

ADHD

nei Servizi di

Neuropsichiatria

in Italia



La Comorbilità

nell'ADHD

Milano, 14 dicembre 2016
10.00-18.00

15 dicembre 2016
9.00-18.00 - AULA A

IRCCS
Istituto di Ricerche Farmacologiche Mario Negri
Via G. La Masa 19 - 20156 Milano



ADHD e disturbi dell'apprendimento

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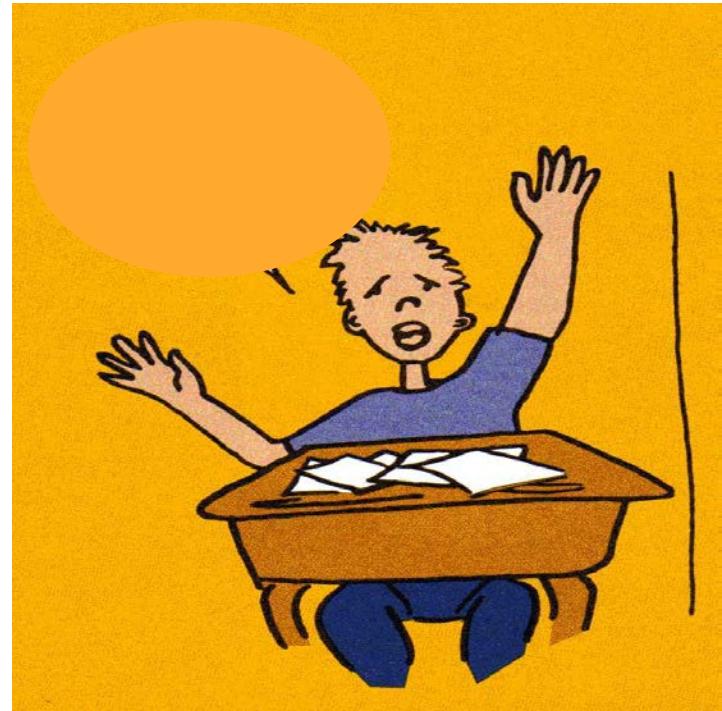
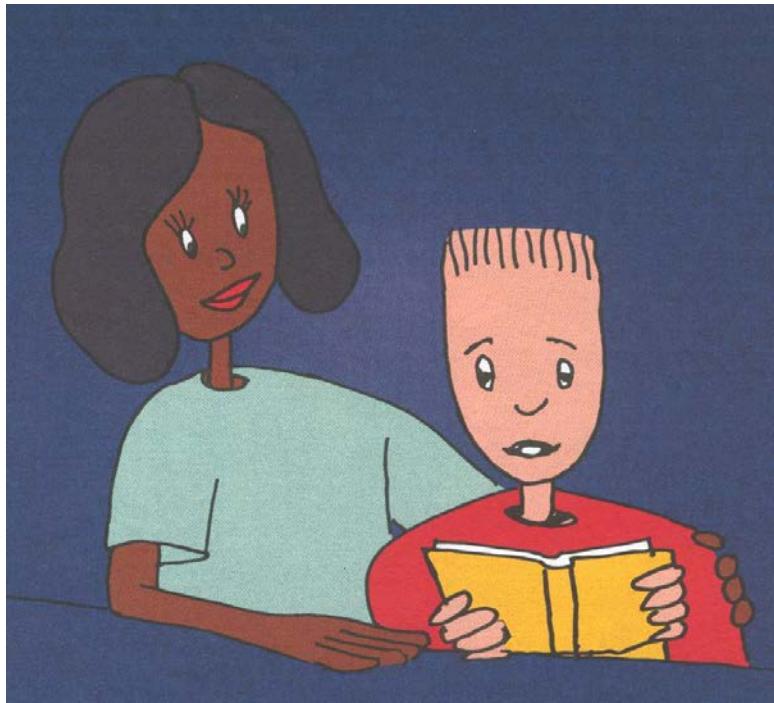
Attention deficit hyperactivity disorder and dyslexia: a history of overlap

Transtorno do déficit de atenção e hiperatividade e dislexia: a história de uma superposição

Alexandra Prufer de Queiroz Campos Araujo

1. Overlap is **more than just the simple case** of two common problems occurring by chance in the same person
2. Both developmental disorders arise from **multiple cognitive deficits**
3. **Common underlying features** may be contributing to the high co-morbidity between these disorders

ADHD: non tutte le difficoltà scolastiche sono dislessia...



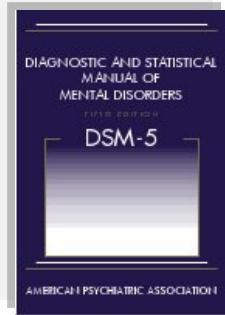
**Difficoltà
scolastiche**



ADHD

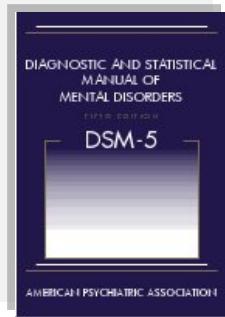
Attention-deficit/hyperactivity disorder

A persistent pattern of inattention or hyperactivity/impulsivity that interferes with **functioning** or development...



(DSM 5-APA, 2013)

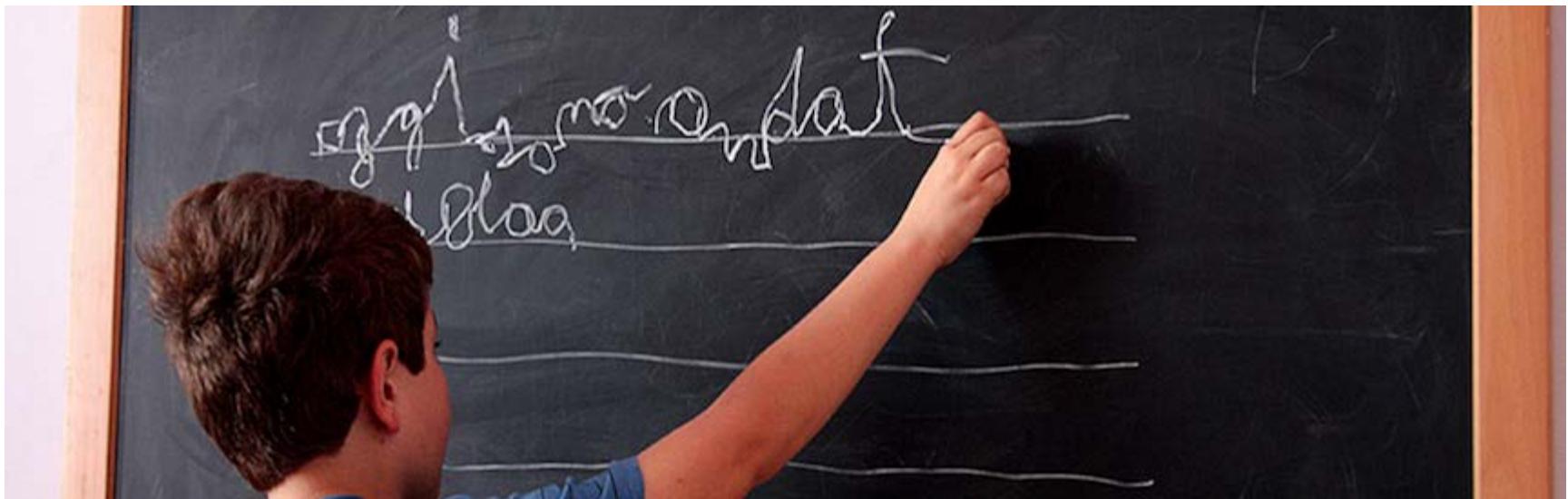
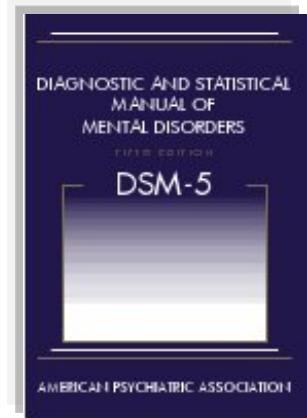
Associated features supporting diagnosis (DSM 5)



- Mild delays in language, motor or social development are not specific but often co-occur
- Low frustration tolerance, irritability, or mood lability
- Even in the absence of specific learning disorder, academic or work performance is often impaired**
- Inattentive behaviour is associated with various underlying cognitive processes (attention, EF or memory)

I problemi scolastici di un bambino con ADHD non sono necessariamente sottese da difficoltà specifiche ma possono riflettere....

....difficulties in performing those skills



The school career of children with HKD is notably impaired

significant performance impairments for

Reading (d=0.73)

Arithmetic (d=0.67)

Spelling (d=0.55)



**high rate of
school dropouts
(10–12%)**

School career, support measures and disciplinary measures, and the costs of measures in hyperkinetic disorder

School career of children with HKD (e2)	Frequency and duration of school measures in HKD (10)	Frequency of disciplinary incidents across grades involving children with HKD (10)	Estimated cost of a school disciplinary act (9, 10)
Lower school leaving level	0 years: 47.6%	5.8% of children with HKD once a week (0.0% of controls)	Additional annual costs of attending a different school (\$ 4181)
Grade retention (e3)	1–3 years: 18%	29.6% of children with HKD once a month (2.5% of controls)	For repeating a year (\$ 222)
Suspension and expulsion from school	4–6 years: 12.2%	45.5% of children with HKD once a quarter (7.9% of controls)	For disciplinary measures (\$ 604)
Absenteeism/truancy	>7 years 22.2%	19.1% of children with HKD less than once a quarter (89.6% of controls)	Additional annual costs incurred to the school system in the USA by HKD \$ 13.4 billion
School drop-out			£ 4155.03 per year school-related costs (compared with total costs from healthcare expenditure of £ 5492.63) incur 75% of the total cost of HKD (9)

(School measures= provvedimenti di supporto)

Schulte-Körne G: Mental health problems in a school setting in children and adolescents. Dtsch Arztebl Int 2016; 113: 183–90.

- Punteggi bassi sui test scolastici standardizzati sono molto frequenti nei pazienti con ADHD (Tannock, 2002)

Il clinico deve determinare se l'impairment accademico è dovuto all'ADHD o se esiste un vero e proprio DSA



Scottish Intercollegiate Guidelines Network (**SIGN**), 2009

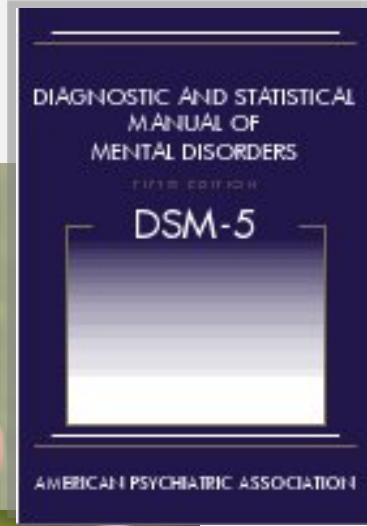
Practice Parameter for the Assessment and Treatment of Children and Adolescents With ADHD,
(AACAP), 2007

Prima di procedere con la valutazione si potrebbe considerare che è meno probabile che ci sia un DSA (comorbidità) se:

- **il bambino migliora molto con una supervisione delle attività scolastiche in rapporto 1:1**

- **le abilità scolastiche migliorano rapidamente (1-2 mesi) dopo l'avvio della terapia per l'ADHD**

Specific Learning Disorders



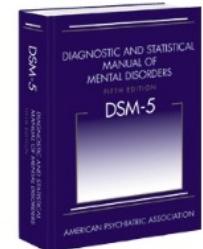
315.00 (F81.0) with impairment in reading

315.2 (F81.81) with impairment in written expression

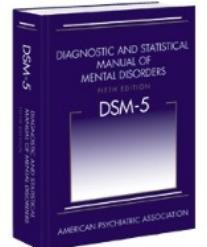
315.1 (F81.2) with impairment in mathematics

Specific learning disorder

Children with specific learning disorder may appear inattentive because of frustration, lack of interest, or limited ability...



DSM-5
2013

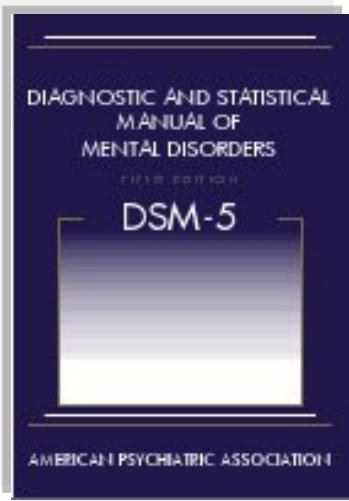


Specific learning disorder

.... l'attenzione di soggetti con disturbi specifici di apprendimento che non hanno l'ADHD...

...non è compromessa fuori dal setting di apprendimento





However, the co-occurrence of SLD and ADHD is more frequent than expected by chance



If criteria for both disorders are met, both diagnoses can be given

Cosa non c'è sul DSM 5 ?

