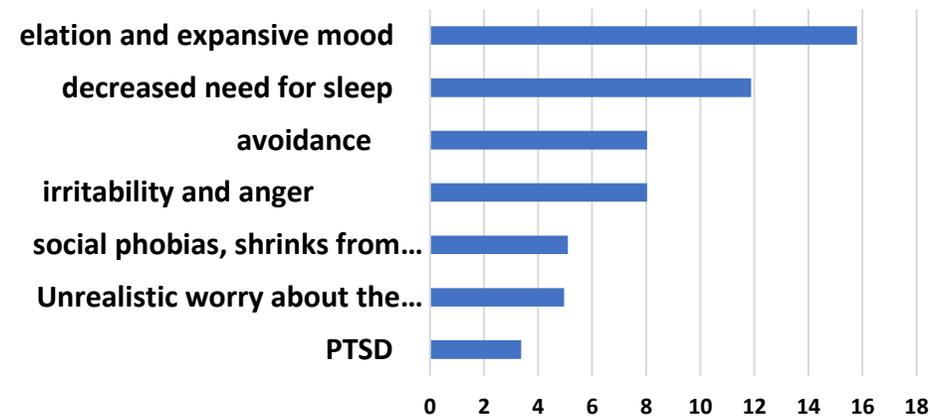
Twin study from childhood (8 years) to adulthood (21–22 years).

*Odds Ratio* Subthreshold ADHD and K-SADS-PL  
Item Boys



This indicates that Subthreshold ADHD is a serious condition for both substance abuse and emotional deregulatory behaviours.

*Odds Ratio* Subthreshold ADHD and K-SADS-PL  
Item Girls



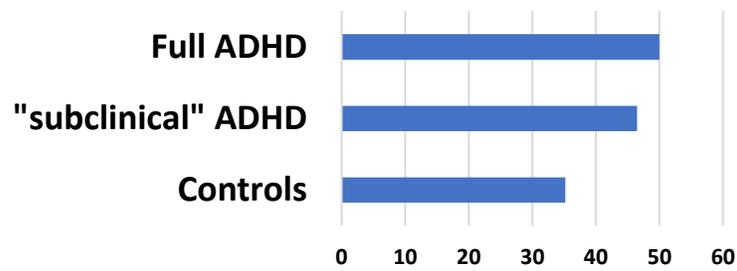
# Classification of Behavior Disorders in Adolescence: Scaling Methods, Predictive Validity, and Gender Differences

David M. Fergusson, Joseph M. Boden, and L. John Horwood  
University of Otago, Christchurch

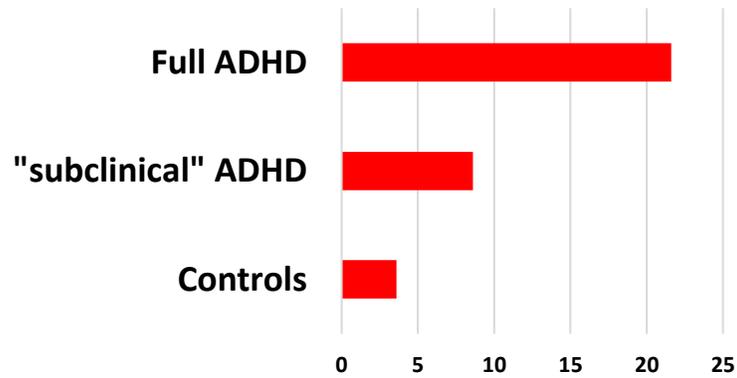
## ADHD full diagnosis and Subclinical ADHD

Data from the *Christchurch* birth cohort of 995 followed-up to age 25 years at the time of publication.

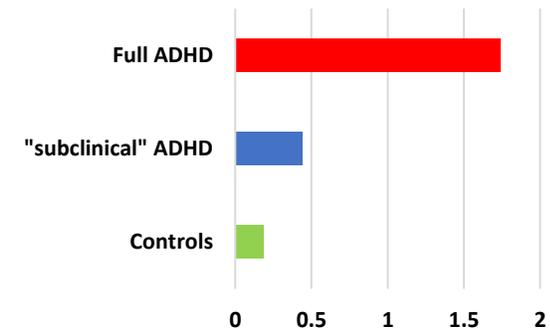
### Depression/Anxiety % of Group



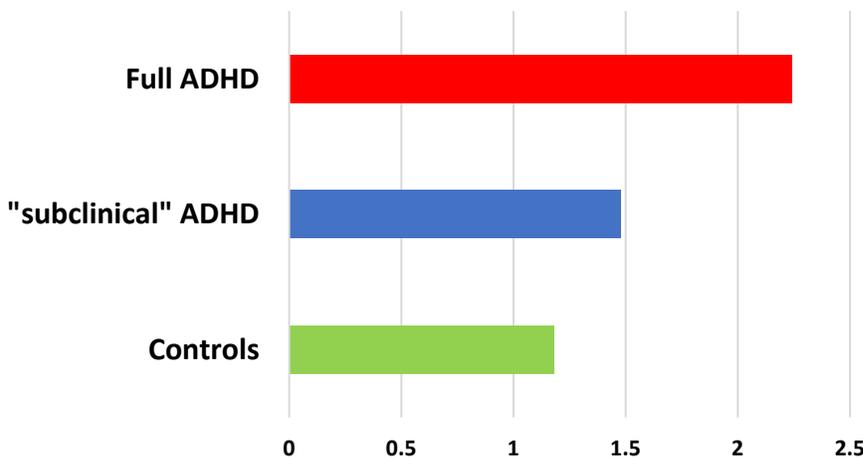
### Parents by 20 years



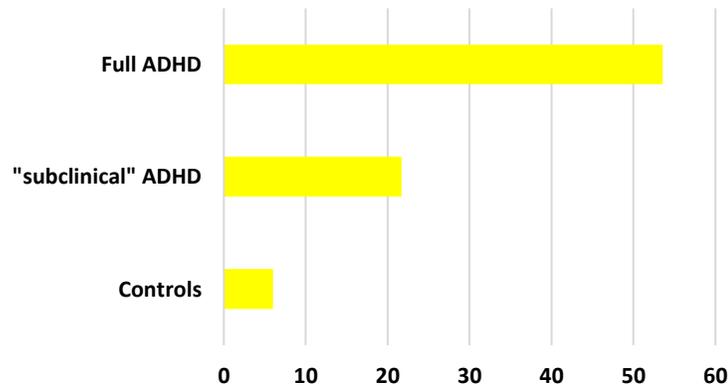
### Number of arrests 18 - 25 years



### Number Alcohol Abuse symptoms 18-25 yrs



### % Leaving school without qualification



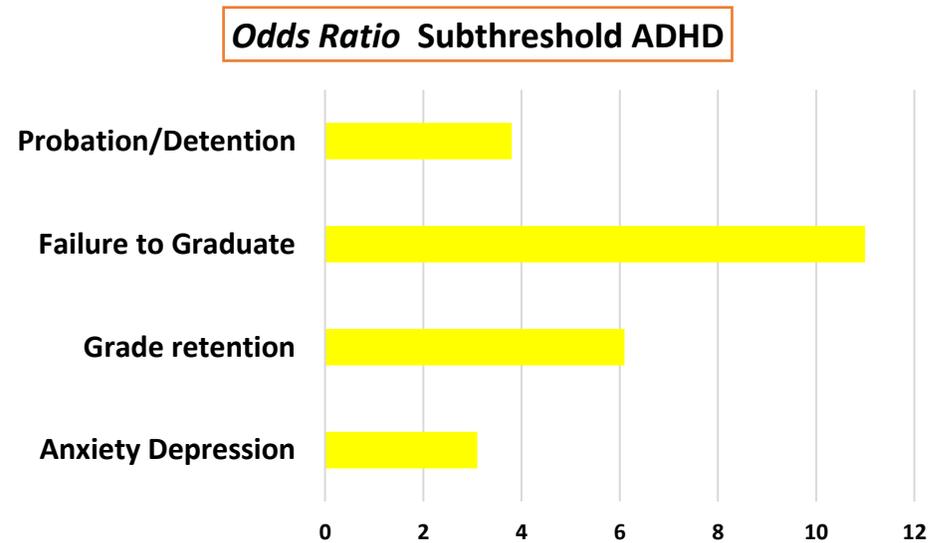
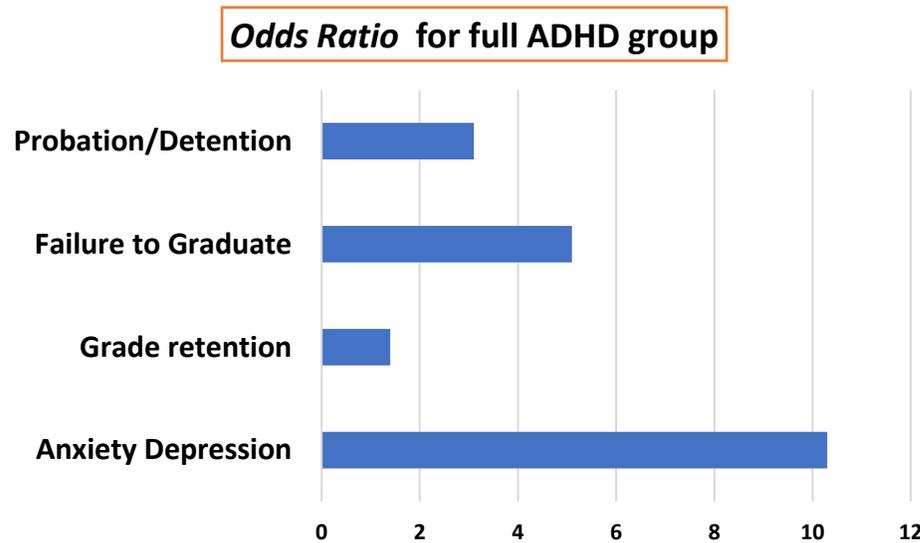
Severe psycho and socio-pathology present both in Full ADHD group *and* "Subclinical"/subthreshold ADHD.

# Adolescent Outcomes of Childhood Attention-Deficit/Hyperactivity Disorder in a Diverse Community Sample

J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(6): 595–605

School district sample: 1,615 students aged 5 to 11 years followed-up study 8 years later. High-risk youths meeting full (n = 94) and subthreshold (n=75) DSM-IV ADHD criteria were matched with low-risk peers (n = 163).

Regina Bussing, M.D., M.S.H.S., Dana M. Mason, B.S., Lindsay Bell, M.Ed., Phillip Porter, B.M., Cynthia Garvan, Ph.D.



**Subthreshold ADHD, but not full ADHD, increased the risk of grade retention. Both conditions increased the risk of graduation failure.**

**Anxiety/Depression more probable in full ADHD group but also present in subthreshold ADHD.**

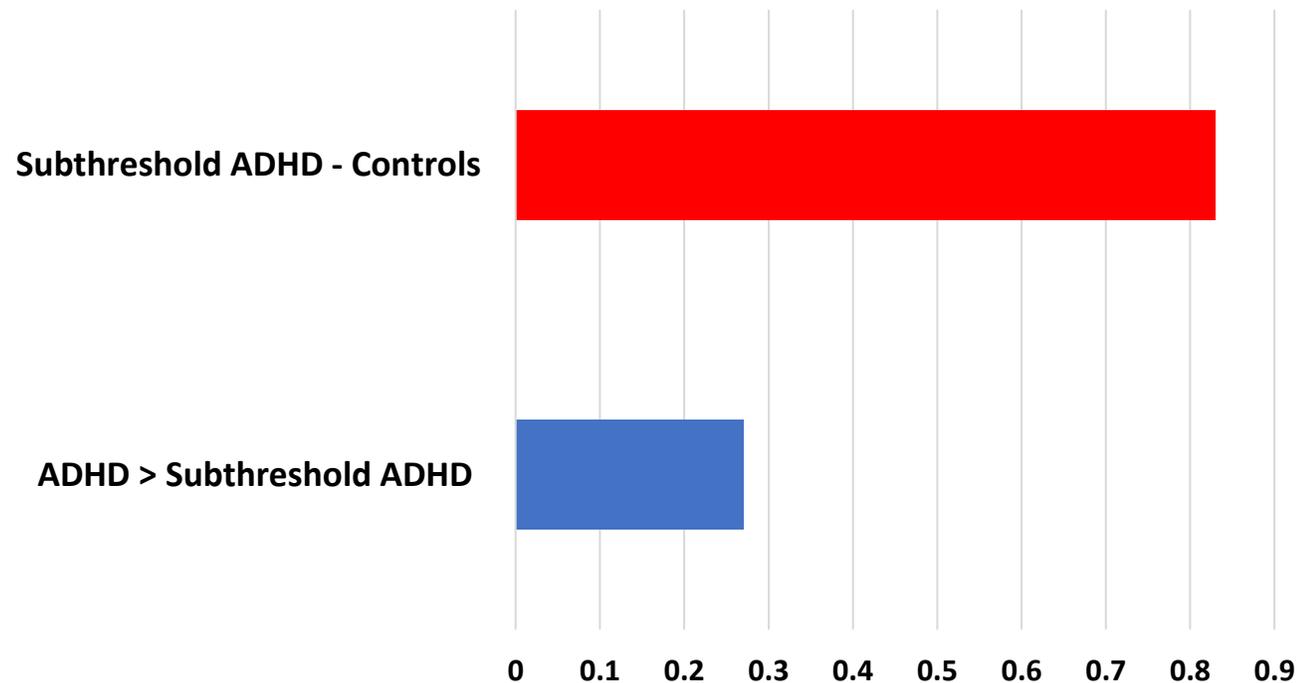
# Are subsyndromal manifestations of attention deficit hyperactivity disorder morbid in children? A systematic qualitative review of the literature with meta-analysis

Psychiatry Research 274 (2019) 75–90

Analysis of 9 Follow-up Studies  
N = 11,111

Anna-Mariya Kirova<sup>a</sup>, Caroline Kelberman<sup>a</sup>, Barbara Storch<sup>a</sup>, Maura DiSalvo<sup>a</sup>,  
K. Yvonne Woodworth<sup>a</sup>, Stephen V. Faraone<sup>c,d</sup>, Joseph Biederman<sup>a,b,\*</sup>

*Effect size* Subthreshold - Controls - Full ADHD  
Overall Functional Continuous Variables & Psychiatric Risk



Full ADHD group more disturbed than Subthreshold cases. Subthreshold cases more disturbed than controls.