ADHD

impairments in 2 symptom domains, **distinct but highly related**

- inattention
- hyperactivity/impulsivity

More recently

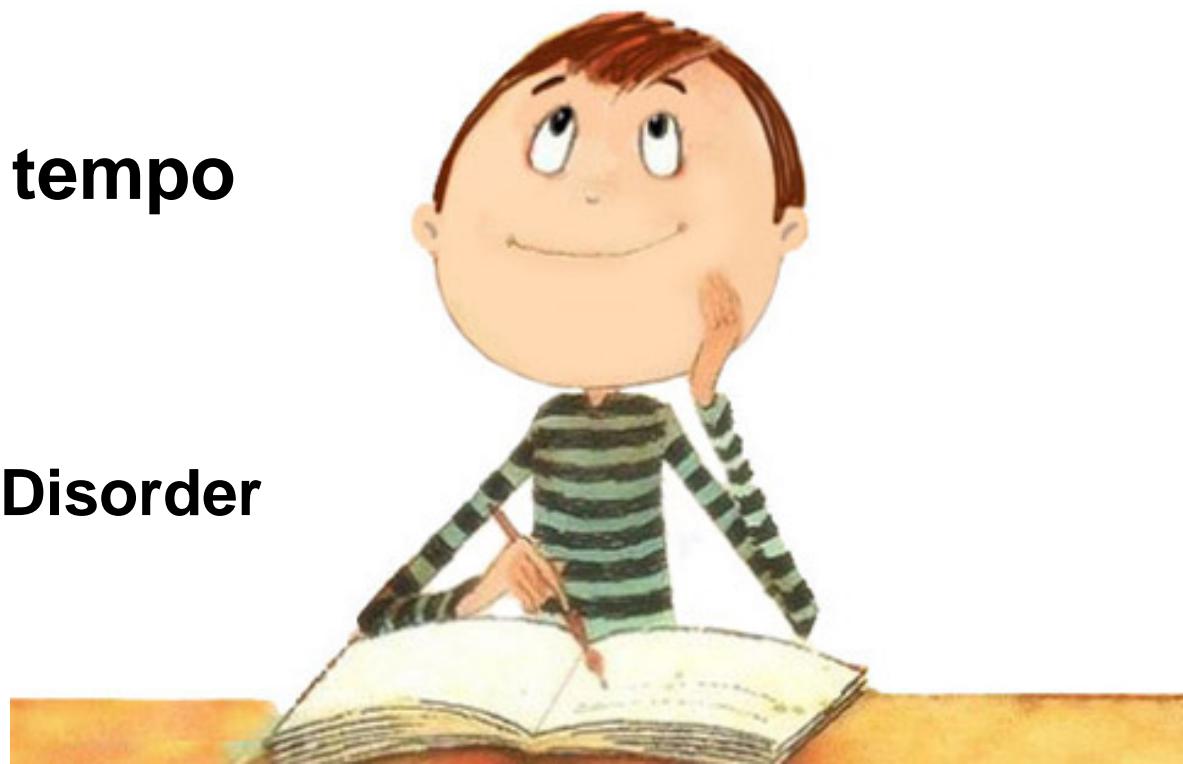
... an additional **symptom domain** has been associated with ADHD

(Penny et al., 2009)

sluggish cognitive tempo (SCT)

Or...

Concentration Deficit Disorder



Sluggish Cognitive Tempo

is an impairment of attention in hypoactive appearing individuals, which first presents in childhood

Barkley, R. A. (2013). Journal of Clinical Child and Adolescent Psychology, 42, 161-173.

Cognitive dimension

- Daydreaming
- Sleepy
- Staring
- Spaciness
- Mental fogginess
- Confusion
- low motivation

Motor dimension

- Slow movement
- Hypoactivity
- Lethargy
- Passivity/lacking initiative



SCT is **positively** correlated with the symptom domain of **inattention**

Willcutt et al., 2012



SCT may be **negatively** correlated with **hyperactivity/impulsivity**

Lee et al., 2014; Penny et al., 2009

SCT is associated with...

social impairment, social withdrawal.

low **academic performance**

risk for internalizing symptoms
especially **anxiety and depression**

Barkley, R. A. (2013). Distinguishing sluggish cognitive tempo from ADHD in children and adolescents: executive functioning, impairment, and comorbidity. *Journal of Clinical Child and Adolescent Psychology*, 42, 161-173.



Is *Sluggish Cognitive Tempo* a specific risk factor for academic impairment in ADHD ?



relation between Sluggish Cognitive Tempo (SCT) and academic functioning

52 ADHD adolescents (40 m, 12 f, mean age = 13.75)

The **parent-rated SCT *Slow* subscale** predicted

- overall academic functioning
- organizational skills impairment
- homework problems

The **teacher-rated SCT *Low Initiation/Persistence* subscale** predicted

- homework problems
- inadequate school grades

above and beyond

- ADHD symptoms
- intelligence
- academic achievement
- family income

Joshua M. Langberg, Stephen P. BeckerMelissa R. Dvorsky The Association Between Sluggish Cognitive Tempo and Academic Functioning in Youth with ADHD, Journal of Abnormal Child Psychology January 2014, Volume 42, Issue 1, pp 91–103

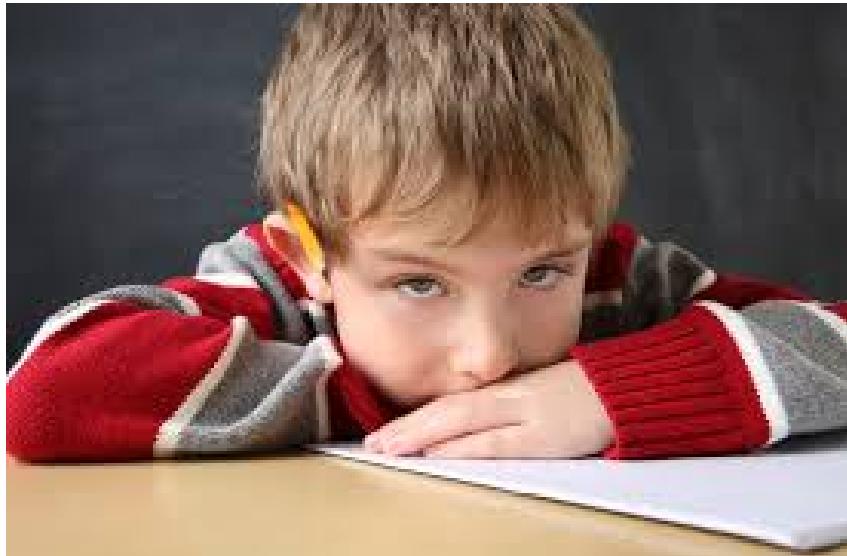
clinic-referred sample of youth (N = 209; 23 % female) aged 6 to 17 years

3 different groups

ADHD Combined Type (n = 80)

ADHD-I with **low SCT** symptoms (n = 74)

ADHD-I with **high SCT** symptoms (n = 55)



- **elevated withdrawal**
- **low leadership**
- **low peer-directed relational**
- **overt aggression**
- **more homework problems**

Marshall, et al, J Social and Academic Impairment in Youth with ADHD, Predominately Inattentive Type and Sluggish Cognitive Tempo. Journal of Abnormal Child Psychology January 2014, Volume 42, Issue 1, pp 77–90

Tamm L, Garner AA et al, Slow sluggish cognitive tempo symptoms are associated with poorer academic performance in children with ADHD. Psychiatry Res. 2016 Aug 30;242:251-9.

252 ADHD children (ages 6-12, 67% boys)

Parent-rated SCT *Slow* predicted

- poorer reading and spelling but not math achievement
- greater academic impairment across all domains



Teacher-rated SCT *Slow* predicted

- poorer spelling and math but not reading achievement
- greater impairment in writing only

Parent and teacher SCT *Sleepy and Daydreamy* ratings were not
significant predictors of academic performance

SCT *Slow* appears to be precisely related to academic problems in ADHD

Krause MB

Pay Attention!: Sluggish Multisensory Attentional Shifting as a Core Deficit in Developmental Dyslexia.

Dyslexia. 2015 Nov;21(4):285-303.

Review

Amodal sluggish attentional shifting (SAS)

Lallier M, Tainturier MJ, Dering B, Donnadieu S, Valdois S, Thierry G. Behavioral and ERP evidence for amodal sluggish attentional shifting in developmental dyslexia. Neuropsychologia. 2010 Dec;48(14):4125-35.

SAS theory, (Hari & Renvall, 2001)

when dyslexics deal with rapid stimulus sequences, their automatic attention system **cannot disengage fast enough** from one item to the next one, yielding slow and degraded processing



atypical perception of rapid stimulus sequences both sub-lexical auditory-phonological (e.g., syllables and/or phonemes) and visual-orthographic (e.g., syllables and/or grapheme) representations

non-linguistic deficits in dyslexia

inefficient multi-sensory processing of perceptual stimuli



low ability to detect relevant stimuli when encountering signal interference induced by spatially or temporally close noise



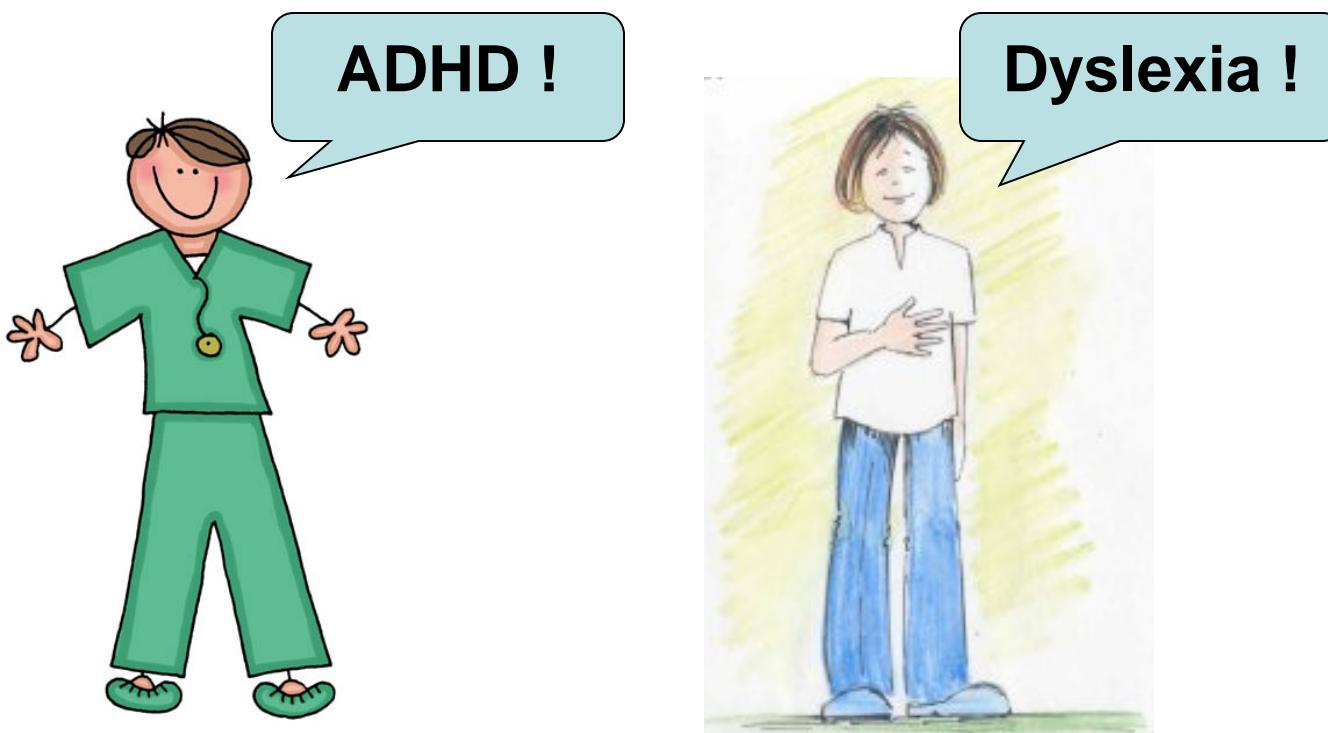
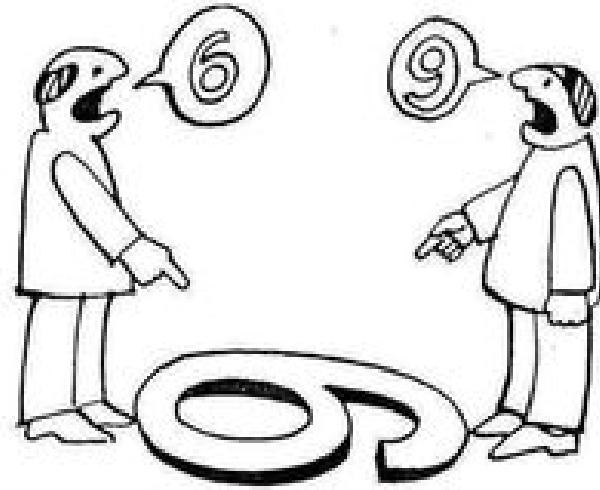
slower time course of focused multimodal attention (FMA) in children with dyslexia

Ruffino, M., Trussardi, A.N., Gori, S., Finzi, A., Giovagnoli, S., Menghini, D., et al. (2010). Attentional engagement deficits in dyslexic children. *Neuropsychologia* 48, 3793–3801.

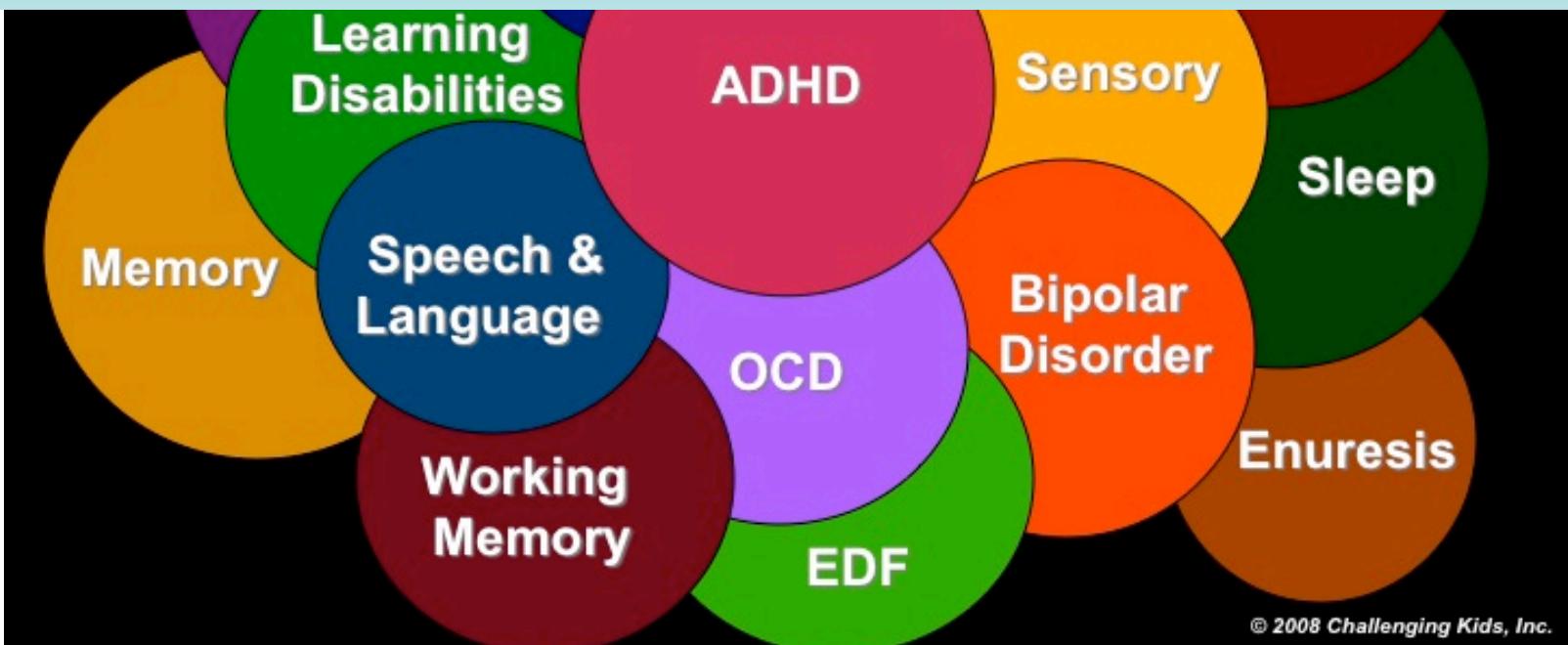
Facoetti A, Trussardi AN, Ruffino M, Lorusso ML, Cattaneo C, Galli R, Molteni M, Zorzi , M Multisensory spatial attention deficits are predictive of phonological decoding skills in developmental dyslexia. *J Cogn Neurosci*. 2010 May;22(5):1011-25.

multisensory "**sluggish attention shifting**" related to a temporo-parietal dysfunction selectively impairs the sublexical mechanisms critical for reading development.