A minority (17.7%) of clinically referred and non-referred children met a priori definitions of subthreshold ADHD.

Overall Functioning of subthreshold ADHD had higher rates:

- Family dysfunction,
- Cognitive impairment, executive dysfunction,
- Interpersonal and school deficits,
- Temperament problems,
- Psychiatric comorbidity, and
- Juvenile delinquency

Six-year follow-up study of combined type ADHD from childhood to young adulthood: Predictors of functional impairment and comorbid symptoms

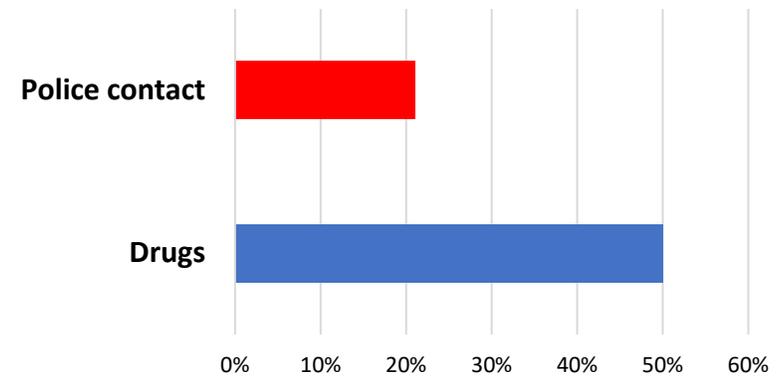
T. Cadman<sup>a,\*1</sup>, J. Findon<sup>a,1</sup>, H. Eklund<sup>a</sup>, H. Hayward<sup>a</sup>, D. Howley<sup>a</sup>, C. Cheung<sup>b</sup>, J. Kuntsi<sup>b</sup>, K. Glaser<sup>c</sup>, D. Murphy<sup>a</sup>, P. Asherson<sup>b</sup>

European Psychiatry 35 (2016) 47–54

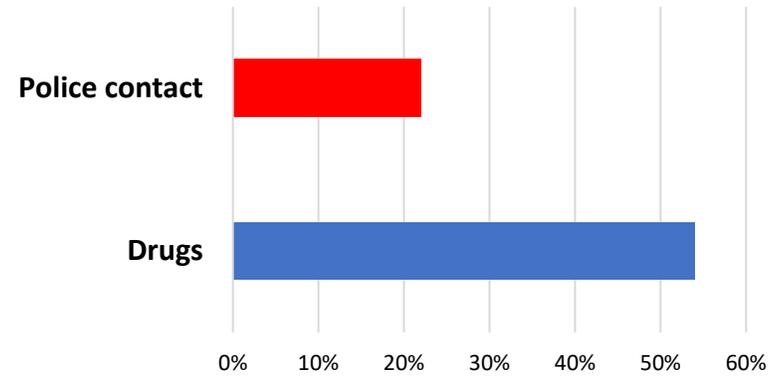
**Group which did not meet full DSM-IV criteria for ADHD (sub-threshold ADHD with continued impairment):**

**15.1% in partial remission and 4.7% in total remission.**

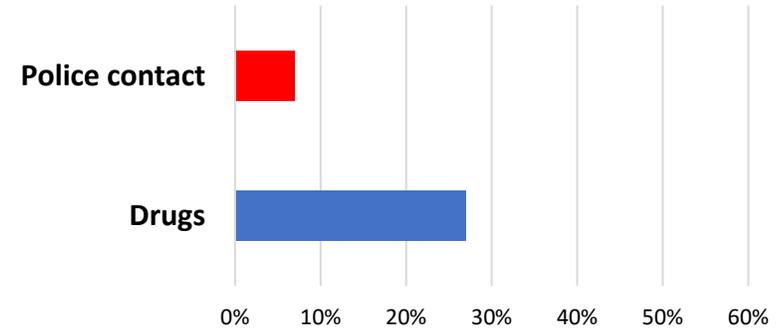
**Proportion of Persistent Group**



**Proportion of Subthreshold Group**



**Proportion of Control Group**



**Comorbid mental health problems were predicted by current symptoms of hyperactivity-impulsivity, and not by childhood ADHD severity.**

**This study replicates those of Fergusson et al, (2010)**

# Young adult mental health and functional outcomes among individuals with remitted, persistent and late-onset ADHD

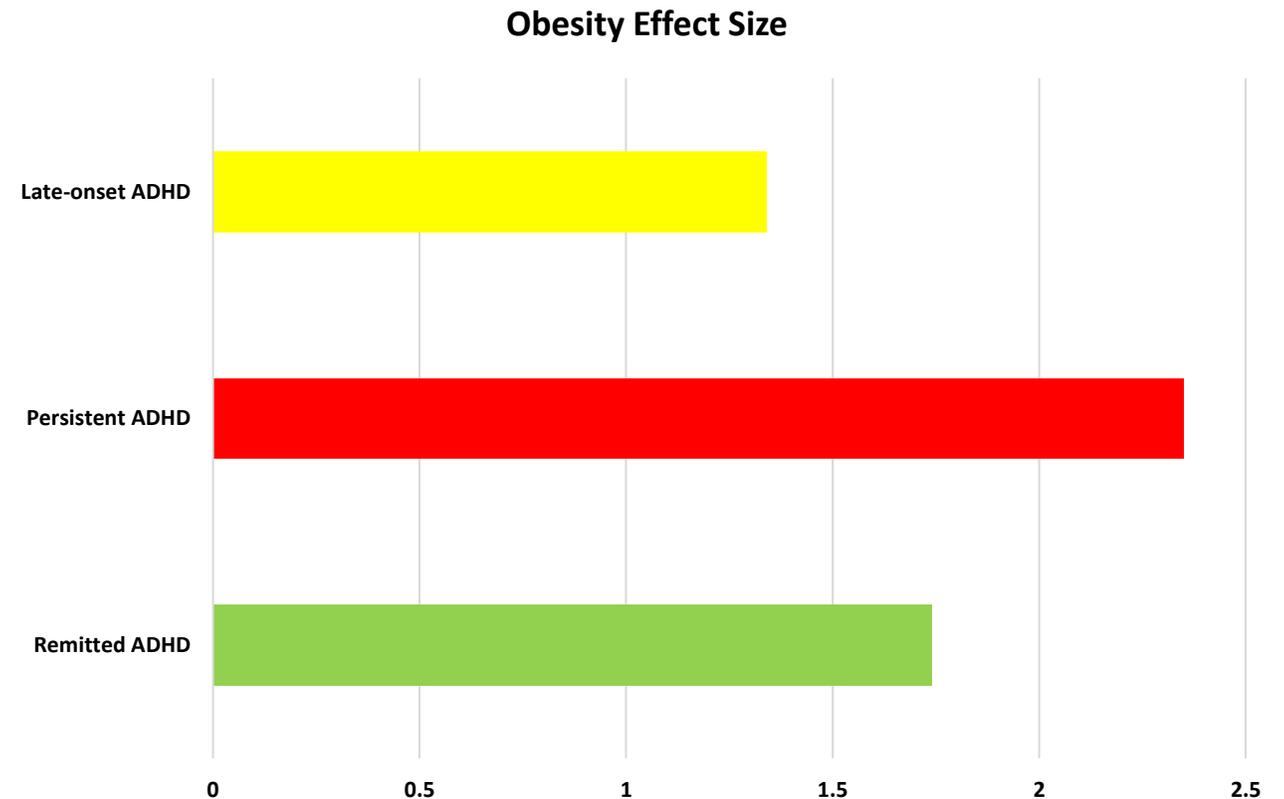
Jessica C. Agnew-Blais, Guilherme V. Polanczyk, Andrea Danese, Jasmin Wertz, Terrie E. Moffitt and Louise Arseneault

The British Journal of Psychiatry (2018)

Page 1 of 9. doi: 10.1192/bjp.2018.97

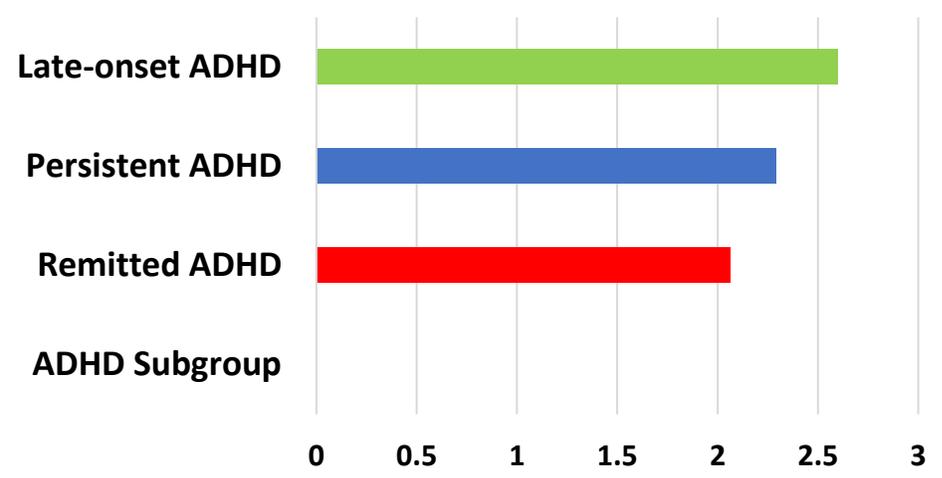
**Thus, even in “remission”, ADHD in childhood presents a significant somatic medical risk.**

**Participants aged 18 years at follow-up.**



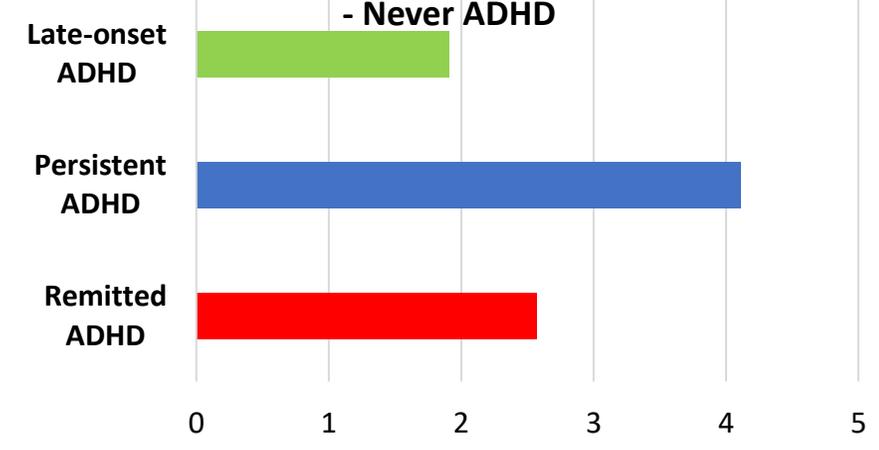
**Both remitted and persistent groups showed greater *obesity* risk compared with those who had never had ADHD. The late-onset group did *not*, suggesting a long-term effect of childhood ADHD, rather than also in adult onset cases.**

### Daily cigarette smoking ES - Never ADHD



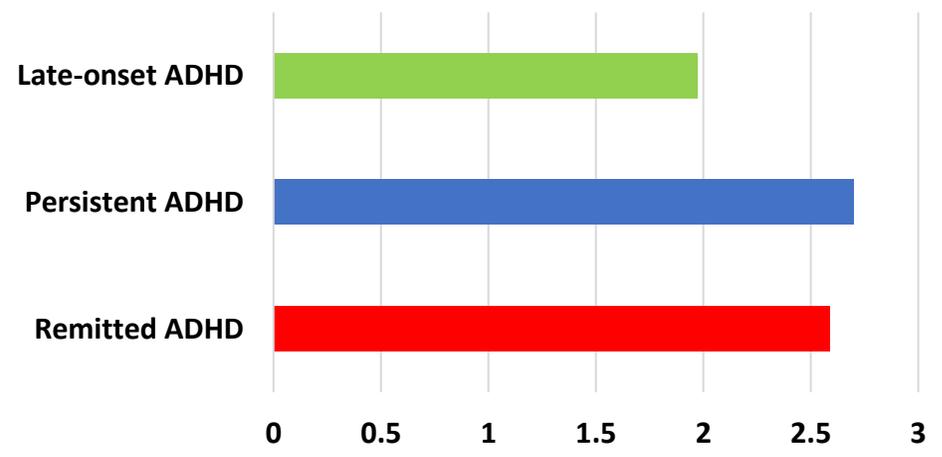
Risk of daily cigarette *smoking* was elevated in *all* ADHD groups compared with controls

### Not in education, employment or training ES - Never ADHD



All ADHD groups showed higher risk for *not in education, employment or training*.