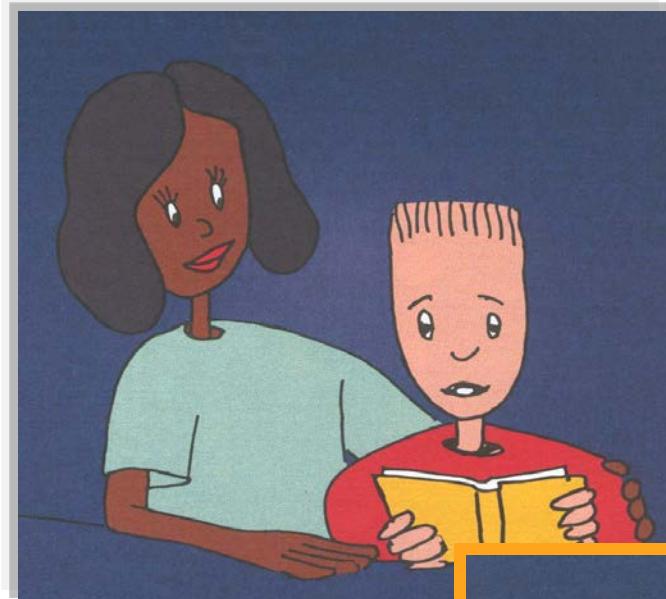
Ruffino M, Gori S, Boccardi D, Molteni M and Facoetti A, Spatial and temporal attention in developmental dyslexia **Frontiers in Human Neuroscience** , May2014|Volume8|Article331



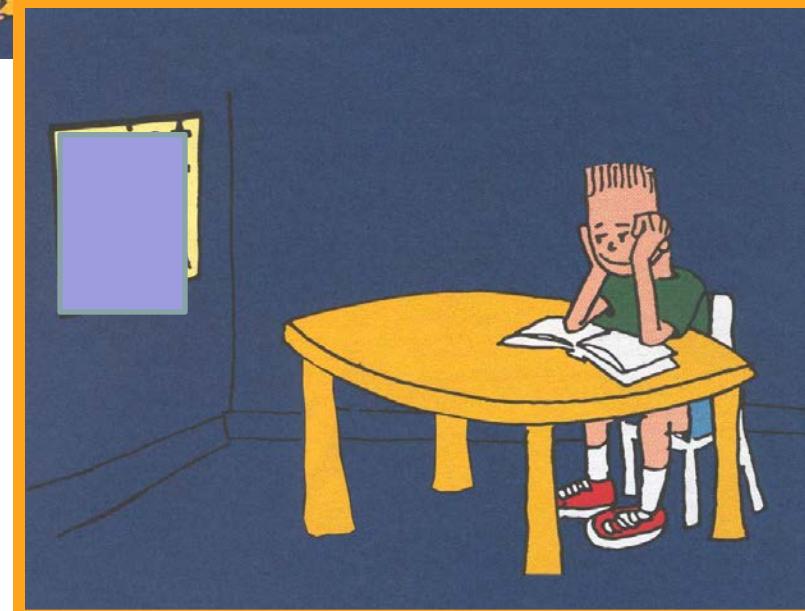
Comorbidity ?



DYS



ADHD



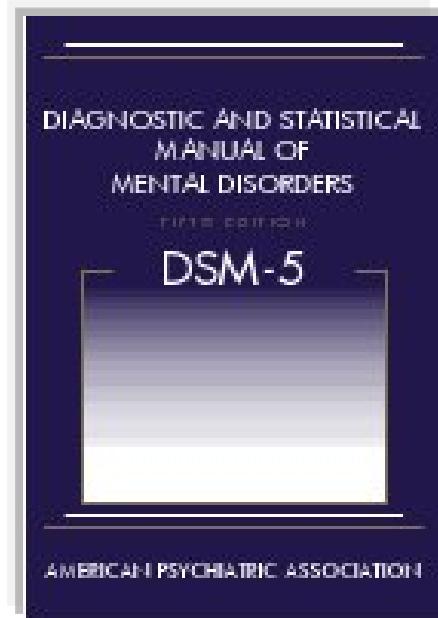
ADHD + DYS

Disturbi del neurosviluppo

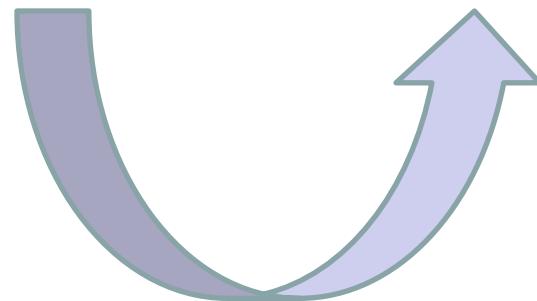
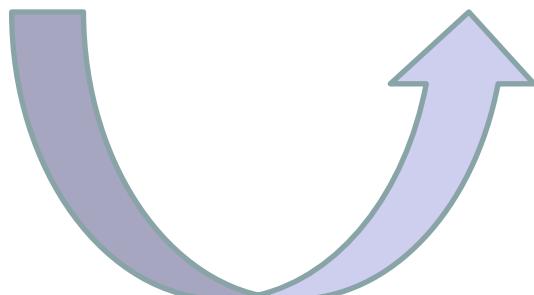


Il presupposto che ha portato alla creazione della macro-area è che questi disturbi poggiano tutti su atipie morfo-funzionali del neurosviluppo, frequentemente co-occorrono e condividono profili genetici ed endofenotipici

beyond



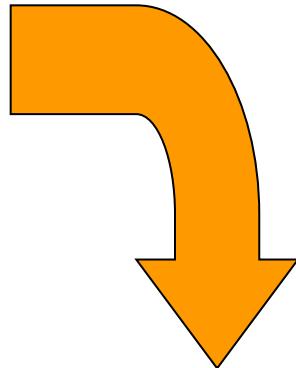
before



Subgroup model

(Shao, 2003; Silverman, 2002)

- **Categorie discrete**
- **meccanismi etiologici diversi**
- **contributi genetici distinti**
- **Parziale overlapping**



Severity model

(Costantino , 2004; Ring, 2008)

- **spettro**
- **gradiente di severità**
- **Continuum di tratti nella popolazione generale**
- **Sintomi sottosoglia nei familiari (quantitative traits)**

Evidence exists for 5 domains of development

(each related to different brain systems):

Silliman and Berninger, Top Lang Disord 2011;31:6-23.

- (a) cognition and memory**
- (b) receptive and expressive language**
- (c) sensory and motor systems**
- (d) social and emotional systems**
- (e) attention and executive function systems**



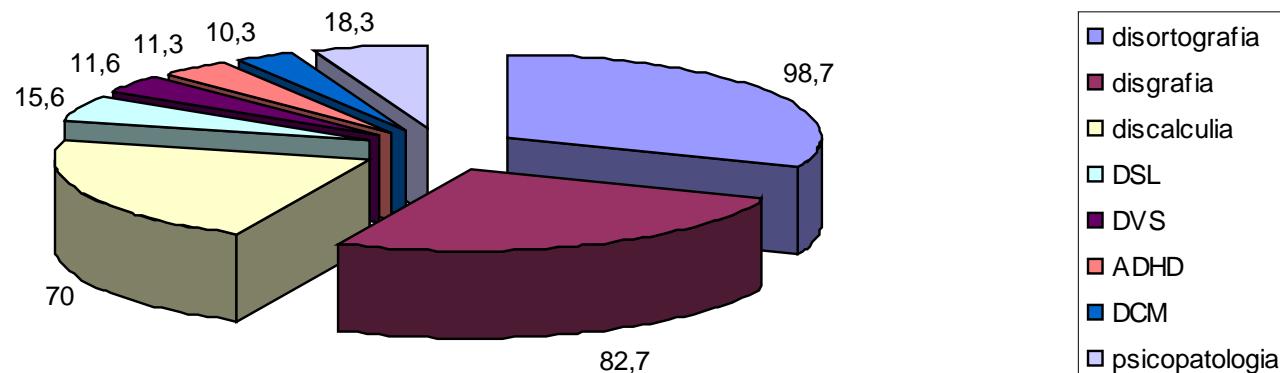
Individuals who fall outside the normal range in one or more but not all developmental domains have specific developmental disabilities (SDDs) those who fall outside the normal range in all developmental domains have pervasive developmental disabilities (PDDs)

Le comorbidità nella dislessia: studio di un campione di soggetti in età evolutiva con disturbo di lettura

Antonella Gagliano, Eva Germanò, Tiziana Calarese, Angela Magazù,
Rosa Grosso, Rosa Maria Siracusano e Clemente Cedro

Vol. 4, n. 1, gennaio 2007 (pp. 27-45)

DISLESSIA



Quattro fattori n = 301

Fattori o Clusters (C)	I C	II C	III C	IV C	
% della varianza totale spiegata	17,5	16,0	13,1	11,7	
Numero disturbi	0,729	0,630			
ADHD	0,731				
Psicopatologia	0,657				
Disturbo Visuo-Spaziale		0,792			
Disturbo Coordinazione Motoria		0,627			
Disgrafia			0,763		
Discalculia			0,592		
Disortografia			0,545	0,468	
Disturbo Linguaggio	0,307			0,662	
Età diagnosi	0,339			-0,585	

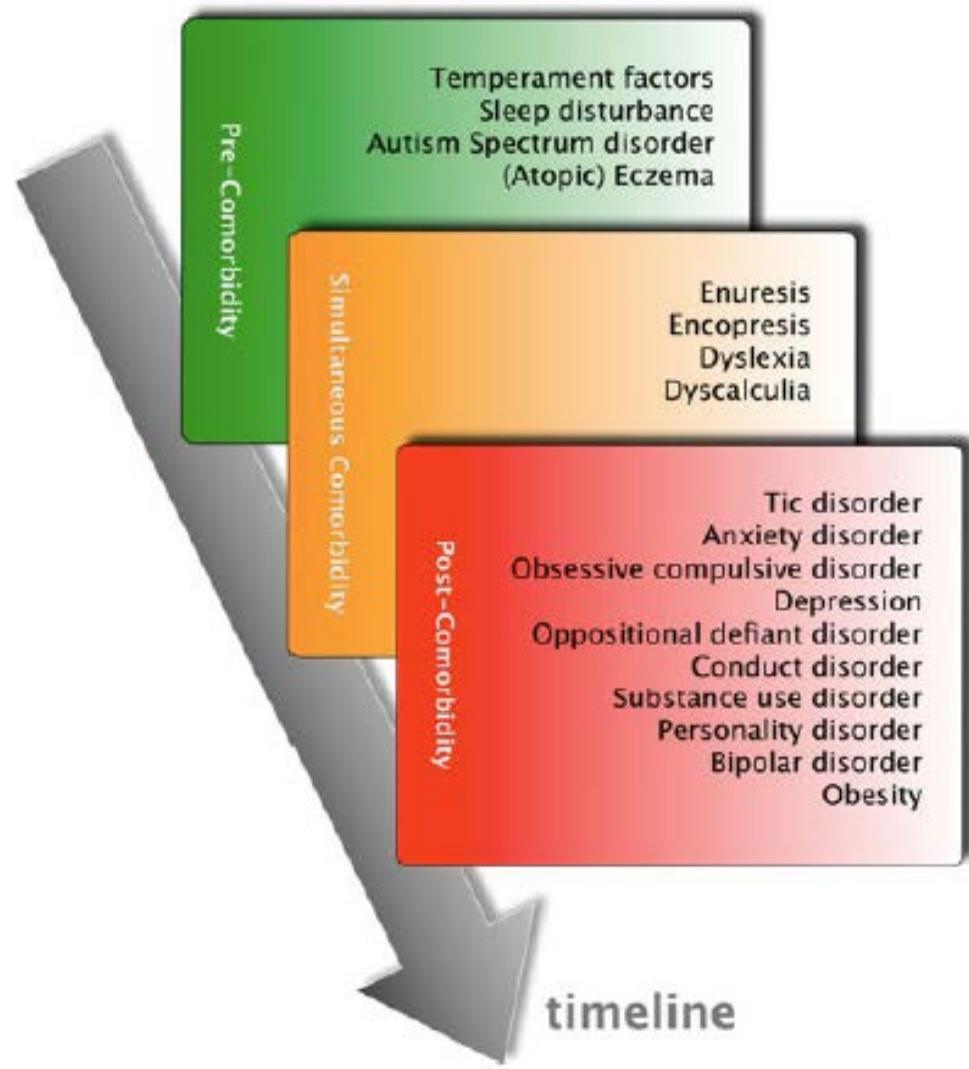
I C Linguistico-Esecutivo

II C Non-verbale o Visuo-Prassico

III C Capacità scolastiche

IV C Verbale

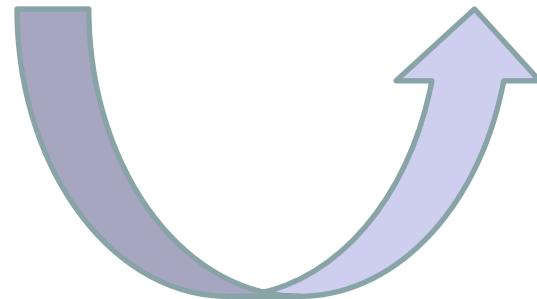
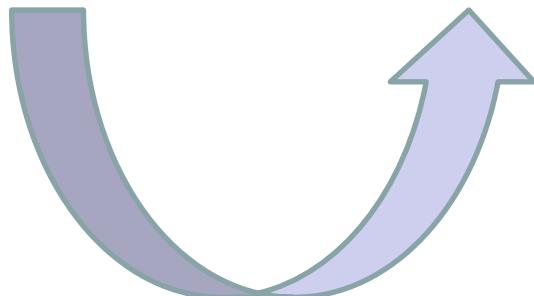
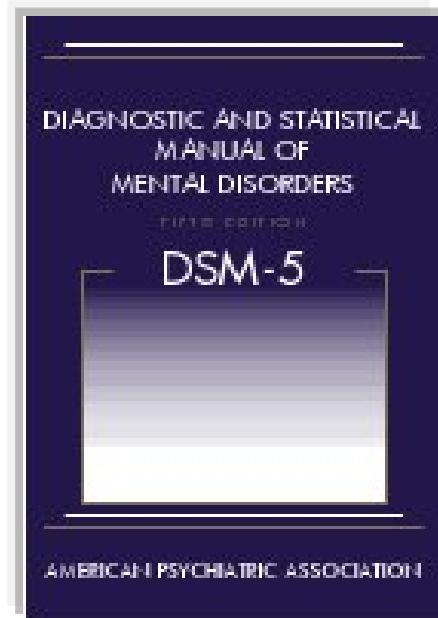
Developmental comorbidity



Taurine et al, Atten Def Hyp Disord, 2010, Review Article

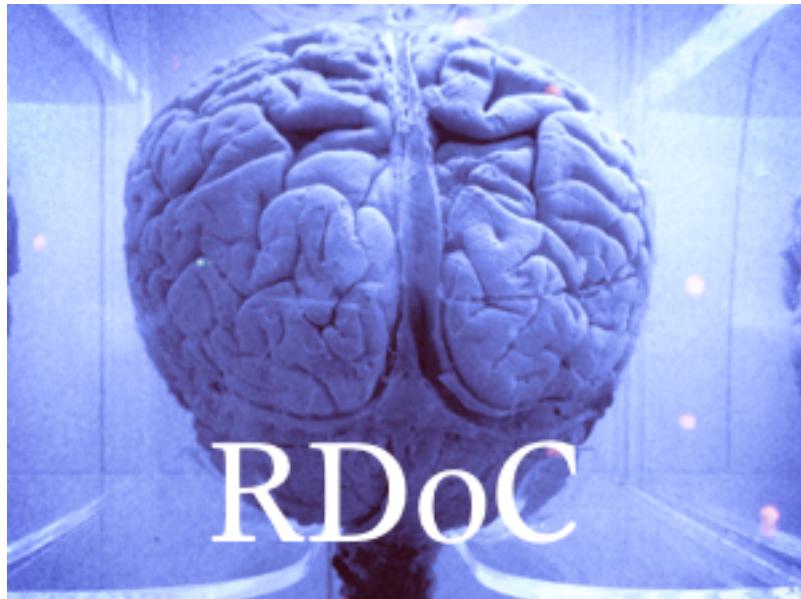
beyond

before





RDoC Research domain criteria

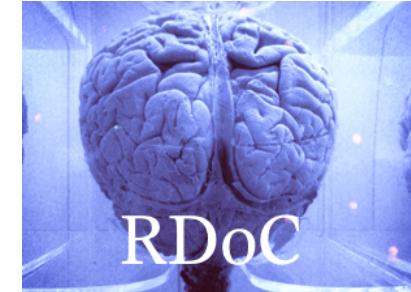


RDoC strategy has recently been adopted by the National Institute of Mental Health

(e.g., Casey et al., 2014; Insel et al., 2010)

<http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>

Rather than focusing on diagnostic categories...



...the RDoC approach uses **neurophysiological and etiologically-informative methods** to identify dimensions...

... such as attentional functioning that may cut across multiple diagnostic categories.

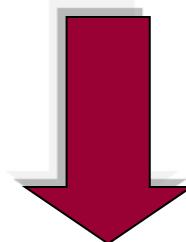
RDoC is a **dimensional system**

(es. reflecting circuit-level measurements, behavioral activity, etc.)
spanning the range from normal to abnormal and defining different levels of impairment (e.g., mild, moderate, and severe)

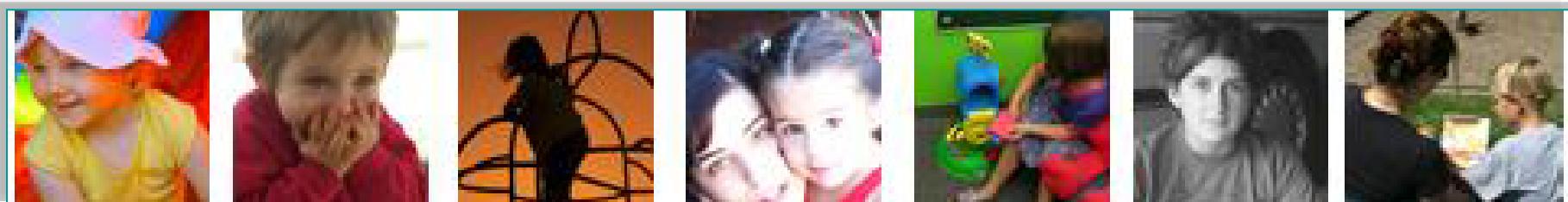
neuropsychological heterogeneity

(Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005)

**independent effects of different
neuropsychological functions**



different neuropsychological subtypes



Sjöwall, et al, Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits, Journal of Child Psychology and Psychiatry 54:6 (2013), pp 619–627

Il gruppo dei bambini con ADHD aveva nel complesso una deficit di executive functioning e RT variability

Ma se il gruppo veniva diviso in impaired o unimpaired...

Solo 1/3 aveva un impairment nelle EF



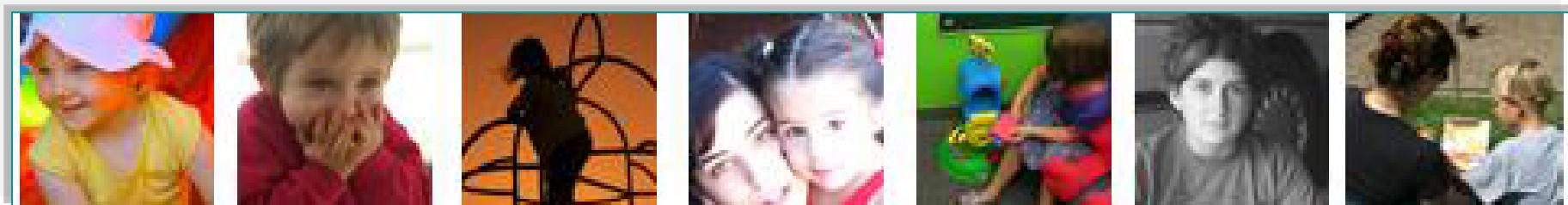
Solo metà aveva unimpairment nell' RT variability



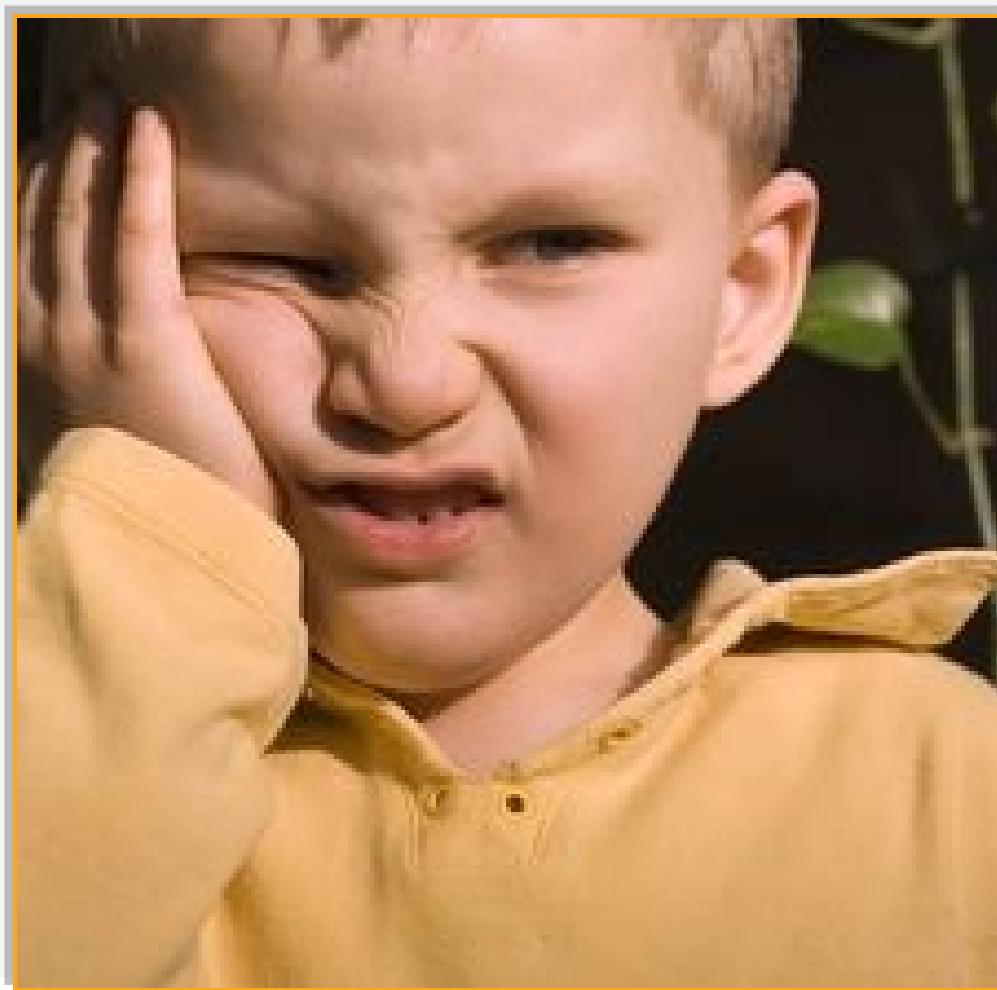
different neuropsychological subtypes ...



...or different neuropsychological PRESENTATION !



Fenotipo ADHD e Dislessia... ...una diversa presentazione



Comorbidity of ADHD and Dyslexia

Eva Germanò and Antonella Gagliano

Division of Child Neurology and Psychiatry

*Pediatric Department of Policlinico G. Martino, University of Messina
Gazzi-Messina, Italy*

Paolo Curatolo

*Pediatric Neurology Unit, Tor Vergata, Department of Neuroscience
University of Rome, Roma, Italy*





Quanto frequentemente si associano?

Quanto frequentemente si associano?

Epidemiological Data

Author	Cases	RD in ADHD	ADHD in RD
August & Garfinkel, 1990	115 boys ADHD	39%	
Dykman & Ackerman, 1991	182 ADHD	45%	
Semrud-Clikeman et al., 1992	60 ADHD	38%	
Ginger et al., 1992	140 RD		39%
Willcutt & Pennington, 2000	209 RD		42% in males 18% in females
Mayes et al., 2000	86 ADHD	26%	
Loo et al., 2004	407 ADHD	18-23%	
Gayán et al., 2005	505 RD		36%
Wisniewska et al., 2007	28 ADHD	18%	

ADHD = attention deficit hyperactivity disorder; RD = reading disorder.

LISApplus + GINIplus studies

(a germanic population-based birth cohort studies on more than 3.000 subjects for each study)

8.1% with ADHD symptoms



25% with ***also*** reading/spelling difficulties

risk for reading/spelling disorder compared to children without ADHD

(Odds Ratio (OR) = **2.80**, p = 6.59610213)



Cosa condividono in termini genetici ?

forte componente ereditaria tanto per la dislessia che per l'ADHD

(Gayan & Olson, 2001; Willcutt, Pennington & DeFries, 2000c; Friedman et al., 2003; Dell'homme et al., 2007)

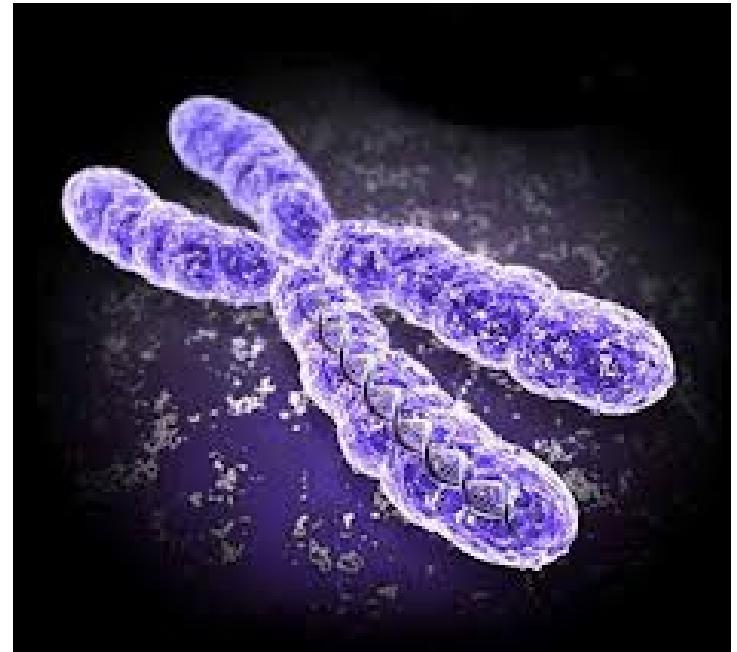
Coefficiente di ereditabilità

ADHD 70-80%

(Faraone et al., 2005; Biederman, 2005)

Dislessia 40-60%

(Gayan et al., 1999; Ziegler et al., 2005)



Loci genetici di rischio comuni a Dislessia e ADHD

(identificati con studi di linkage : LOD scores >1)

Overview of Risk Loci Shared by RD and ADHD Identified in Linkage Studies

<i>Chromosome</i>	<i>RD</i>	<i>ADHD</i>
1p36	DYX8 (de Kovel et al., 2007)	Zhou et al., 2008
2q22-35	Raskind et al., 2005	Romanos et al., 2008
3p12-q13	DYX5 (Nopola-Hemmi et al., 2001)	Bakker et al., 2003
4q12-13	Fisher et al., 2002	Arcos-Burgos et al., 2004
6p21-22	DYX2 (Grigorenko et al., 2003)	Willcutt et al., 2002
6q 12-14	DYX4 (Petryshen et al., 2001)	Ogdie et al., 2003
13q22-33	Fisher et al., 2002a; Igo et al., 2006	Bakker et al., 2003
15q15-21	DYX1 (Chapman et al., 2004)	Bakker et al., 2003

Approximately LOD scores >1. ADHD = attention deficit hyperactivity disorder; RD = reading disorder.

shared genetic influences are responsible

(Gayán et al., 2005; Rosenberg et al., 2012; Stevenson et al., 2005; Willcutt et al., 2010; Willcutt, Pennington, et al., 2007; Willcutt et al., 2002).