### Criminal cautions/convictions ES - Never ADHD



All ADHD groups showed higher risk for Criminal Cautions/convictions with no significant difference between the Persistent and Remitted ADHD groups.

Further replication of Fergusson et al, (2010)

## Brief Summary this section:

- **Early longitudinal studies showed that in childhood, subthreshold cases had both cognitive and clinically significant dysfunctioning.**
- **In the last decade, using longitudinal designs, subthreshold cases have emerged as having severe psycho-socio-pathology, similar to that of persistent ADHD individuals. Lower educational impairments observed in remission/subthreshold and persistent ADHD subgroups.**
- **Increased risk of obesity in subthreshold cases compared with persistent ADHD and controls.**

**What might be a factor requiring further study to determine the ADHD symptomatic and neuropsychological trajectory?**

ADHD and subthreshold symptoms in childhood and life outcomes at 40 years in a prospective birth-risk cohort

Nella Schiavone<sup>a,\*</sup>, Maarit Virta<sup>a</sup>, Sami Leppämäki<sup>b</sup>, Jyrki Launes<sup>a</sup>, Ritva Vanninen<sup>c</sup>, Annamari Tuulio-Henriksson<sup>a</sup>, Satu Immonen<sup>a</sup>, Ilkka Järvinen<sup>a</sup>, Eliisa Lehto<sup>a</sup>, Katarina Michelsson<sup>d</sup>, Laura Hokkanen<sup>a</sup>

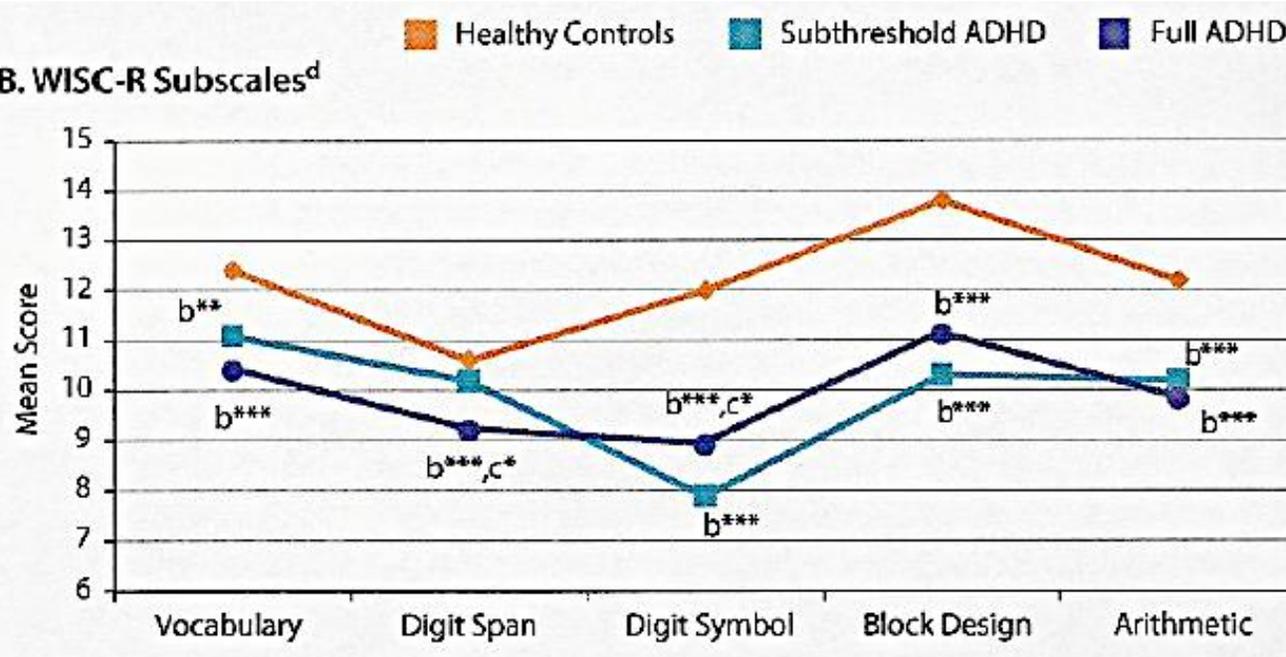
[Psychiatry Research 281 \(2019\) 112574](#)

**At age 40, the childhood ADHD group had lower educational level, more executive dysfunction, and higher rates of drug use than the other groups.**

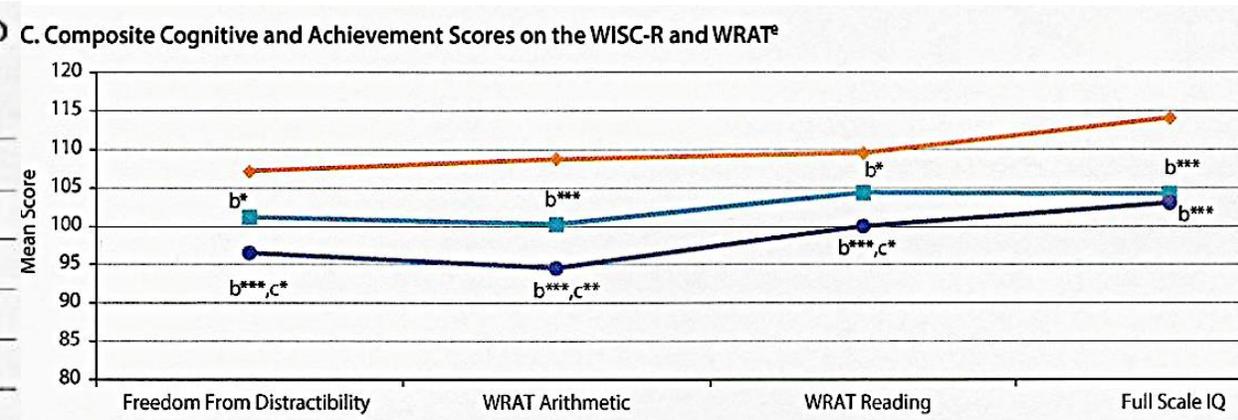
**Higher ADHD scores associated with higher ratings: disinhibitory self-control, flexibility, and poorer emergent metacognition. Early subthreshold ADHD with minor neuropsychological defects may increase with age and potentially predispose such individuals to increased psycho-social pathology.**

# **Subthreshold, Persistent, De Novo ADHD and Neuropsychological Functioning**

Biederman, J., Fitzgerald, M., Kirova, A., Woodworth, K.Y., Biederman, I., Faraone, S.V., (2018). Further evidence of morbidity and dysfunction associated with subsyndromal ADHD in clinically referred children. *J. Clin. Psychiatry*, 79.



Subthreshold group had lower scores than controls on: Vocabulary, Digit symbol, Block Design, and arithmetic.



Full ADHD differed from controls and Subthreshold ADHD:

- Freedom From Distractibility
- WRAT Reading and
- WRAT Arithmetic but not full-scale IQ
- The subthreshold ADHD group had significantly *higher* Digit Span but *lower* Digit Symbol than full ADHD group.

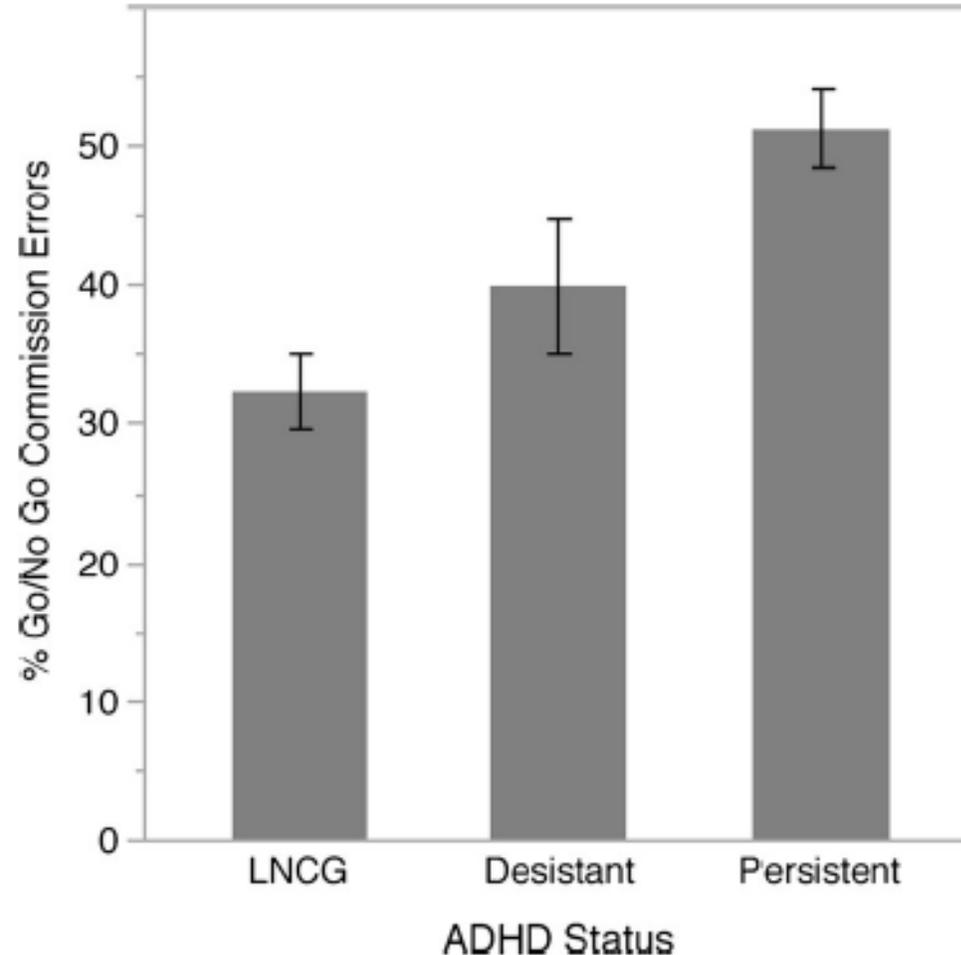
This study shows that syndromatic symptom fluctuations occur but that neuropsychological tests continued to show deficits. Suggested as a trait or structural feature of ADHD.

## Go/No Go task performance predicts cortical thickness in the caudal inferior frontal gyrus in young adults with and without ADHD

Erik Newman<sup>1</sup> · Terry L. Jernigan<sup>1,2,3,4</sup> · Krista M. Lisdahl<sup>5</sup> · Leanne Tamm<sup>6</sup> · Susan F. Tapert<sup>3</sup> · Steven G. Potkin<sup>7</sup> · Daniel Mathalon<sup>8</sup> · Brooke Molina<sup>9</sup> · James Bjork<sup>10</sup> · F. Xavier Castellanos<sup>11,12</sup> · James Swanson<sup>13</sup> · Joshua M. Kuperman<sup>4,14</sup> · Hauke Bartsch<sup>14</sup> · Chi-Hua Chen<sup>3,14</sup> · Anders M. Dale<sup>2,4,14,15</sup> · Jeffery N. Epstein<sup>6</sup> · MTA Neuroimaging Group

**This study suggests that disinhibition is present in both full and subthreshold ADHD.**

## Follow-up MTA subsample, original Child ADHD diagnosis and current status.



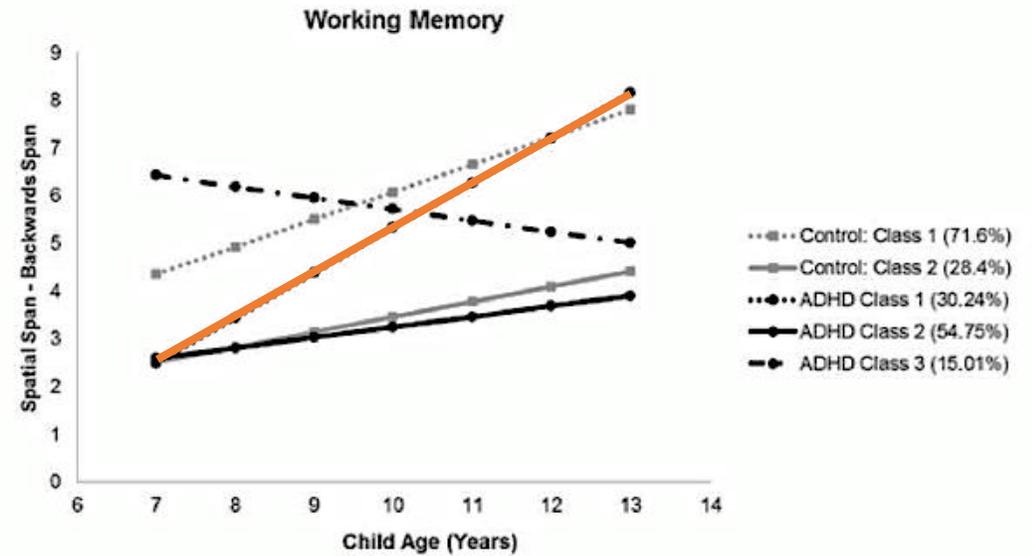
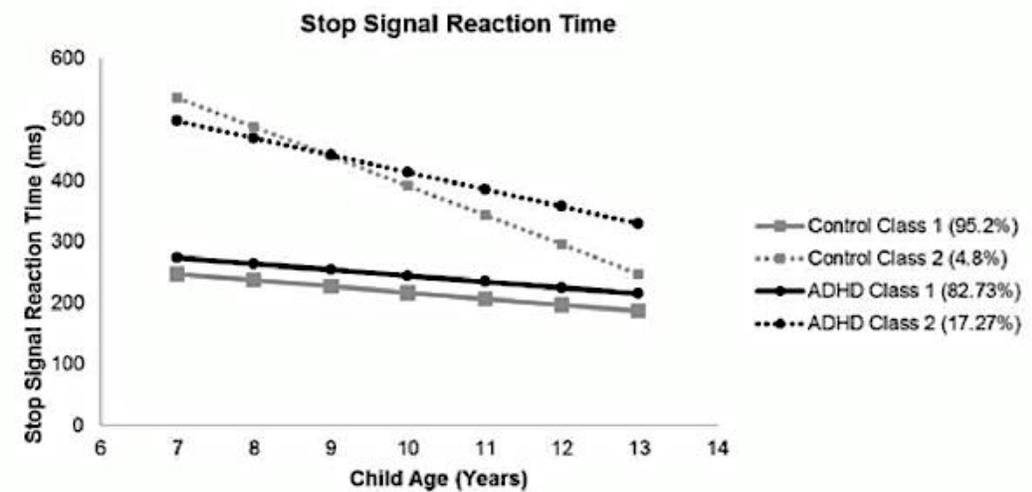
**More commission errors (Conners CPT) observed in persistent ADHD *adolescent* group than Desistant ADHD subgroup. Desistant (subthreshold) participants made more errors than LNCG (control) participants.**