[Willcutt EG](#), [Pennington BF](#), [Olson RK](#), [Defries JC](#). *Understanding comorbidity: A twin study of reading disability and attention-deficit/hyperactivity disorder.* Am J Med Genet B Neuropsychiatr Genet 2007; Apr 17

componente ereditaria più forte per i soggetti ADHD/Dys che per quelli con uno dei due disturbi isolati

International Longitudinal Twin Study of Early Reading Development

(ILTSERD; Byrne et al., 2002)

from kindergarten through grade 2
(989 twin pairs ; 493 MZ and 496 DZ pairs)



**stronger association between
reading and inattention
than between reading and hyperactivity/impulsivity**

Ebejer JL, Coventry WL, Byrne B, Willcutt EG, Olson RK, Corley R, Samuelsson S. Genetic and environmental influences on inattention, hyperactivity-impulsivity, and reading: Kindergarten to grade 2. *Scientific Studies of Reading*. 2010; 14:293–316.

Greven CU, Rijsdijk FV, Asherson P, Plomin R. A longitudinal twin study on the association between ADHD symptoms and reading. Journal of Child Psychology and Psychiatry. 2012; 53(3):234–242.

7000 twin pairs (age 7–12 years)
Twins Early Development Study (**TEDS**)



Both reading performance and ADHD symptoms are highly heritable

$a^2 = .68$ (ADHD) and $.71$ (Dys) in middle childhood and $.54$ (ADHD) and $.67$ (Dys) in early adolescence

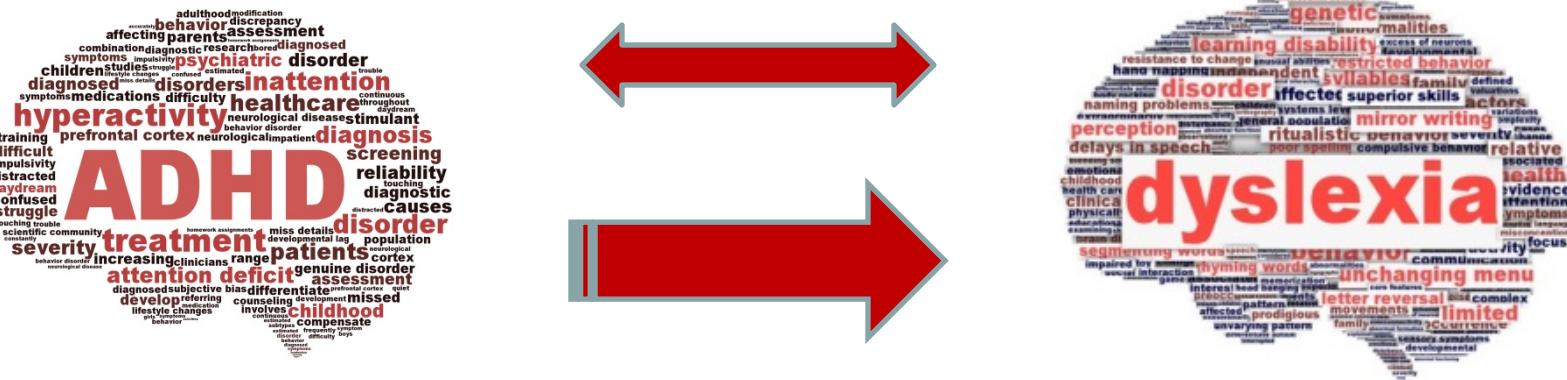
their association at each age is primarily (68%) due to genetic influences



Inattention predicted reading performance significantly better than hyperactivity/impulsivity

Greven CU, Rijsdijk FV, Asherson P, Plomin R. A longitudinal twin study on the association between ADHD symptoms and reading. Journal of Child Psychology and Psychiatry. 2012; 53(3):234–242.

ADHD symptoms and reading performance significantly predicted each other



however

ADHD predicted reading performance to a significantly greater degree than reading performance predicted ADHD

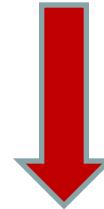
the first longitudinal twin study of RD and ADHD

94 twin pairs

at least one member of the pair met criteria for proband status for RD at initial assessment

60% of the proband deficit at initial assessment *was due* to genetic influence

the reading deficits at follow-up *were due* to the same genetic influences



**genetic influences on
reading difficulties
are highly stable**

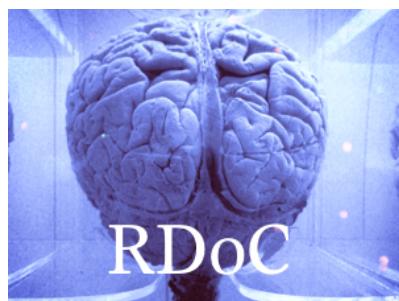
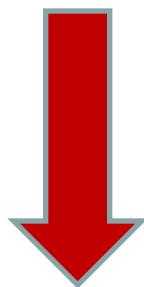
Inattention

Common genetic influences accounted for **60% of contemporaneous** and **over 60% of the longitudinal comorbidity**

hyperactivity/impulsivity

common genetic influences accounted for **20% of the contemporaneous** and about **10% of the longitudinal comorbidity**

L'influenza genetica è più forte nell'associazione tra Dislessia e fenotipo Inattentivo



**the results support a dimensional models of RD and ADHD
... according to the trans-diagnostic RDoC approach**

Non solo geni....

Fattori di rischio ambientali

Prematurity or very low birth weight increases the risk for specific learning disorder, as does prenatal exposure to nicotine.



Acta Paediatr. 2012 Nov;101(11):The incidence of prematurity or low birth weight for gestational age among children with dyslexia.

Long-term effects of preterm birth on language and literacy at eight years

- Non c'è un ritardo cognitivo ma sottili difficoltà in specifiche abilità linguistiche (grammar, lexicon, phoneme synthesis and deletion of the first syllable)
- Difficoltà evidenti nella velocità della lettura e nell'accuratezza della scrittura



Traiettorie atipiche del neurosviluppo con effetti sulle competenze linguistiche e accademiche

The interruption of the fetal maturation, even when occurs at 32nd or 36th of the gestational week, can increase the risk to develop ADHD

Krain AL, Castellanos FX. Brain development and ADHD. Clin Psychol Rev 2006;26:433-44.

Lindström K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. Pediatrics 2011;127:858-65.



moderately preterm children (>32/<35 weeks) show attention and self-control disorders since preschool age though at a less severe level when compared with severely preterm cases

van Baar AL, Vermaas J, Knots E, et al. Functioning at school age of moderately preterm children born at 32 to 36 weeks' gestational age. Pediatrics 2009;124:251-7.

Kelly Cho, Jan C. Frijters, Heping Zhang, Laura L. Miller, and Jeffrey R. Gruen,

Prenatal exposure to nicotine and impaired reading performance,

J Pediatr. 2013 April ; 162(4): 713–718

Prenatal nicotine exposure is associated with increased risk of underperformance in specific reading skill outcomes after adjusting for potential confounders



	Prenatal nicotine exposure			
	None	Low	High	Overall
Mother's age at delivery *	29.7 (4.3)	28.0 (4.9)	27.4 (5.1)	29.4 (4.5)
Phonology	20.9 (9.2)	20.6 (8.8)	19.2 (9.3)	20.8 (9.1)
Total IQ *	107.4 (15.0)	104.4 (14.3)	99.9 (13.8)	106.7 (15.0)

* Indicates χ^2 p value < .05 from univariable analyses of each covariate and prenatal nicotine exposure outcome.

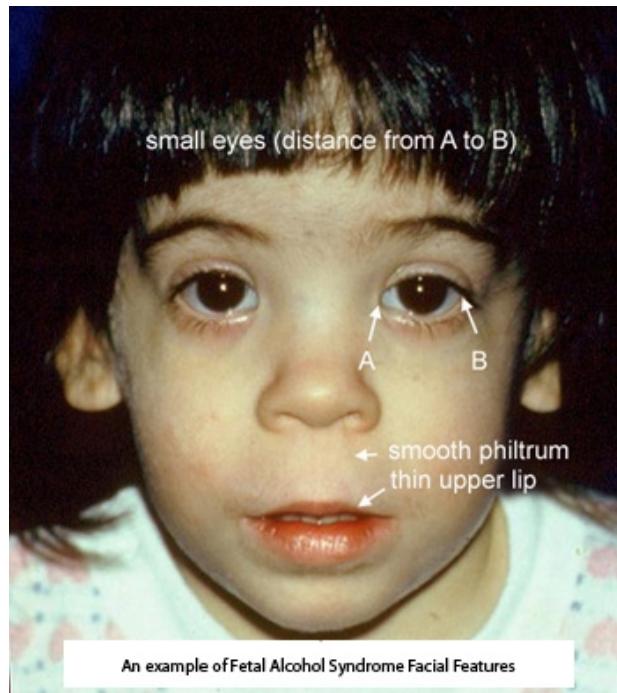
Is alcohol binge drinking in early and late pregnancy associated with behavioural and emotional development at age 7 years?

Niclasen et al. Eur Child Adolesc Psychiatry. 2014 Jan 5

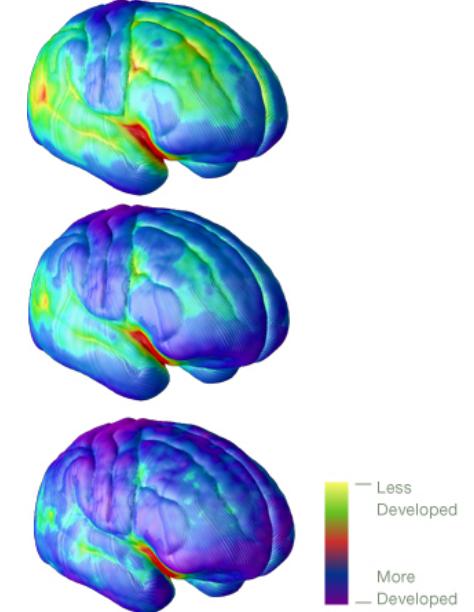
37,315 children, 7 y (being term-born from the Danish National Birth Cohort)

3 exposure groups in early, middle and late pregnancy

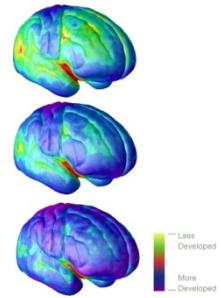
1. 'no binge' group
2. 'early bingers'
3. 'late bingers' (last part of pregnancy only)



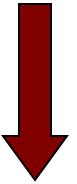
children exposed to binge drinking in early and late pregnancy had significantly higher mean externalizing scores than unexposed children



Cosa condividono in termini morfofunzionali ?



se si confrontano gli studi condotti su soggetti che hanno solo uno dei due disturbi....



Molte delle aree per le quali sono state evidenziate atipie morfologiche o funzionali nei singoli disturbi coincidono !

Functional/Structural Neuroimaging Alterations Shared in RD and ADHD

<i>Neuroimaging Alterations</i>	<i>RD</i>	<i>ADHD</i>
Lower cerebellar volume	Eckert et al., 2003; Kronbichler et al., 2008	Berquin et al., 1998; Mostofsky et al., 1998; Castellanos et al., 2002; Hill et al., 2003; Mackie et al., 2007
Dysfunctions in temporal regions	Temple et al., 2001; Shaywitz et al., 2002; Kronbichler et al., 2006; Hoeft et al., 2007	Smith et al., 2006; Rubia et al., 2007; Shafritz et al., 2004
Striatal dysfunction	Shafritz et al., 2004	Shafritz et al., 2004; Rubia et al., 2007
Asymmetry of hemisphere structures	Planum temporale: Dalby et al., 1998; Eckert and Leonard, 2000; Foster et al., 2000 Lobar asymmetries: Zadina et al., 2006	Caudate nucleus: Hynd et al., 1993; Pueyo et al., 2000; Schrimsher et al., 2002; Pineda et al., 2002; Uhlíkova et al., 2007 Putamen nucleus: Wellington et al., 2006 Globus pallidus: Uhlikova et al., 2007 Prefrontal cortical convolution: Li et al., 2007 Frontal lobe: Pueyo et al., 2000

ADHD = attention deficit hyperactivity disorder; RD = reading disorder.

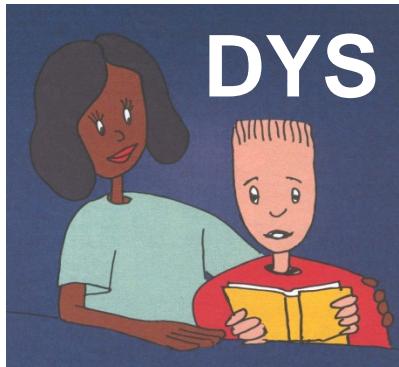
Cosa condividono in termini neuropsicologici ?



Neuropsychological Correlates and Models for RD + ADHD Comorbidity

<i>Authors</i>	<i>Comorbid Phenotype</i>	<i>Models and Hypothesis</i>
Pennington et al., 1993	Comorbid group had the symptoms of ADHD, but not the underlying executive deficit	Phenocopy hypothesis
Faraone et al., 1993	The cognitive profile of comorbid phenotype is consistent with the additive combination of the deficits of the RD-only and the ADHD-only phenotypes	Cross Assortment hypothesis
Purvis & Tannock, 1997; Willcutt et al., 2001	ADHD subjects are impaired on executive abilities, but not on phonological abilities; RD subjects exhibit phonological processing deficits, but not executive functions deficits; comorbid phenotype arises from an additive combination of all previous neuropsychological deficits	Double dissociation hypothesis
Rucklidge & Tannock, 2002	Comorbid group was slower with rapid naming and had slower reaction times. It is a specific subtype, more clinically impaired	Specific subtype hypothesis
Willcutt et al., 2005; Shanahan et al., 2006	Processing speed deficit is a shared cognitive deficit	Multiple deficit model/Common aetiology hypothesis
Bental & Tirosh, 2007	Comorbid group shows a more severe impairment in verbal WM and a unique deficit in rapid naming	Specific subtype hypothesis
Tiffin-Richards et al., 2008	Working memory is a shared cognitive deficit; phonological short-term memory deficits and central executive deficits coexist	Multiple deficit model/Common aetiology hypothesis
Felton et al., 1987; Semrud-Clikeman et al., 2000; Raberger & Wimmer, 2003; Chan et al., 2008	Slower performances in rapid automatized naming tasks (RAN) in RD and in comorbid phenotype but not in ADHD only phenotype	Double dissociation hypothesis

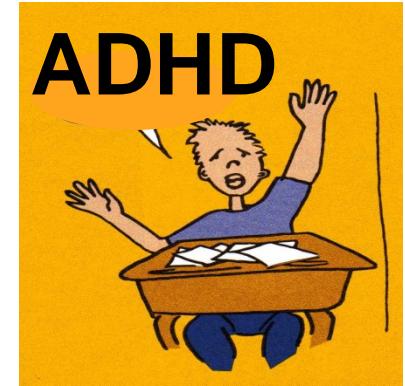
ADHD = attention deficit hyperactivity disorder; RD = reading disorder; WM = working memory.



+

Combinazione additiva dei “core deficits” di entrambi i disturbi

=



3 fenotipi indipendenti

1. Dys: phoneme awareness /verbal working memory deficit
2. ADHD: executive/inhibition deficit
3. comorbid phenotype: sum of the previous deficits

(Willcutt et al., 2001)

Ma...



**vengono trovati deficit neuropsicologici
comuni a Dys e ADHD**

(pienamente smentita l'ipotesi della doppia dissociazione)

executive function deficits in dyslexia

(Purvis & Tannock, 2000; Rucklidge & Tannock, 2002; Willcutt et al., 2001)



subtle verbal deficits in ADHD

(Martinussen & Tannock, 2006).

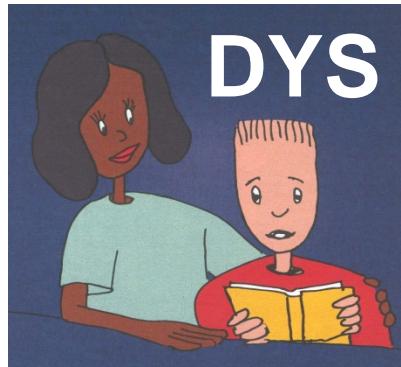


co-existence of phonological short-term memory deficits and central executive deficits

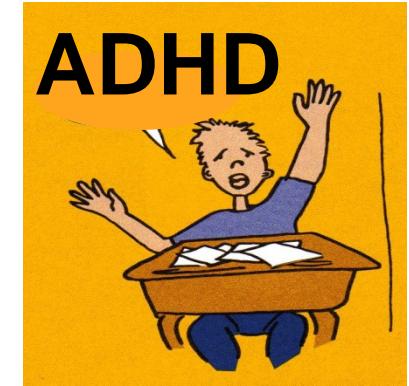
(Tiffin-Richards et al., 2008)



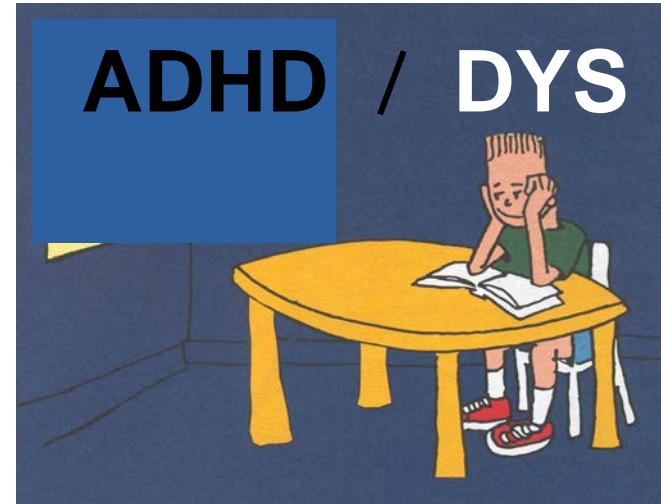
incomplete dissociation of executive and linguistic functions in dys and ADHD



3 different pathways



combinazioni
diverse di deficit
cognitivi...



alcuni condivisi
altri non
condivisi...

Shared deficits

Memoria di lavoro

..un altro importante denominatore comune



1. [Korkman M, Pesonen AE](#). *A comparison of neuropsychological test profiles of children with attention deficit-hyperactivity disorder and/or learning disorder*. J Learn Disabil 1994; 27: 383-92.
2. Shaywitz BA, Fletcher JM, et al, *Interrelationships between reading disability and attention deficit-hyperactivity disorder*. Child Neuropsychology 1995; 1: 170-186.

memoria di lavoro

[Denckla MB](#). J Dev Behav Pediatr 1996;17:114-9.

[Westby C](#), [Watson S](#). Semin Speech Lang 2004; 25:241-54.

WM

**zona di sovrapposizione
tra ADHD, dislessia e
disturbi del linguaggio**



Bental B, Tirosh E. The relationship between attention, executive functions and reading domain abilities in attention deficit hyperactivity disorder and reading disorder: a comparative study. *J Child Psychol Psychiatry* 2007; 48: 455-63

27 soggetti con ADHD/Dislessia

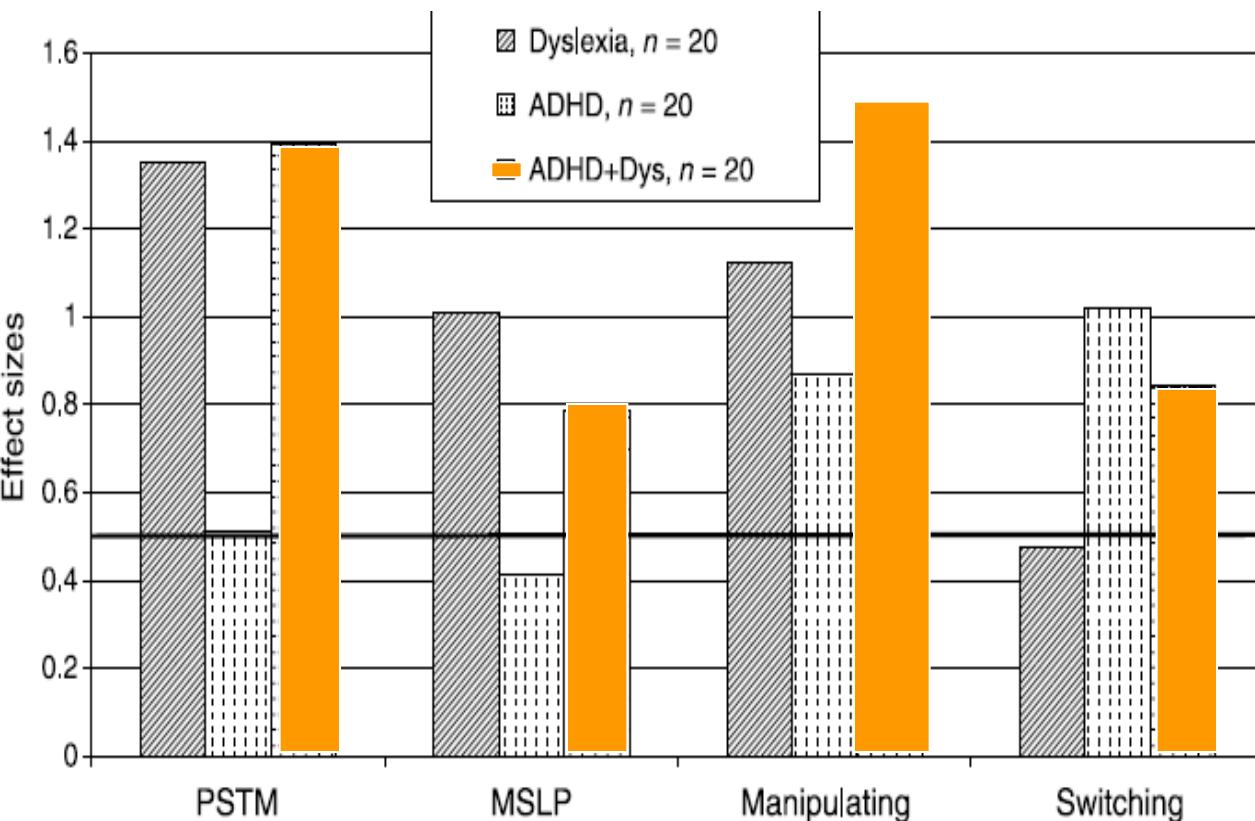
condividono

- disabilità nell'attenzione e nelle funzioni esecutive con ADHD
- difficoltà accademiche con il gruppo con Dys

profilo peculiare e maggiormente deficitario

- deficit specifico nei compiti di denominazione rapida automatica (RAN)
- un impairment più severo della WM

M. C. Tiffin-Richards, M. Hasselhorn, W. Woerner, A. Rothenberger, T. Banaschewski
 Phonological short-term memory and central executive processing in attention-deficit hyperactivity disorder with/without dyslexia – evidence of cognitive overlap, J Neural transmission, 2007



Soggetti comorbidi

- deficit nella memoria fonologica a breve termine
- deficit WM verbale

Fig. 1. Effect sizes for cognitive impairment for the three clinical groups in relation to the non-impaired control group; Phonological short-term memory (*PSTM*), morpho-syntactical language processing (*MSLP*, adjusted means after controlling for age as covariate), executive function *manipulating* and executive function *switching*. The line at Cohen $d=0.5$ marks the value above which effect sizes are regarded as significant

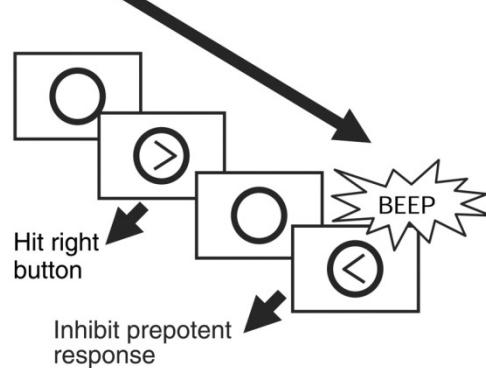
Memoria fonologica a breve termine

Processing linguistico morfosintattico

Memoria di cifre indietro WM

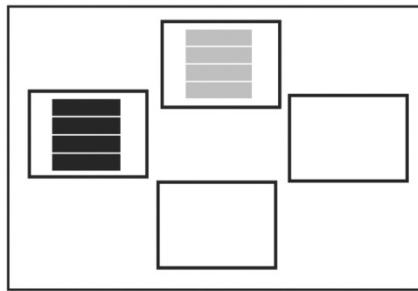
Funzioni esecutive

A



deficit in response inhibition

B



It is one of several possible endophenotypes of ADHD

(Castellanos & Tannock, 2002; Doyle et al., 2005)

It has also been found in dyslexia

(Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005)

Performance patterns in Conners' CPT

Table 2. Means and standard deviations of CCPT measurements for each group.

CCPT measures	ADHD group	LD group	Control group	p
#Omissions	35.1 (27.5)*#	18.4 (12.8)	13.2 (13.4)	p=0.00002
%Omissions	10.9 (8.5) *#	5.7 (4.0)	5.0 (5.4)	p=0.00002
#Commissions	22.6 (7.7)*	20.6 (8.2)	17.4 (8.6)	p=0.0018
%Commissions	66.9 (19.2)*	57.2 (22.8) *	45.4 (22.3)	p _s <0.009
Hit RT	572.0 (140.6)	471.7 (87.0)	554.6 (133.9)	p=0.294
Hit RT SE	22.9 (11.9)*#	12.7 (5.4)	13.2 (8.9)	p _s =0.00002
Variability	43.2 (24.4)*#	26.1 (18.3)*	18.9 (13.3)	p _s <0.01
Detectability (d')	0.3 (0.3)*	0.4 (0.4)	0.6 (0.4)	p=0.0002
Response Style (b)	1.0 (0.5)	1.4 (1.7)	1.3 (1.8)	p=0.46
Perseverations	18.6 (19.2)*#	10.3 (21.0) *	2.9 (3.5)	p _s <0.00002
Hit RT Block Change	0.02 (0.05)	0.02 (0.05)	0.00 (0.05)	p=0.06
Hit SE Block Change	0.08 (0.12)	0.11 (0.12)*	0.05 (0.10)	p=0.004
Hit RT ISI Change	0.13 (0.10)*#	0.06 (0.06)	0.05 (0.09)	p=0.0002
Hit SE ISI Change	0.20 (0.17)*#	0.08 (0.26)	0.04 (0.17)	p=0.00002

CCPT: Conners' Continuous Performance Test; ADHD: Attention deficit hyperactivity disorder; LD: Learning disabilities; Hit RT: Hit Reaction Time; Hit RT SE: Hit Reaction Time Standard Error; Hit RT BC: Hit Reaction Time Block Change; Hit SE BC: Hit Standard Error Block Change; Hit RT ISI Change: Hit Reaction Time ISI Change; Hit SE ISI Change: Hit Standard Error ISI Change. * Differs from control; # ADHD differs from LD.