# Heterogeneity in Development of Aspects of Working Memory Predicts Longitudinal Attention Deficit Hyperactivity Disorder Symptom Change

Sarah L. Karalunas, Hanna C. Gustafsson,  
Nathan F. Dieckmann, and Jessica Tipsord  
Oregon Health & Science University

Suzanne H. Mitchell  
Oregon Health & Science University and Oregon Institute of  
Occupational Health Science, Portland, Oregon

Joel T. Nigg  
Oregon Health & Science University



**Improvement in response inhibition unrelated to ADHD symptom change.**

**Stop signal RT: lower values are associated with better performance.**

**Improvement in visual spatial working memory maintenance predicted symptom *remission* in ADHD.**

**ADHD Class 1: “ADHD: impaired, recovering,” included children who had impaired VWM at age 7 compared to the “Control: normally developing” improved significantly faster over time than the normally developing controls and normalized on VWM performance by age 13.**

# A Longitudinal Twin Study of the Direction of Effects between ADHD Symptoms and IQ

PLoS ONE 10(4): e0124357.  
doi:10.1371/journal.pone.0124357

General population, Twin N = 4771 pairs

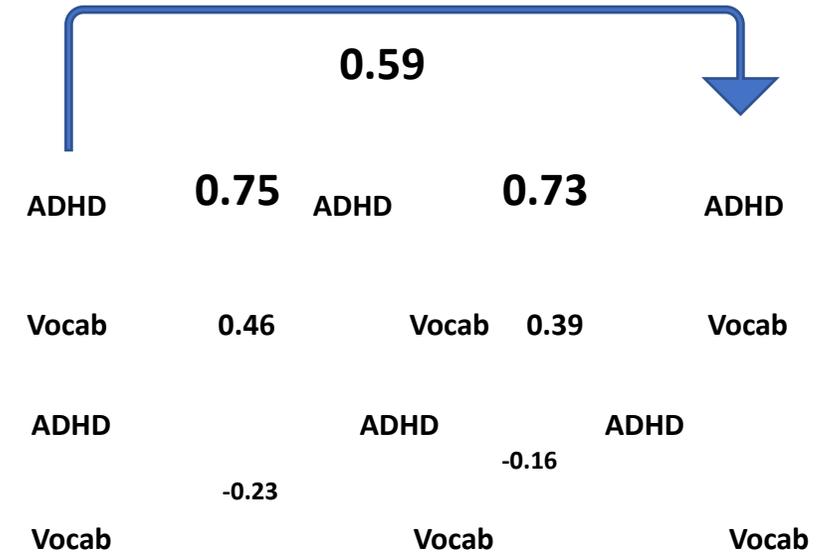
Anna Sophie Rommel<sup>1</sup>, Frühling Rijdsdijk<sup>1</sup>, Corina U. Greven<sup>1,2,3</sup>, Philip Asherson<sup>1</sup>,  
Jonna Kuntsi<sup>1\*</sup>

ADHD symptoms and IQ scores significantly predicted each other over time.

- ADHD symptoms at age 12 ( $t_1$ ) years were a significantly stronger predictor of vocabulary at age 14 ( $t_2$ ) years but not at 16 years ( $t_3$ ).

The results suggest:

- ADHD symptoms may put adolescents at risk for lower IQ scores and
- when measurement occurs can give different predictive results.



*Stable* aetiological factors and *time-specific genetic and environmental influences* emerge for each trait at e.g.  $t_2$  and  $t_3$  versus  $t_1$  and  $t_3$  (ADHD)

$t_1$  and  $t_2$  versus  $t_1$  and  $t_3$  (IQ) at two year intervals.

# Are changes in ADHD course reflected in differences in IQ and executive functioning from childhood to young adulthood?

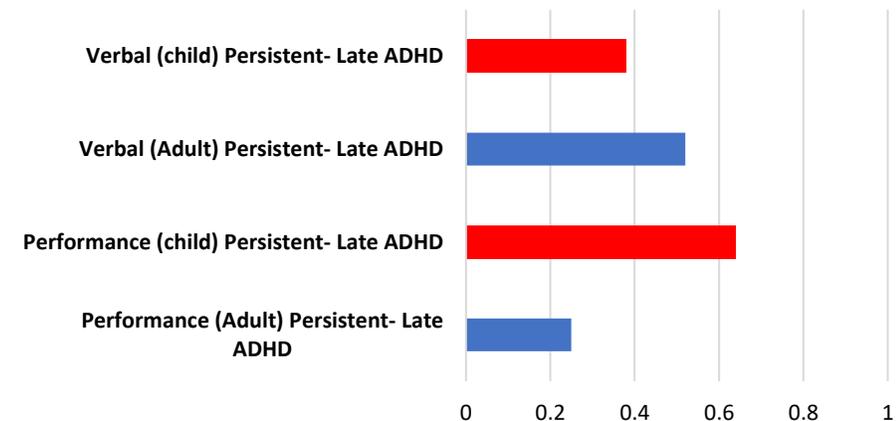
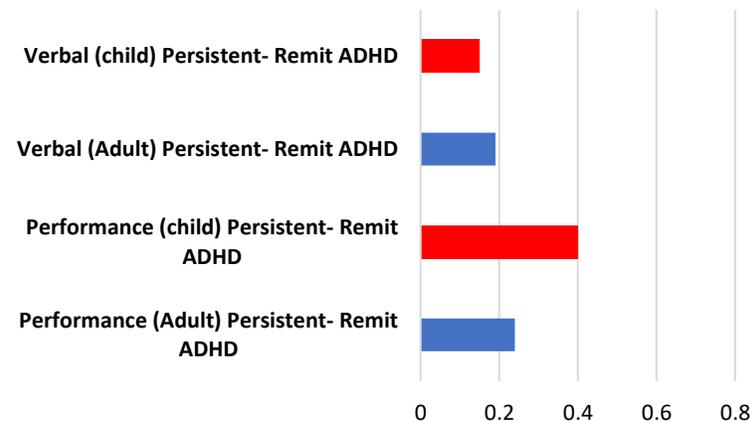
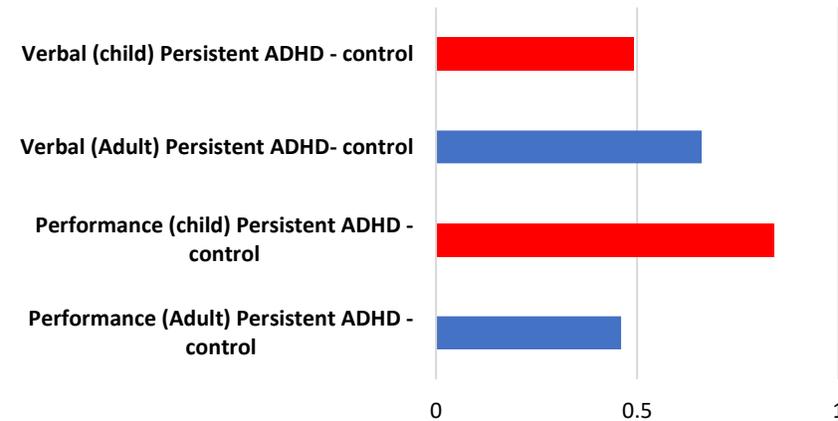
Jessica C. Agnew-Blais<sup>1</sup> , Guilherme V. Polanczyk<sup>2</sup>, Andrea Danese<sup>3</sup>, Jasmin Wertz<sup>5</sup>, Terrie E. Moffitt<sup>1,5,6</sup> and Louise Arseneault<sup>1</sup>

ADHD at any point in development (7, 10, 12, and 18 years) associated with *lower* average IQ. N = 2232 twins.

ES Persistent ADHD versus Control

ES Persistent versus Remitted ADHD

ES Persistent versus Late Onset



ADHD groups showed deficits in IQ across development compared to controls

Persistent ADHD greatest IQ deficit, followed by Remitted ADHD.

Persistent ADHD differed from late-onset ADHD.

ADHD groups did not differ from controls in their *developmental trajectory* of IQ. Hence, changes in ADHD symptomatology appear *independent* of IQ, which reflects a spectrum of cognitive functions. Differences in cognitive functioning between controls and ADHD subgroups were present.

# Are changes in ADHD course reflected in differences in IQ and executive functioning from childhood to young adulthood?

Jessica C. Agnew-Blais<sup>1</sup> , Guilherme V. Polanczyk<sup>2</sup>, Andrea Danese Jasmin Wertz<sup>5</sup>, Terrie E. Moffitt<sup>1,5,6</sup> and Louise Arseneault<sup>1</sup>

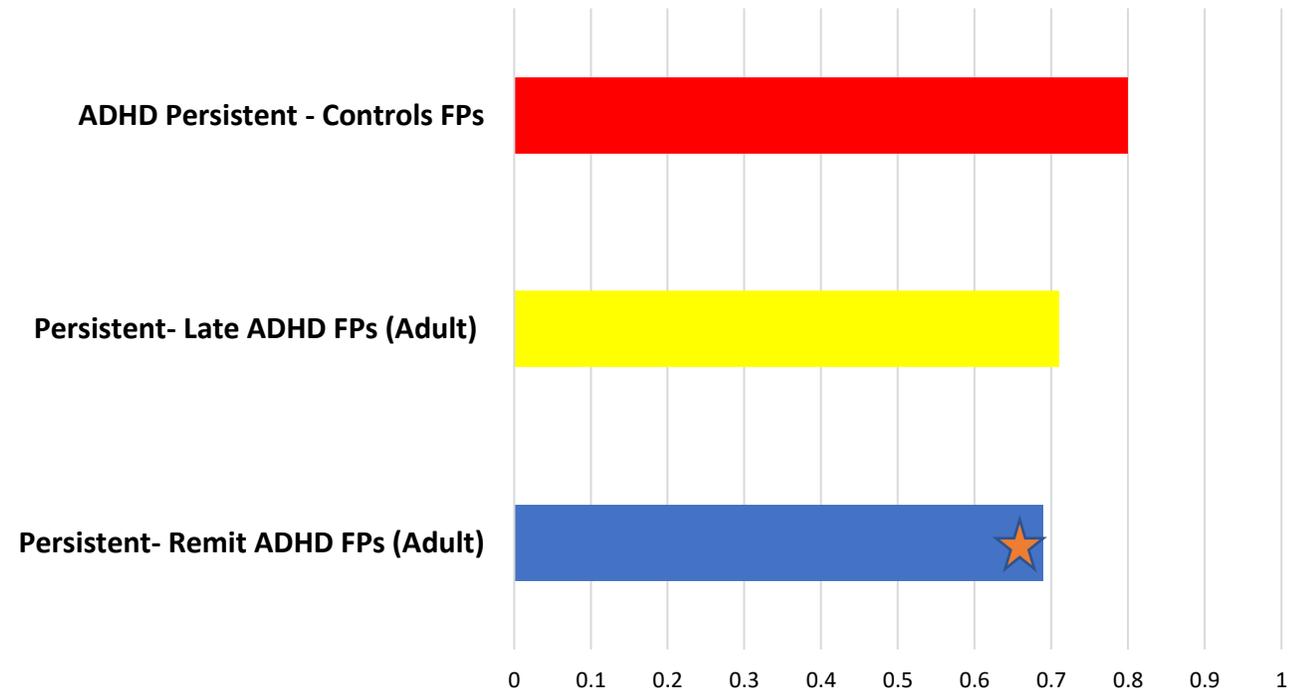
**Persistent ADHD poorer executive functioning than remitted ADHD.**

**Remitted ADHD at 18 still significantly impaired compared to controls.**

**Having ADHD at any point in development was associated with poorer executive functioning at ages 5 and 18 years.**

**No differences observed in working memory between Persistent & Remitted ADHD and both with poorer working memory than controls.**