I bambini dislessici confrontati ai controlli

- commission errors (failures in inhibitory control)
- RT variability
- perseveration responses
- inconsistency in the reaction time

Performance patterns in Conners' CPT

Confronto tra ADHD e Dislessici

CCPT measures	ADHD group
#Omissions	35.1 (27.5)*#
%Omissions	10.9 (8.5) **#
#Commissions	22.6 (7.7)*
%Commissions	66.9 (19.2)*
Hit RT	572.0 (140.6)
Hit RT SE	22.9 (11.9)*#
Variability	43.2 (24.4)*#
Detectability (d'')	0.3 (0.3)*
Response Style (b)	1.0 (0.5)
Perseverations	18.6 (19.2)*#
Hit RT Block Change	0.02 (0.05)
Hit SE Block Change	0.08 (0.12)
Hit RT ISI Change	0.13 (0.10)*#
Hit SE ISI Change	0.20 (0.17)*#

Even if....ADHD vs Dys displayed

- greater attention deficits (higher omission errors)
- highly variable reaction times
- Higher RT variability
- higher rate of anticipatory responses (perseverations)
- slower processing speed
- inconsistent response style

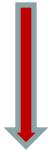
Slowed processing speed

(Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008)

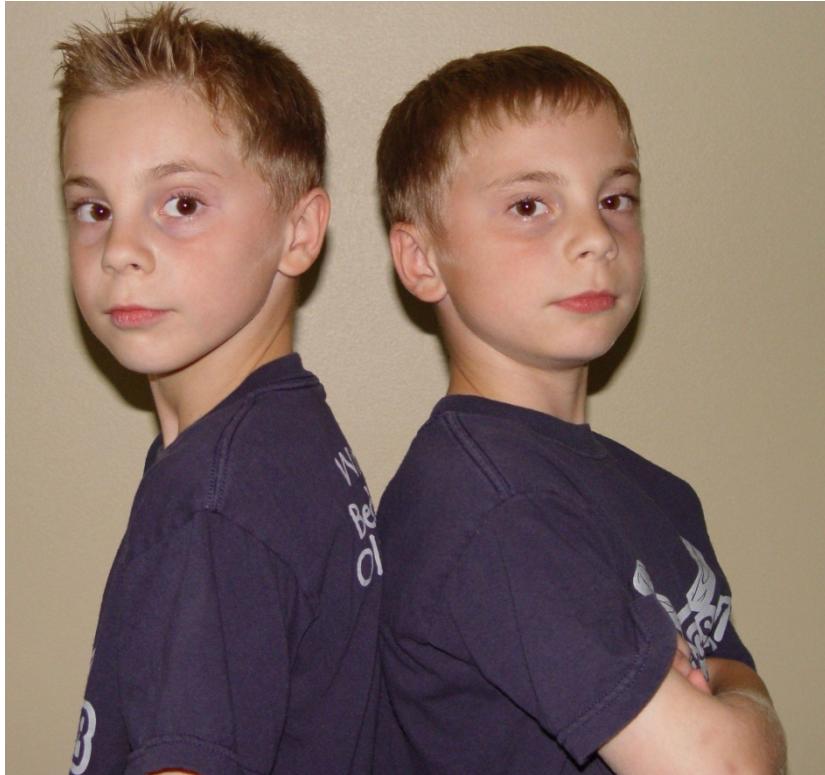
sensitive but not specific characteristic of a broad range of childhood disorders

twins with ADHD and/or reading disorders

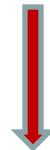
**phonological
deficits**



**word reading
difficulties**



'inhibition' deficit

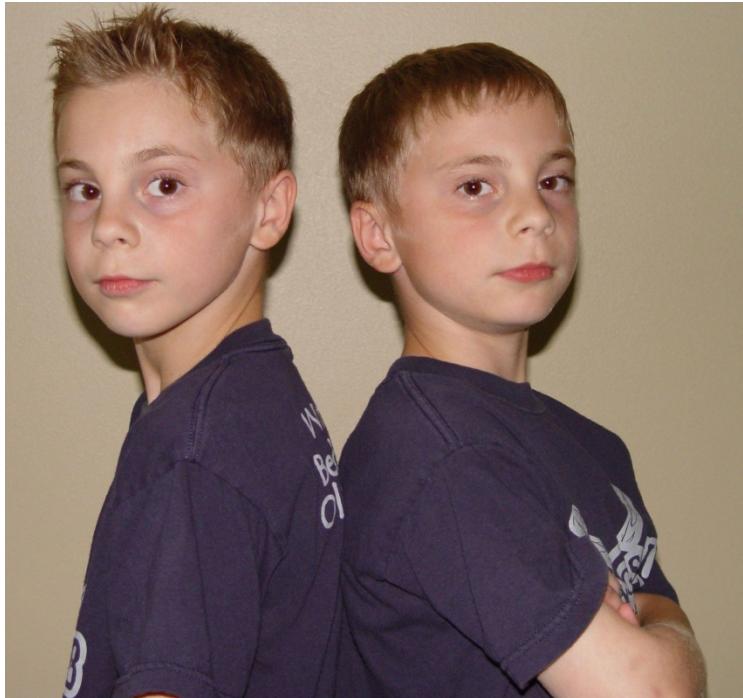


**inattention and
hyperactivity
impulsivity**

McGrath, et al. (2011). A multiple deficit model of reading disability and attention-deficit/hyperactivity disorder:
Searching for shared cognitive deficits. Journal of Child Psychology and Psychiatry, 52, 547–557

But...

processing speed factor



Predittore sia delle abilità di lettura che dei livelli di attenzione

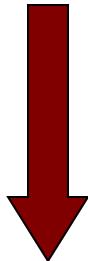
Sia l'ADHD che le abilità di decodifica possono influenzate da un comune deficit nella velocità di processamento cognitivo

McGrath, et al. (2011). A multiple deficit model of reading disability and attention-deficit/hyperactivity disorder: Searching for shared cognitive deficits. *Journal of Child Psychology and Psychiatry*, 52, 547–557

I bambini ADHD hanno una fluenza di lettura più bassa anche quando non sono dislessici

(Ghelani, Sidhu, Jain, & Tannock, 2004; Willcutt, Pennington, Olson, & DeFries, 2007).

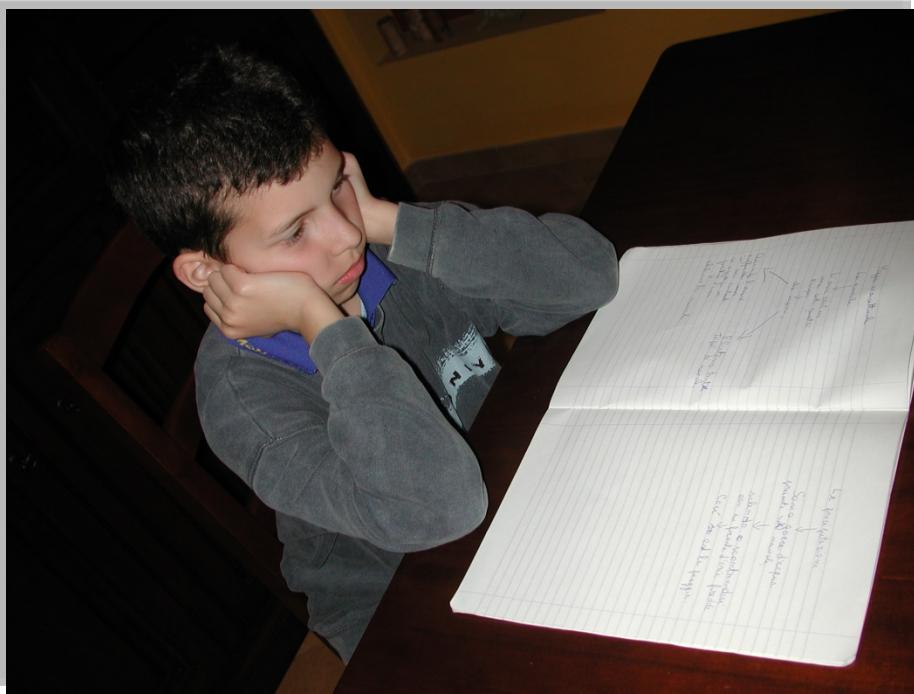
velocità di processamento più bassa



Processing speed deficit in ADHD can contribute to reading difficulties

(Denckla & Cutting, 1999; Rucklidge & Tannock, 2002; Willcutt, 2005)

particularly on efficiency of reading fluency



**ADHD reduced reading fluency
(no accuracy)**

Avere tempi di latenza della risposta più lunghi può tradursi in performance accademiche più basse

[Jacobson LA](#), [Ryan M](#), [Denckla MB](#), [Mostofsky SH](#), [Mahone EM](#), Arch Clin Neuropsychol Jul 9. 2013

La fluenza può interferire con le attività di apprendimento più complesse come la comprensione della lettura



Ma anche...

slower naming speed

Ryan M, et al, Rapid automatized naming (RAN) in children with ADHD: An ex-Gaussian analysis. Child Neuropsychol. 2016 Apr 24:1-17. [Epub ahead of print]

In particolare....

- **per le lettere e le cifre nella dislessia**
- **per gli oggetti e i colori nell'ADHD**

(Tannock, Martinussen, & Frijters, 2000; Ghelani et al., 2004).

RAN Prova di denominazione rapida di colori

Valutazione in età prescolare



La velocità di denominazione, valutata prima dell'inizio dell'insegnamento formale della lingua scritta, è un buon predittore della successiva abilità di lettura

de Jong e van der Leij, 2003; Scalisi et al., 2005, G. Stella et al., 2011

Prova di denominazione rapida di colori

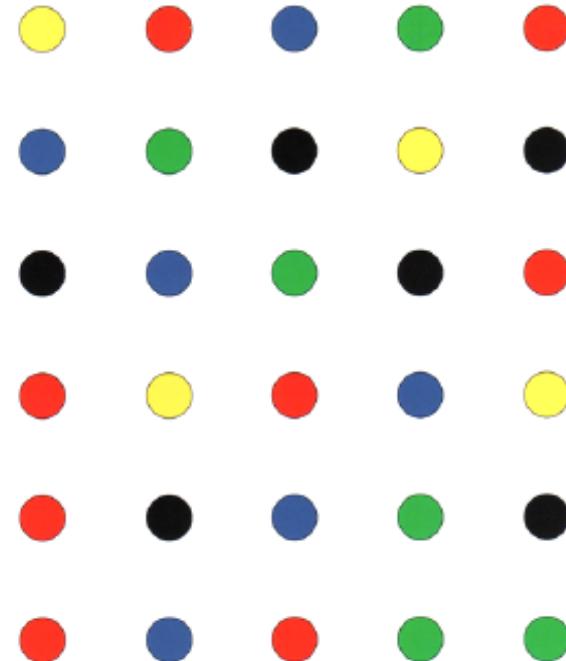
Foglio di prova



La prova consiste nel denominare correttamente e il più velocemente possibile una tavola di colori

G. Stella et al., 2011

Foglio di somministrazione



Prova di denominazione rapida di colori

Tempo totale (in secondi)	
Numero autocorrezioni	
Numero errori	
Non eseguibile (non conosce i colori)	
Non eseguita (rifiuto)	

32 Secondi Tra 32-50 secondi + 50 Secondi	Media Medio rischio Forte rischio
---	---

deficit della RAN (Rapid Automatized Naming)

uno dei fattori di rischio più strettamente condivisi tra Dys e ADHD



**RAN come
ENDOFENOTIPO del
fenotipo comorbido**

[Shanahan MA](#), [Pennington BF](#), et al et al. *Processing speed deficits in attention deficit/hyperactivity disorder and reading disability*. J Abnorm Child Psychol 2006; 34: 585-602.



Deficit specifici ?

visual processing deficits are impaired in reading disabilities

(Facoetti et al., 2008; Vidyasagar and Pammer, 2010; Germano et al., 2014)

other cognitive deficits common to ADHD, such as **attention, working memory and executive functioning deficits**, may be contributing to RD

visual processing in ADHD may be intact when spatial demands are low, but poor when spatial demands are high (Aman et al., 1998; Johnson et al., 2010).

Kibby MY, Dyer SM, Vadnais SA, Jagger AC, Casher GA and Stacy M (2015) Visual processing in reading disorders and attention-deficit/hyperactivity disorder and its contribution to basic reading ability. Front. Psychol. 6:1635.

264 children, ages 8–12 years.

51 RD, 88 ADHD, 51 RD+ADHD, 74 TD

3 aspects of visual processing

1. perception (discrimination of complex figures)
2. short-term memory (STM) for complex figures
3. STM for sequences of basic shapes



Children with RD or ADHD were commensurate to controls on measures of visual discrimination and visual STM that do not require sequential processing

Both RD groups (RD and RD/ADHD) performed worse than controls on the measure of visual STM that requires memory for order, but children with comorbid RD/ADHD performed worse than those with ADHD

Of the three visual measures, only sequential visual STM predicted reading ability

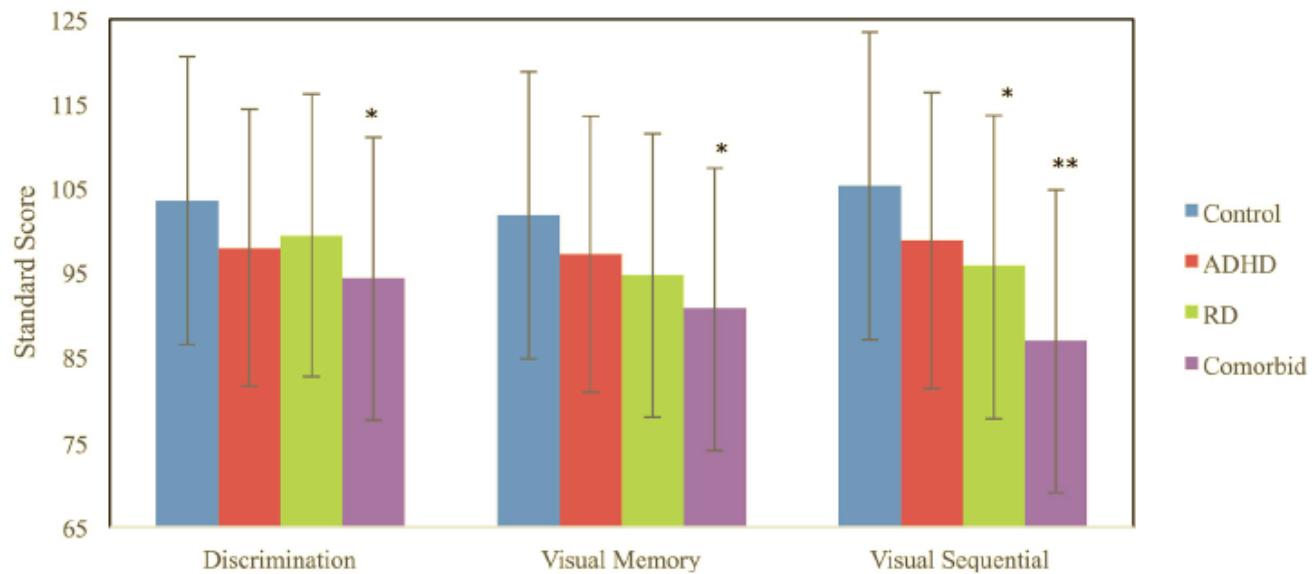


FIGURE 1 | TVPS-R marginal means for each group adjusted for the covariate, Verbal Comprehension Index (VCI). Error bars were derived using SD.