## Inhibition (RVP test Cantab False Positives) at Age 18



# Neuropsychological outcome in adolescents/young adults with childhood ADHD: profiles of persisters, remitters and controls

Jeffrey M. Halperin,<sup>1,2,4</sup> Joey W. Trampush,<sup>2</sup> Carlin J. Miller,<sup>3</sup> David J. Marks,  
and Jeffrey H. Newcorn<sup>4</sup>

## Stroop Replication by:

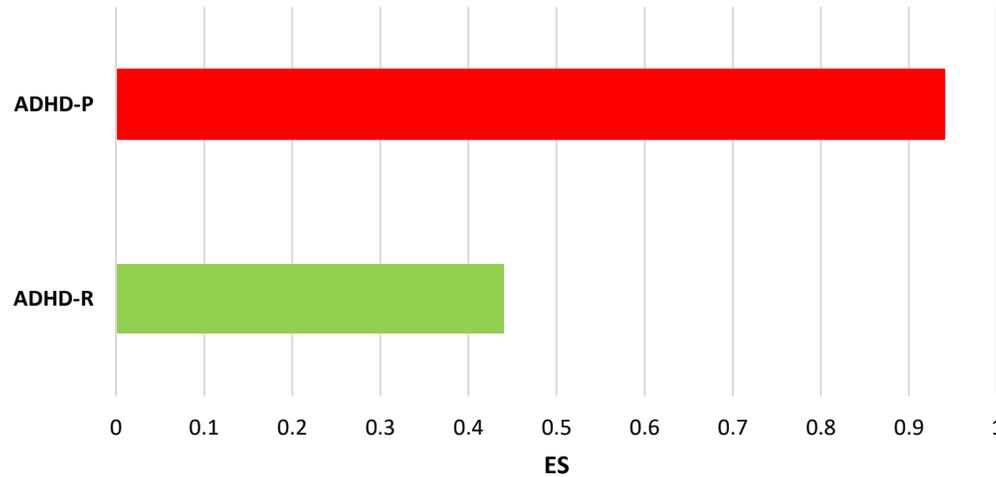
Eur Child Adolesc Psychiatry (2014) 23:627–636  
DOI 10.1007/s00787-013-0501-z

ORIGINAL CONTRIBUTION

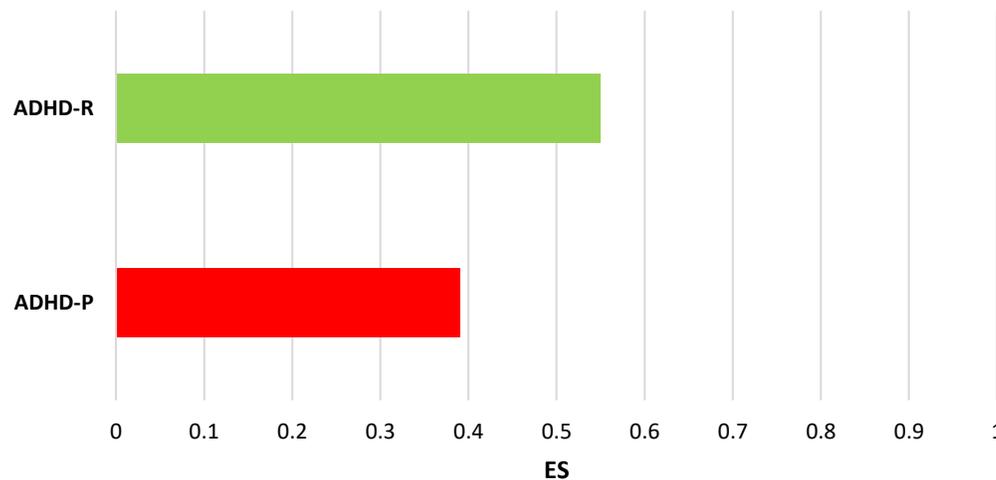
## Subthreshold attention-deficit/hyperactivity disorder is associated with functional impairments across domains: a comprehensive analysis in a large-scale community study

Soon-Beom Hong · Dominic Dwyer · Jae-Won Kim · Eun-Jin Park ·  
Min-Sup Shin · Boong-Nyun Kim · Hee-Jeong Yoo · In-Hee Cho ·  
Soo-Young Bhang · Yun-Chul Hong · Christos Pantelis · Soo-Churl Cho

d' (vigilance) ADHD-P and ADHD-R v. controls



Stroop Word: ADHD-P and ADHD-R v. controls



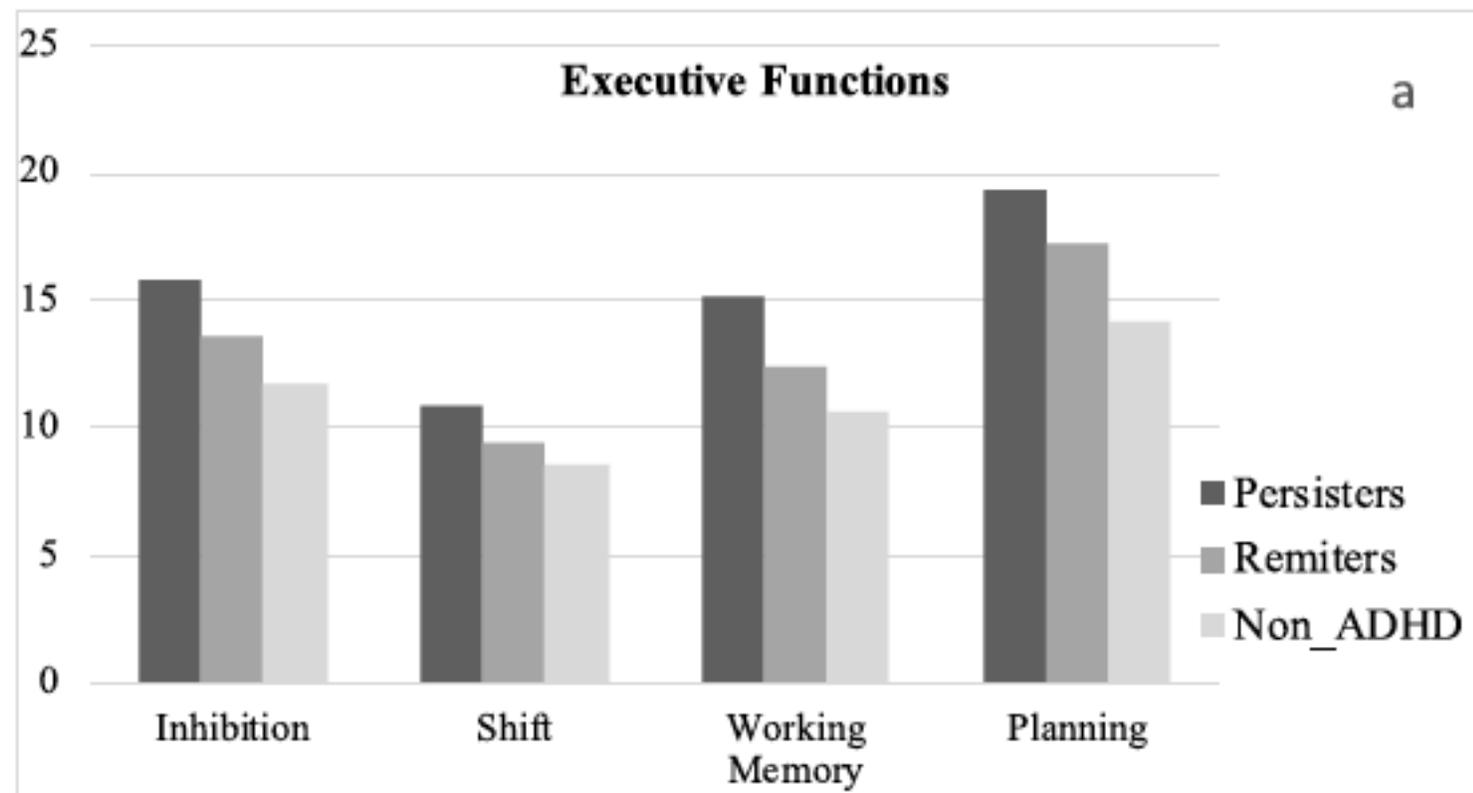
Note: difference greater in ADHD-R (subthreshold) than ADHD-P

# Empirical examination of executive functioning, ADHD associated behaviors, and functional impairments in adults with persistent ADHD, remittent ADHD, and without ADHD

Belén Roselló<sup>1</sup>, Carmen Berenguer<sup>1</sup>, Inmaculada Baixauli<sup>2</sup>, Álvaro Mira<sup>1</sup>, Jose Martinez-Raga<sup>3</sup> and Ana Miranda<sup>1</sup>

Spanish sample of IMAGE longitudinal study, follow-up 12 years succeeding first assessment

Executive Functions Group Effect		partial eta squared
Shift	1 > 3	.13
Plan/Organize	1 > 3; 2 > 3	.27
Inhibition	1 > 3	.31
Working Memory	1 > 2, 3	.33



ADHD-Persisters *not* significantly different from ADHD-Remitters in: inhibition, Planning, Set Shifting.  
 Primary difference between ADHD-Persisters and ADHD-Remitters is in Working Memory performance.

# Heterotypic trajectories of dimensional psychopathology across the lifespan: the case of youth-onset attention deficit/hyperactivity disorder

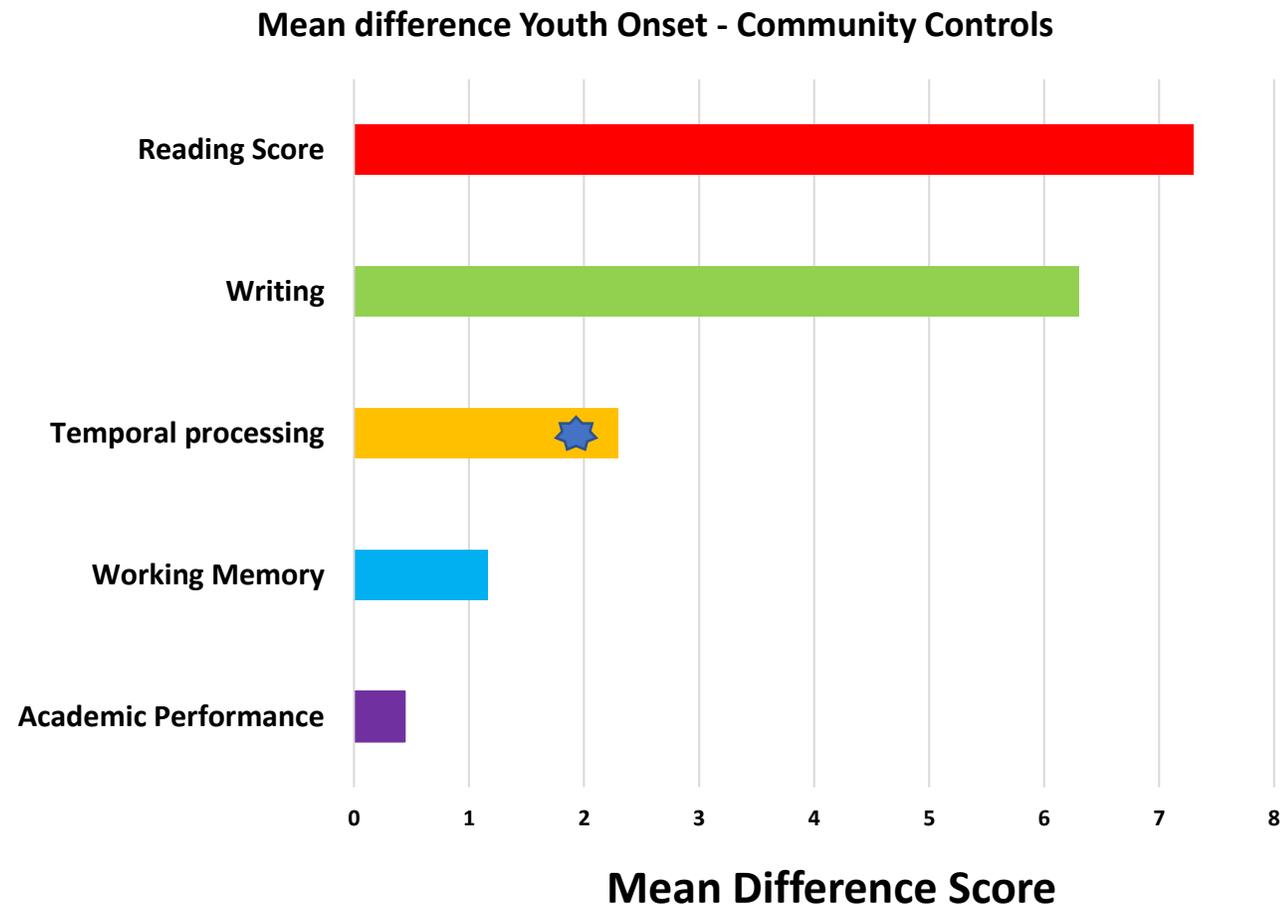
Arthur Gus Manfro,<sup>1,2</sup> Marcos Santoro,<sup>2,3</sup> Guilherme Vanoni Polanczyk,<sup>2,4</sup> Ary Gadelha,<sup>2</sup> Pedro Mario Pan,<sup>2,5</sup> Rodrigo Affonseca Bressan,<sup>2,5</sup> Elisa Brietzke,<sup>2,5</sup> Fernanda Talarico,<sup>2</sup> Sintia Belangero,<sup>2,3</sup> Luis Augusto Rohde,<sup>2,4,6</sup> and Giovanni Abrahão Salum<sup>2,6</sup>

- **Youth-onset ADHD:** children no more than two ADHD symptoms at baseline and ADHD diagnosis at follow-up (n = 28);
- **Persistent ADHD:** children ADHD diagnosis *both* at baseline *and* follow-up assessments (n = 26).

This paper indicates that individuals can commence with no or  $\geq 2$  symptoms and achieve supra-threshold ADHD rating.

Primary defects: academic with Executive dysfunction explained primarily by temporal processing (time anticipation).

Longitudinal study N = 1317



### ***Brief Summary Neuropsychological section:***

- **Syndromatic symptom fluctuations occur.**  
Neuropsychological tests continue to show deficits in both persistent and subthreshold ADHD compared with Typically Developing participants: CPT errors and vigilance measure  $d'$ , Working memory, and other executive functions.
- **Changes in ADHD symptomatology may be *independent* or correlated with cognitive performance both in ADHD remitters and persisters.**
- ***Improvement* in visual spatial working memory maintenance can predict symptom *remission* in ADHD.**
- **Individuals can commence with no or few symptoms and achieve supra-threshold ADHD rating and have executive dysfunction e.g. in time anticipation.**
- ***General* trend (but not always): Persistent greater cognitive deficits than Subthreshold ADHD individuals.**

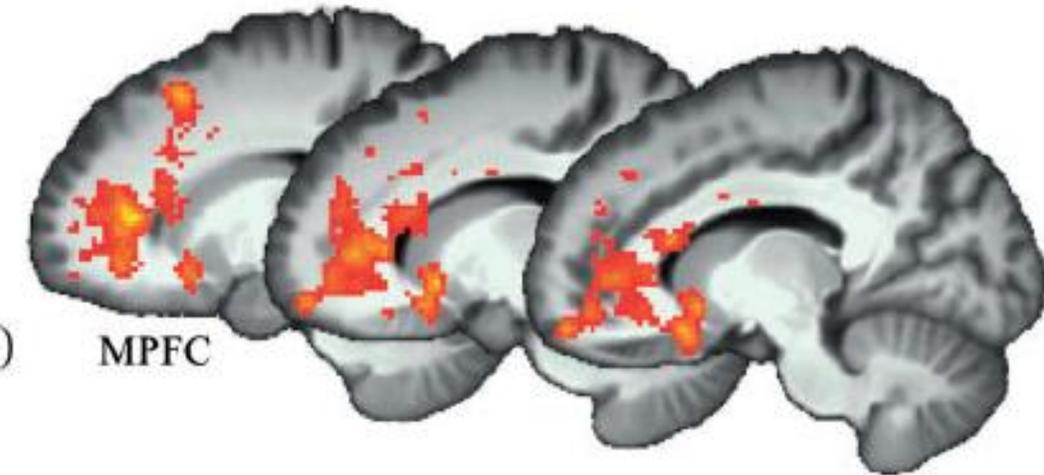
## **Neuroimage, Subthreshold and Full Syndrome ADHD**

### ***Selective Review***

# Brain differences between persistent and remitted attention deficit hyperactivity disorder

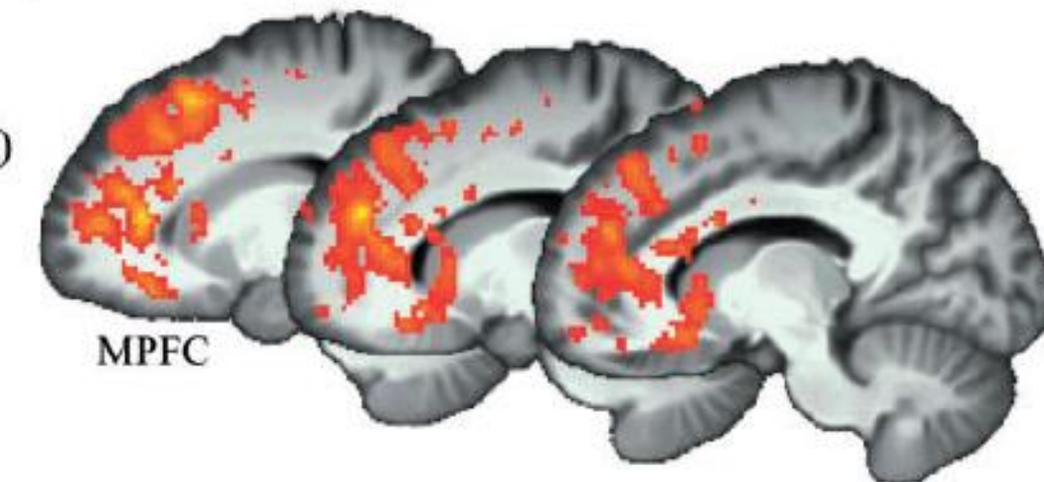
Aaron T. Mattfeld,<sup>1,2</sup> John D. E. Gabrieli,<sup>1,2</sup> Joseph Biederman,<sup>3,4</sup> Thomas Spencer,<sup>3,4</sup> Ariel Brown,<sup>3,4</sup> Amelia Kotte,<sup>3,4,5</sup> Elana Kagan<sup>3,4</sup> and Susan Whitfield-Gabrieli<sup>1,2</sup>

## B Control > Persistent ADHD



Greater positive functional connectivity between posterior cingulate cortex and medial prefrontal cortex for the control group than the persistent ADHD group.

## C Remitting ADHD > Persistent ADHD



(C) The remitted ADHD group also showed greater positive functional connectivity between the posterior cingulate cortex and medial prefrontal cortex than the persistent ADHD group.

Direct comparison of whole-brain correlations of the medial prefrontal cortex seed in the *remitted* and *persistent* groups showed no significant differences at the dorsolateral prefrontal cortex.

# Thalamo-Cortical Activation and Connectivity During Response Preparation in Adults With Persistent and Remitted ADHD

*Am J Psychiatry* 2013; 00:1–9,

Suzanne M. Clerkin, Ph.D.,  
M.S.C.R.

Kurt P. Schulz, Ph.D.

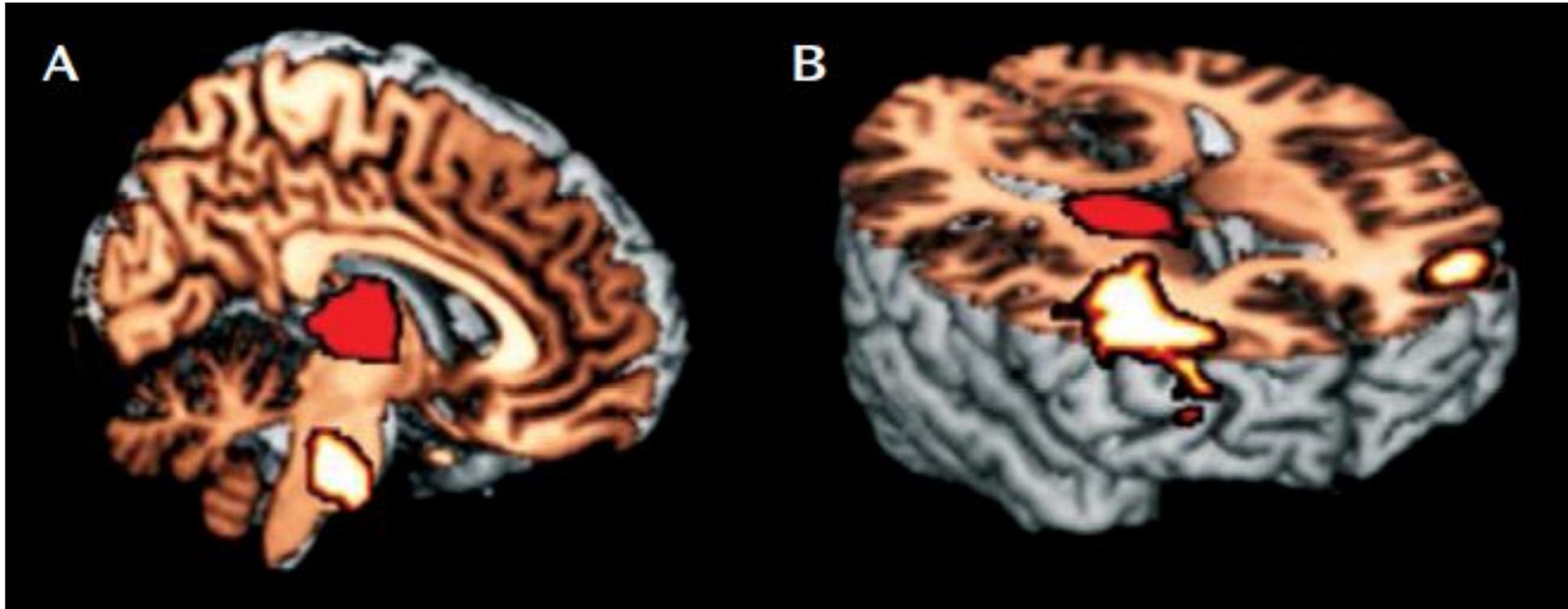
Olga G. Berwid, Ph.D.

Jin Fan, Ph.D.

Jeffrey H. Newcorn, M.D.

Cheuk Y. Tang, Ph.D.

Jeffrey M. Halperin, Ph.D.



**Cue-related connectivity (Panel B) greater between the right thalamus and prefrontal regions: including the left right frontopolar cortex and the left dorsolateral prefrontal cortex, in individuals with *remitted* ADHD relative to those with *persistent* ADHD.**

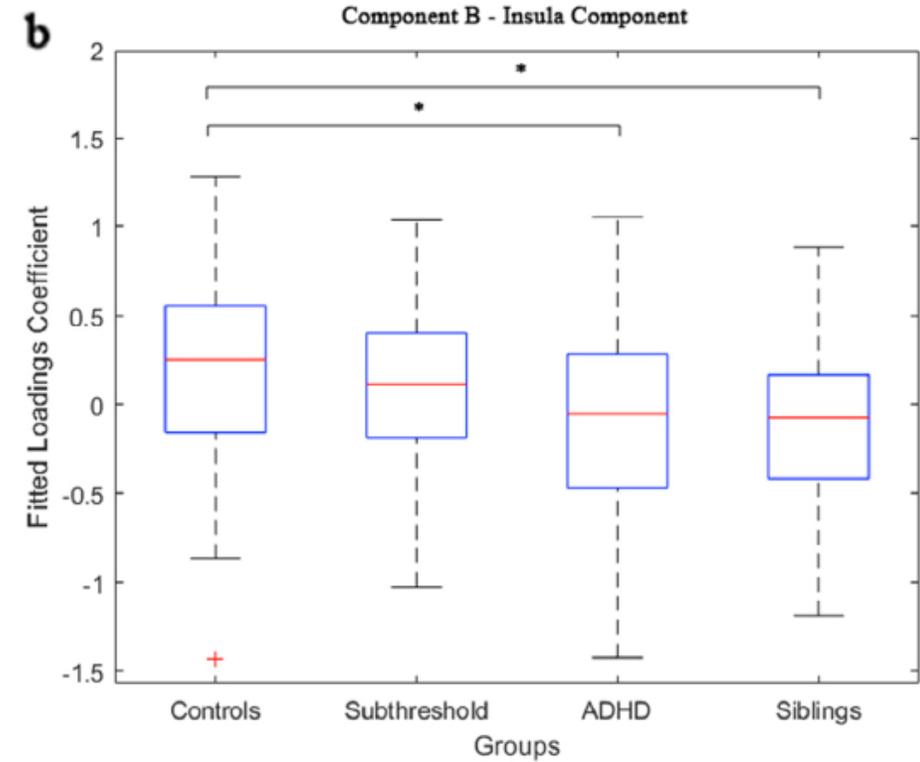
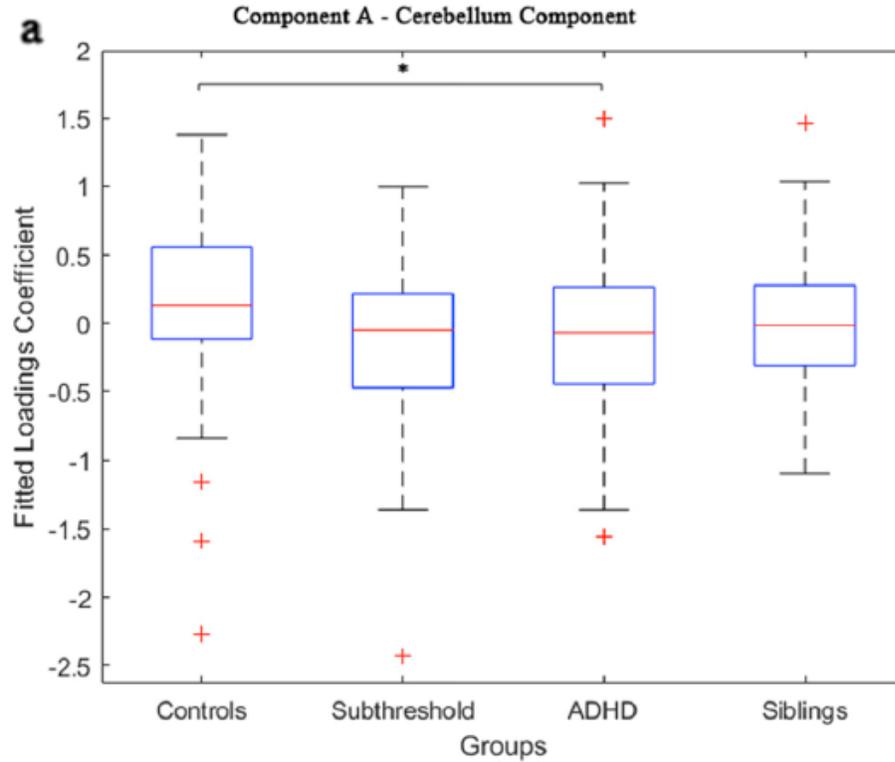
**But**

**no differences in activation between individuals in the *remitted* ADHD group and those in the *persistent* ADHD group in any regions**

Structural brain alterations and their association with cognitive function and symptoms in Attention-deficit/Hyperactivity Disorder families

Wenhao Jiang<sup>a</sup>, Kuaikuai Duan<sup>b</sup>, Kelly Rootes-Murdy<sup>a</sup>, Pieter J. Hoekstra<sup>c</sup>, Catharina A. Hartman<sup>c</sup>, Jaap Oosterlaan<sup>d</sup>, Dirk Heslenfeld<sup>d</sup>, Barbara Franke<sup>e,f</sup>, Jan Buitelaar<sup>g</sup>, Alejandro Arias-Vasquez<sup>e,f</sup>, Jingyu Liu<sup>h</sup>, Jessica A. Turner<sup>a,i,\*</sup>

Six year follow-up

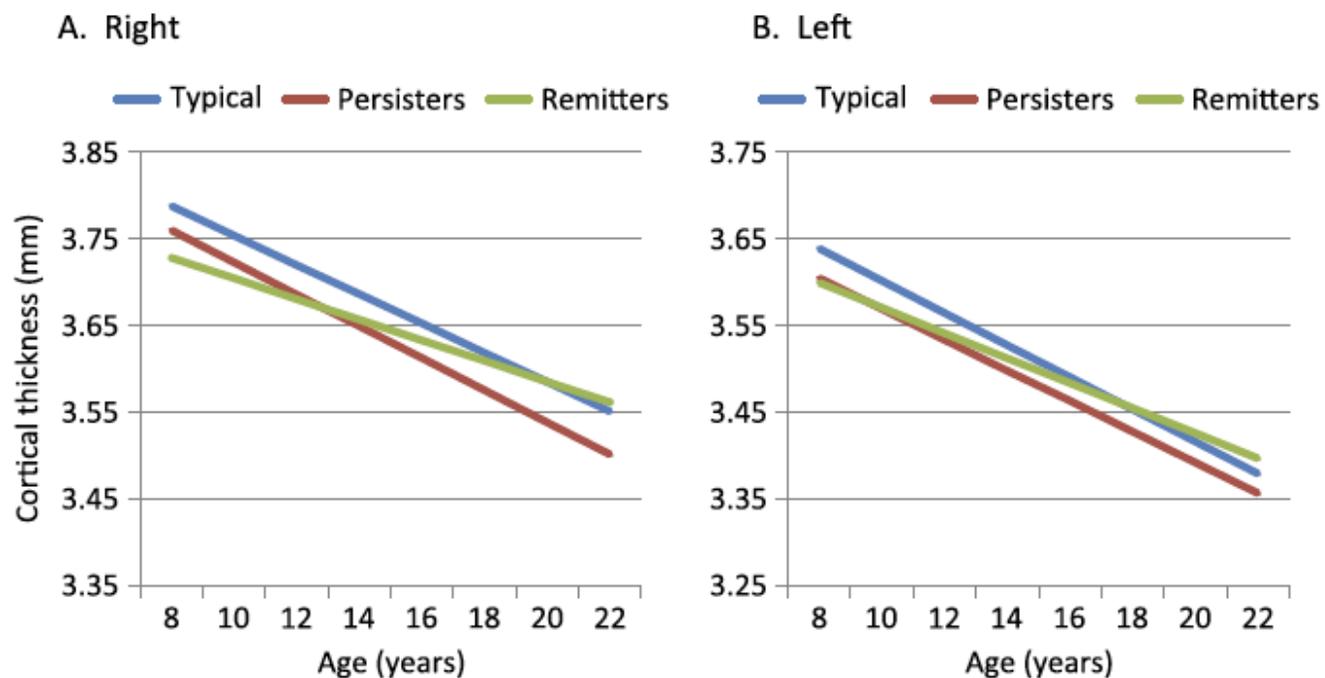
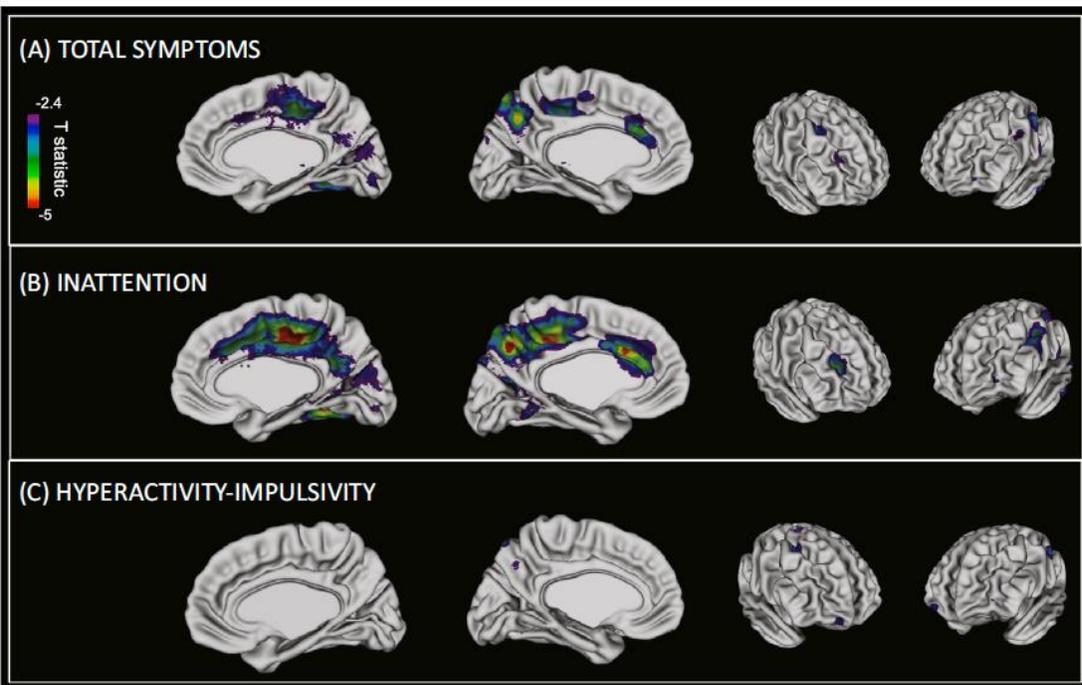


**Component A: mainly located in bilateral Crus I, subthreshold ADHD cases were intermediate between ADHD and typically developing controls.**

# Trajectories of Cerebral Cortical Development in Childhood and Adolescence and Adult Attention-Deficit/Hyperactivity Disorder

BIOL PSYCHIATRY 2013;74:599–606

Philip Shaw, Meaghan Malek, Bethany Watson, Deanna Greenstein, Pietro de Rossi, and Wendy Sharp



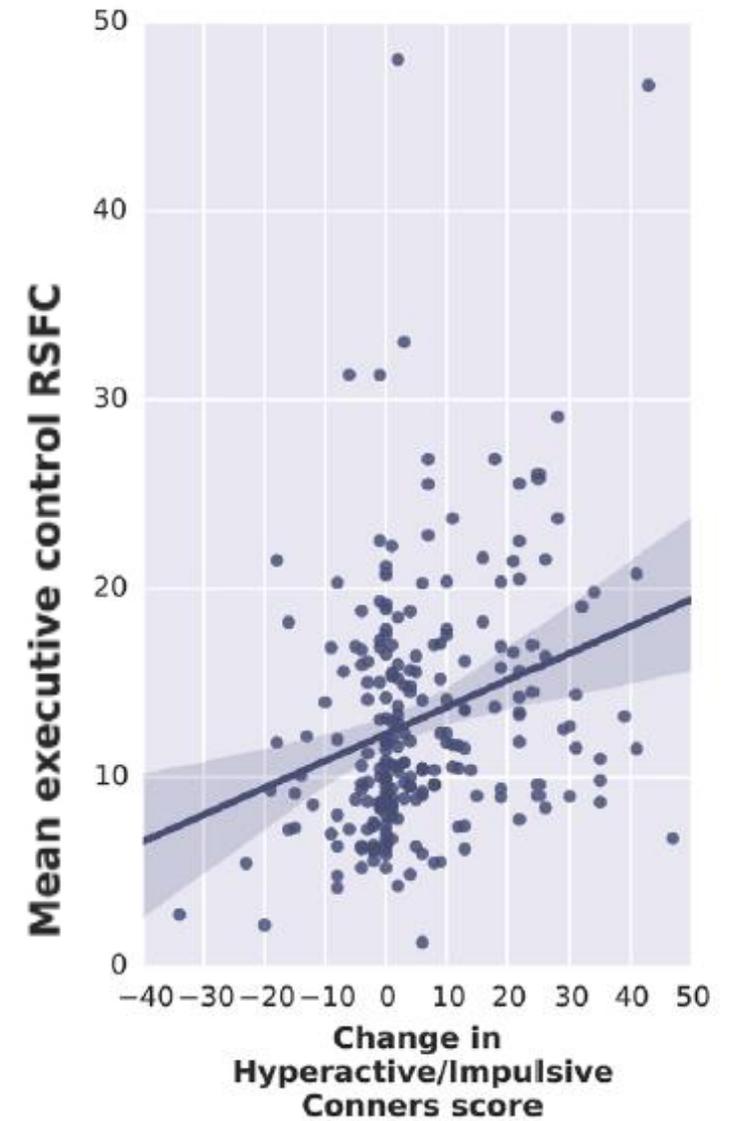
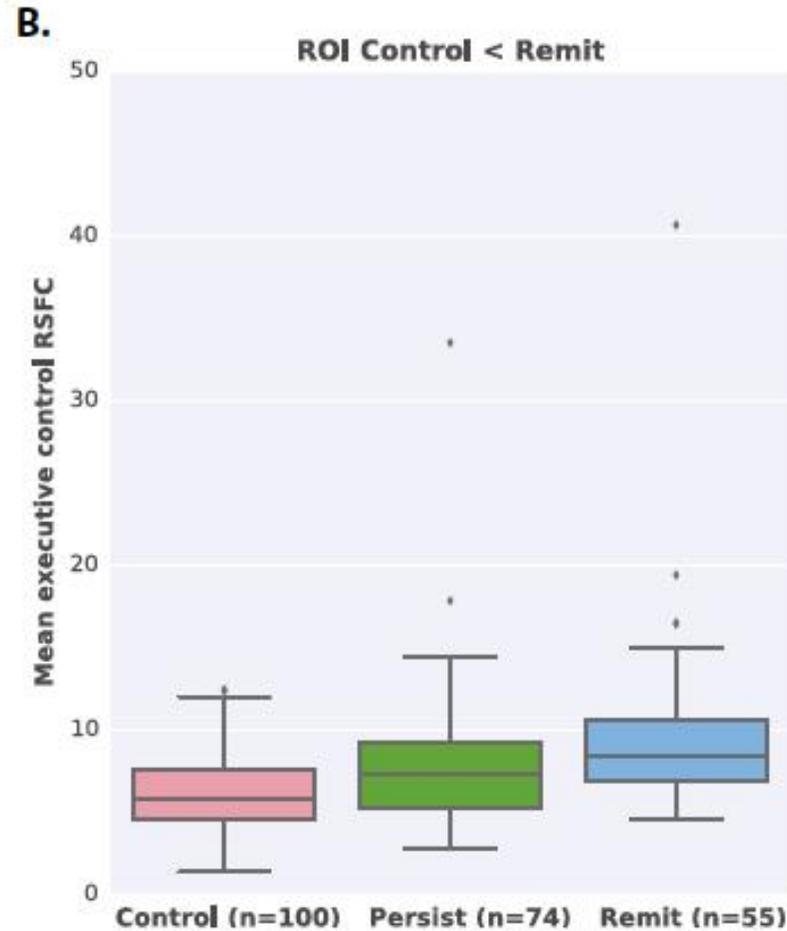
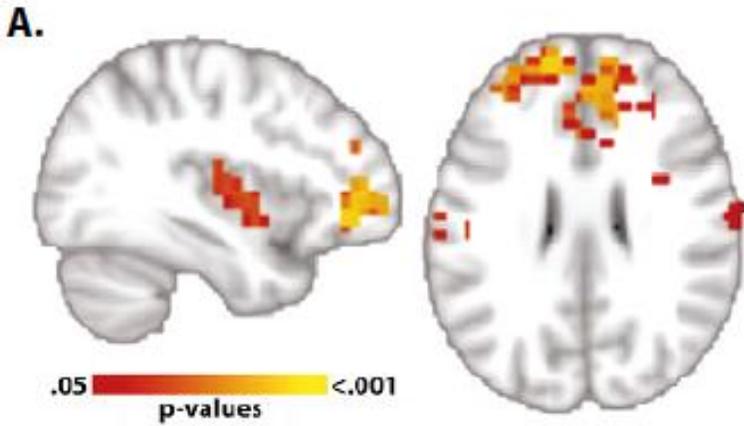
Cortical thickness in regions linked to adult ADHD status for the right (A) and left (B) hemispheres.

Cortical thickening or minimal thinning was found exclusively in individuals with *remitted* ADHD.

The varying ADHD trajectories are centered bilaterally on the: cingulate gyrus and medial prefrontal cortex, extending to the *precuneus* and the *right dorsolateral prefrontal cortex*.

## The executive control network and symptomati improvement in attention-deficit/hyperactivity disorder

Winke Francx<sup>a,b,\*</sup>, Marianne Oldehinkel<sup>a,b</sup>, Jaap Oosterlaan<sup>c</sup>, Dirk Heslenfeld<sup>c</sup>, Catharina A. Hartman<sup>d</sup>, Pieter J. Hoekstra<sup>d</sup>, Barbara Franke<sup>g,h</sup>, Christian F. Beckmann<sup>a,b,e</sup>, Jan K. Buitelaar<sup>a,b,f,1</sup>, Maarten Mennes<sup>a,b,1</sup>

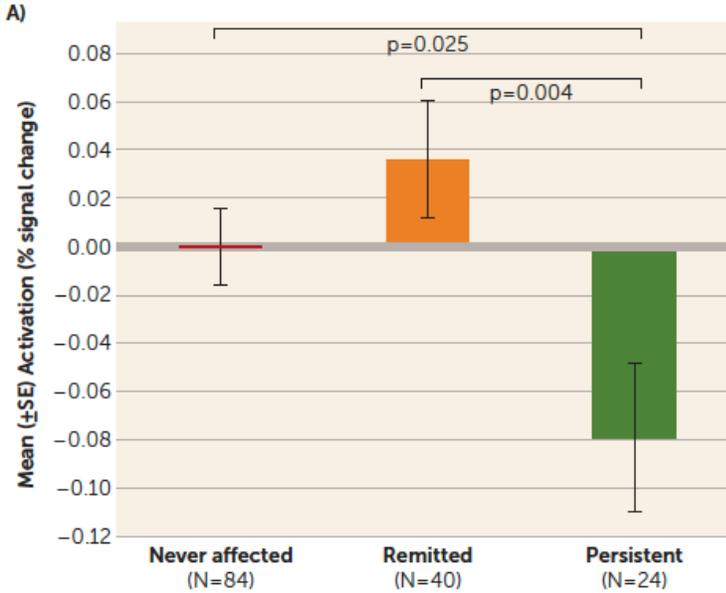


**Suppl fig 5.** Participants with *remitting* ADHD showed significantly higher RSFC executive control network than controls. There were no significant differences between persistent ADHD and controls.

Association between greater RSFC and executive control network due to change (decreasing) in hyperactive/impulsive scores.

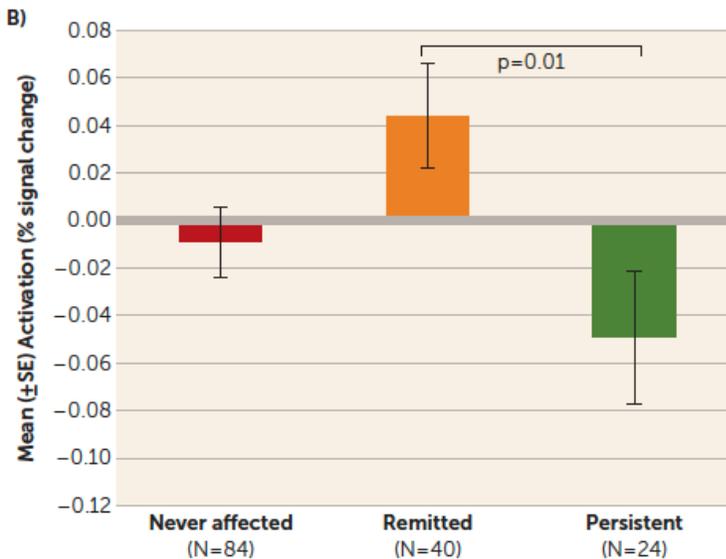
# Defining the Neural Substrate of the Adult Outcome of Childhood ADHD: A Multimodal Neuroimaging Study of Response Inhibition

Eszter Szekely, Ph.D., Gustavo P. Sudre, Ph.D., Wendy Sharp, M.S.W., Ellen Leibenluft, M.D., Philip Shaw, B.M., B.Ch., Ph.D.



## MRI

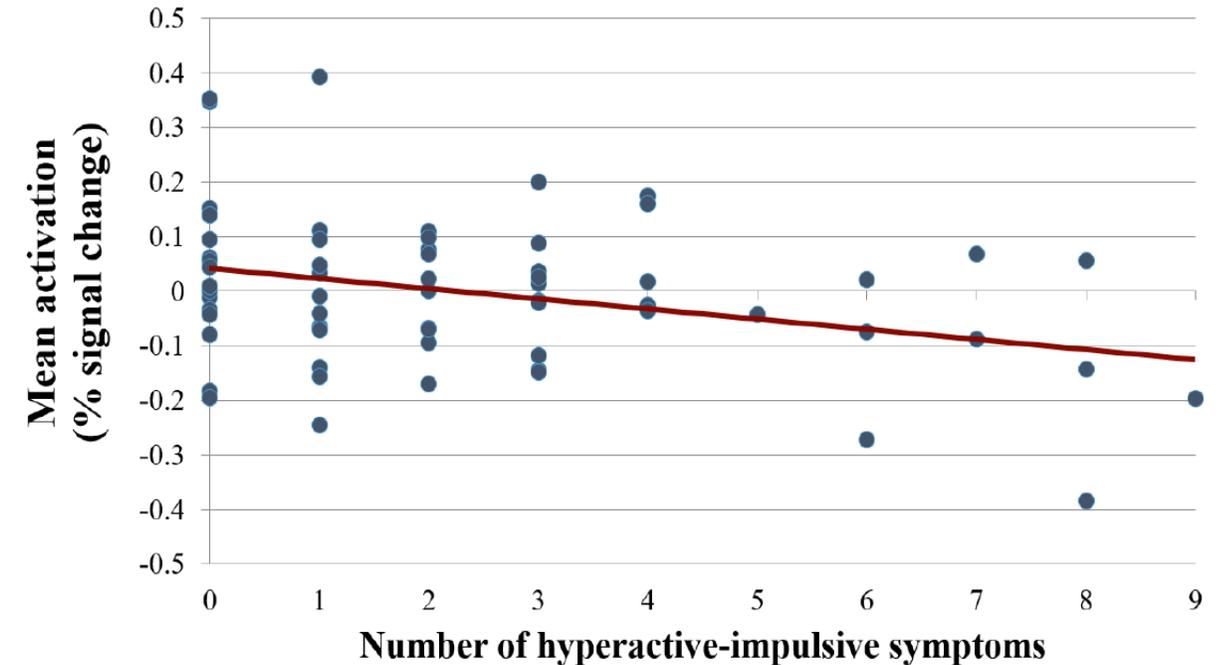
Left inferior frontal cortex activation for failed compared with successful inhibition



Right inferior frontal cortex activation for failed compared with successful inhibition

*AJP in Advance* (doi: 10.1176/appi.ajp.2017.16111313)

This paper suggests that prefrontally mediated cognitive processes are tied to the adult outcome of ADHD. Adult severity of *hyperactive-impulsive* symptoms rather than inattentive symptoms accounted for these findings.



*Persistence* of more hyperactive-impulsive symptoms in adulthood associated with lower left inferior frontal cortex activation during *failed* inhibition.

# Distinct topological properties of cue-evoked attention processing network in persisters and remitters of childhood ADHD

Yuyang Luo<sup>a</sup>, Kurt P. Schulz<sup>b</sup>, Tara L. Alvarez<sup>a</sup>, Jeffrey M. Halperin<sup>c</sup> and Xiaobo Li<sup>a,d,\*</sup>

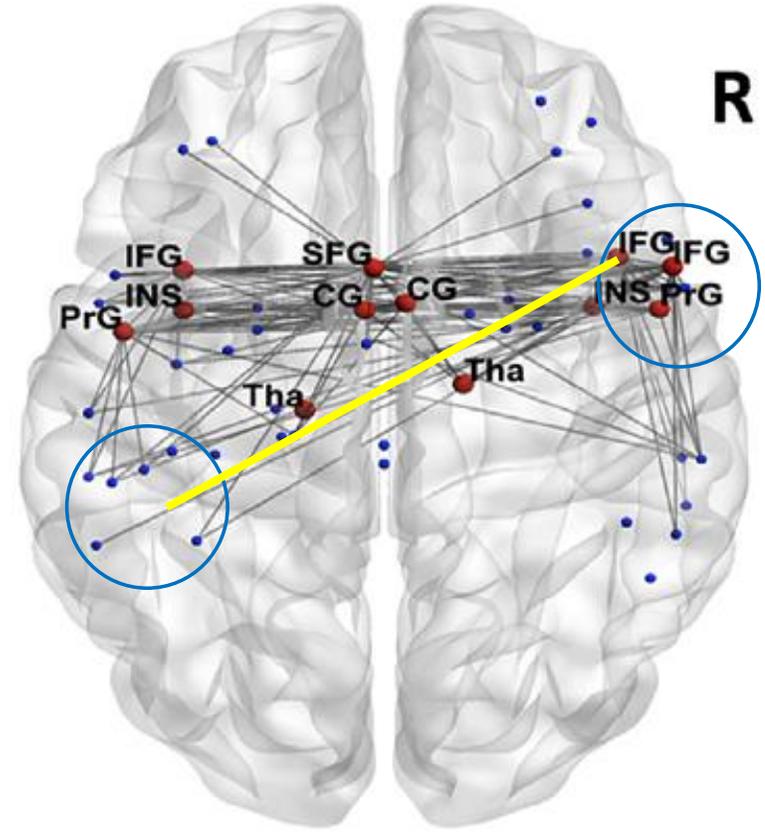
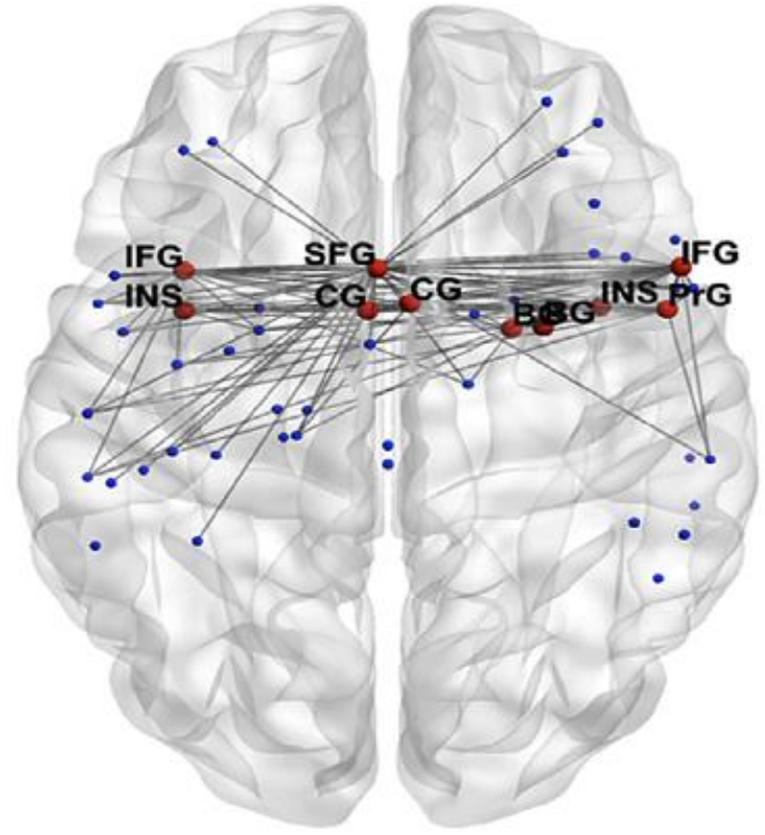
## ADHD-R

higher nodal efficiency of right IFG significantly associated with *lower* inattentive and hyperactive/impulsive symptom severity scores.

## ADHD-P

Higher nodal efficiency of right IFG significantly associated with *higher* inattentive and hyperactive/impulsive symptom severity scores.

Both remitters and persisters relative to controls lower nodal efficiency in *right inferior frontal gyrus* and reduced left side frontal-parietal functional interactions.



Note that the Inferior Frontal gyrus with the parietal lobe play a crucial role in the inattentive network. Functioning of the inattentive network may be crucial in recovery trajectories of ADHD, predictive studies required to test this hypothesis.

## Conclusions:

- **With increasing age, child ADHD wax and wane, with some expressing “remission” or subthreshold ADHD.**
- **Hyperactive-Impulsive symptoms may provide more information on clinical changes and be associated more with brain functioning measures than inattentive items.**
- **Comorbidities increase e.g. affective disorders and addictive behaviours.**
- **ADHD may emerge in “controls” during adulthood.**
- **Hyperactivity/Impulsivity symptoms may prove better predictor of adult functioning than inattention symptoms.**
- **Remission does *not* mean symptoms are absent or “normality” achieved.**
- **Many “Subthreshold” ADHD individuals exhibit Adult Psycho-social pathology.**