*Significantly different from the control group. **Significantly different from both the ADHD and control groups.



there is a deficit in visual sequential STM that is specific to RD and is related to basic reading ability

Spelling mistakes as benchmark ?



Classification of spelling mistakes by semiology

Natural spelling mistakes (*errori fonologici*)

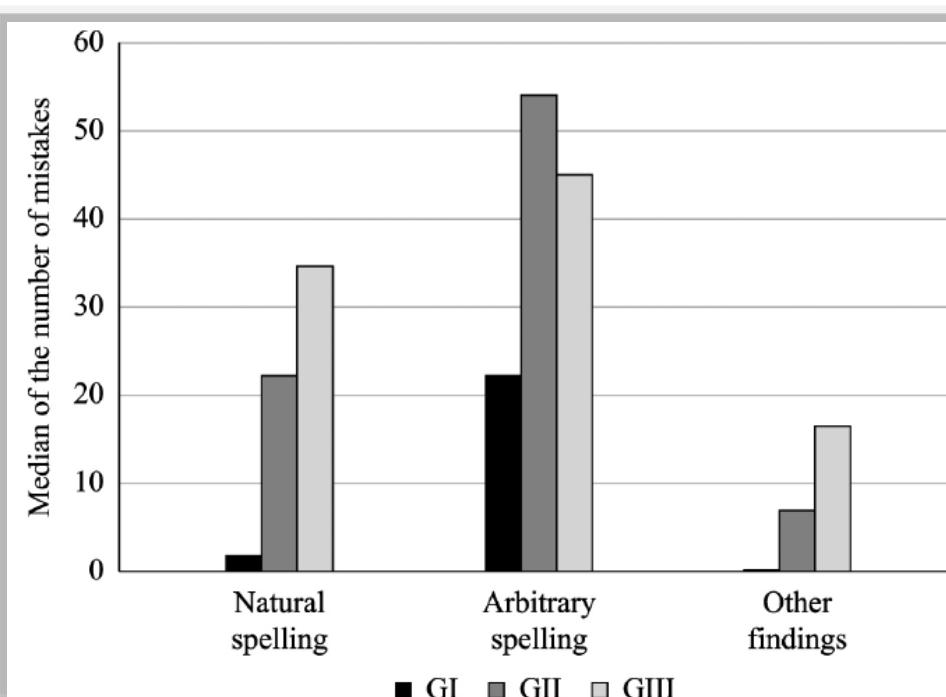
related to the processing of language

Arbitrary spelling mistakes (*errori non-fonologici*)

related to lexicon, morphology, visual memory, and the knowledge of spelling rules

Other Findings

letters with tracing problems /mirroring, writing of another word and/or made up word

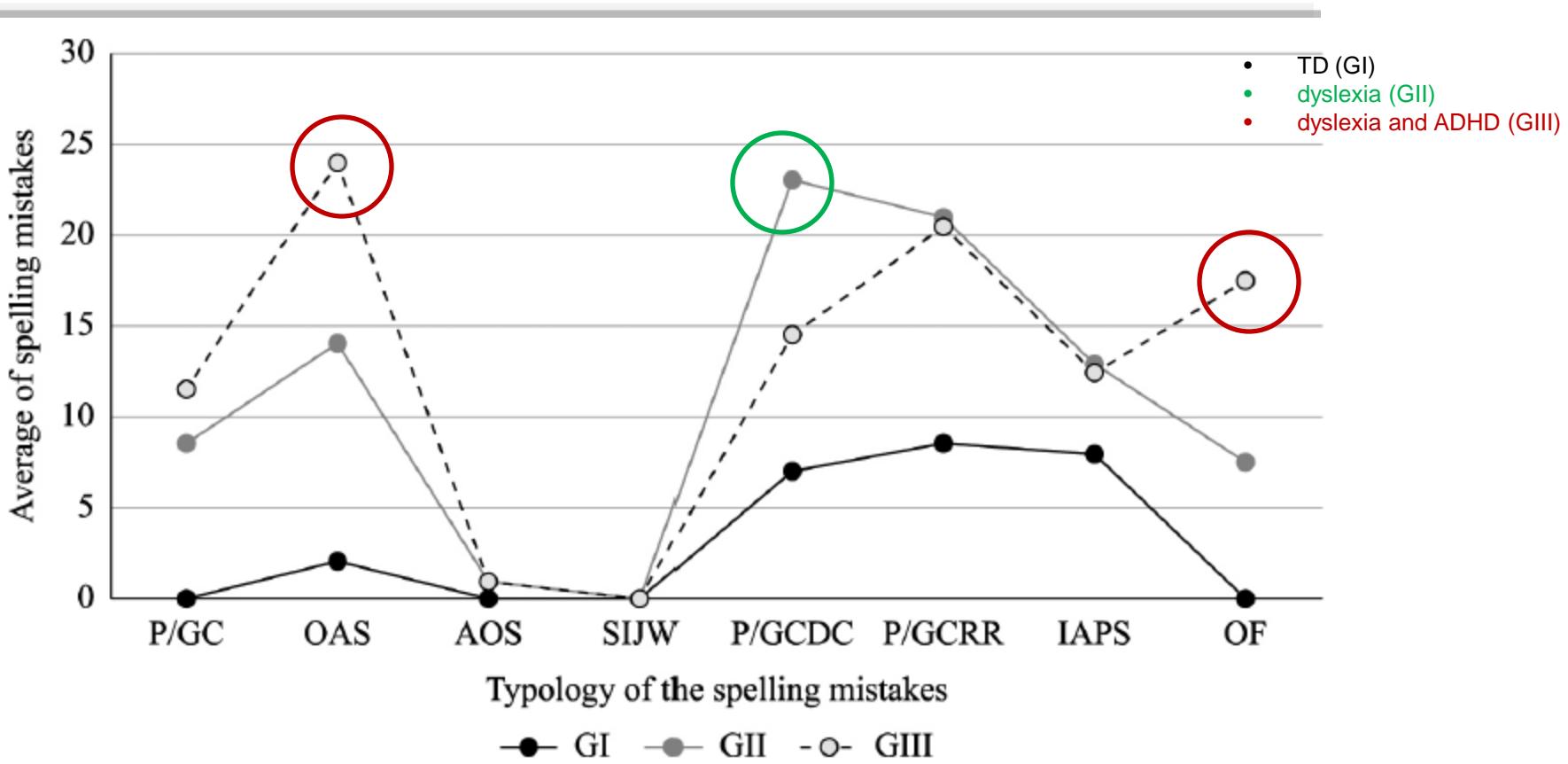


70 students (mean age 9.5 years)

assessed through a standardized word dictation task

- 32 TD (GI)
- 22 with dyslexia (GII)
- 16 with dyslexia and ADHD (GIII)

Median of the number of spelling mistakes of each group, according to the typology of mistakes



Caption: P/GC = Univocal Phoneme–Grapheme Correspondence; **OAS = Omission and Addition of Segments**; AOS = Alteration of the Order of the Segments; SIJW = Separation or Improper Junction of Words; **P/GCDC = Phoneme–Grapheme Correspondence** Depending on the Phonetic Context/Position; P/GCRR = Phoneme–Grapheme Correspondence Regardless Rules; IAPS = Inadequate Absence or Presence of Word Stress; **OF = Other Findings** (letters with tracing problems /mirroring, writing of another word and/or made up word)

implications for treatment

A.G. a.11; Dose test di MPH (0.5 mg IR); osservazione personale Marzo 2012

9) veniva l' omo chiamato uno
volta molto.

10) labirinto non aveva le
mura

11) non sa che cosa si fa

12) non sapeva dove andava

13) non sapeva dove andava

14) non sapeva dove andava

$T = 13$

$M = 2 \quad DS = 2$

$C = C + 2 DS$

6) oggi ha acquistato un
pelle d'orsa.

7) sul pavimento non c'era la
cera.

8) veniva l' omo invitato
una volta sola

9) il bambino non ha preso la
merenda.

10) pensava sia che forse non
è uomo più.

11) non vive troppa almeno.

12) Mario arriva al loro stabil

Baseline

1.5 hours later

Prasad et al, **How effective are drug treatments for children with ADHD at improving on-task behaviour and academic achievement in the school classroom?** A systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2013 Apr;22(4):203-16.

43 studies (2,110 participants)

Drug treatment benefited children in **school work by up to 15%**

less consistently improved children's accuracy in specific types of academic assignments, such as arithmetic...



Similar improvements were seen in classroom behaviour, with up to **14% more** of children's **time spent "on task".**

Methylphenidate, dexamfetamine and mixed amphetamine formulations showed higher cognitive beneficial effects than Atomoxetine

RCTs : methylphenidate vs placebo; children and adolescents (5-18 years) with ADHD

MPH was superior to placebo

- Executive memory**, SMD 0.26; 95% CI -0.39 to -0.13;
- Non-executive memory**, SMD 0.60; 95% CI -0.79 to -0.41;
- Reaction Time** SMD 0.24; 95% CI -0.33 to -0.15;
- Reaction Time Variability**, SMD 0.62; 95% CI -0.90 to -0.34;
- Response Inhibition**, SMD 0.41; 95% CI -0.55 to -0.27

Figure 2: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Executive Aspects of Memory

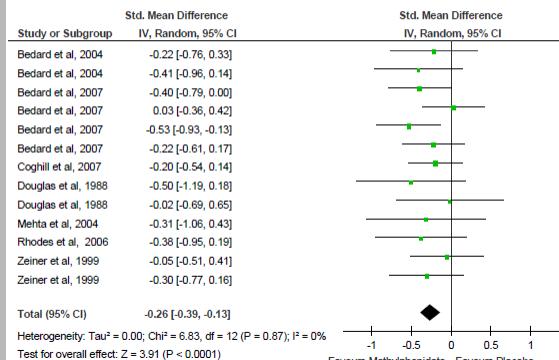


Figure 3: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Non-Executive Aspects of Memory

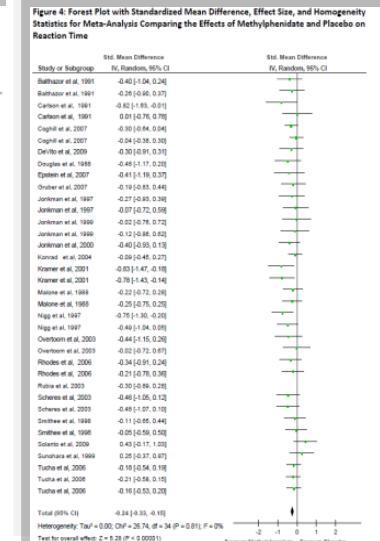
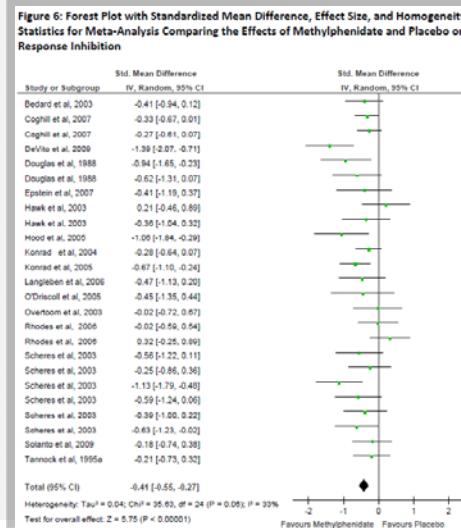
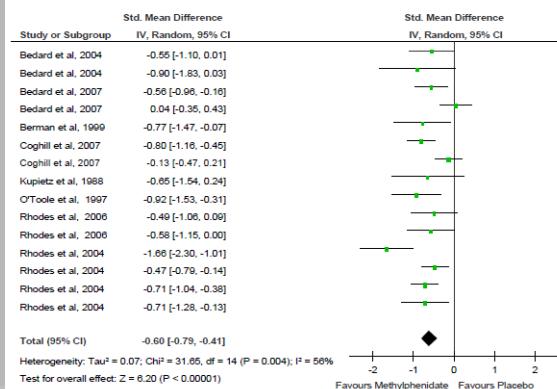
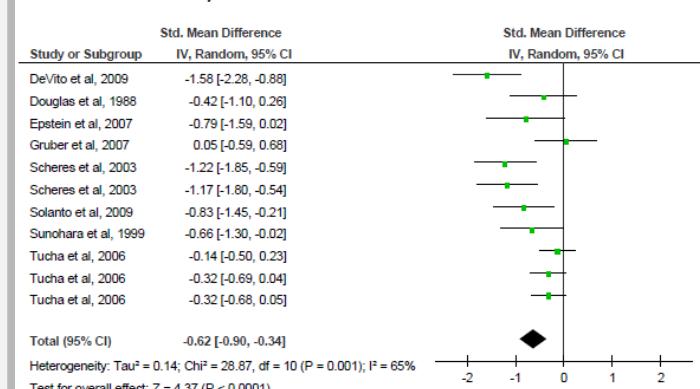


Figure 5: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Reaction Time Variability





Efficacy of atomoxetine in the treatment of attention-deficit hyperactivity disorder in patients with common comorbidities in children, adolescents and adults: a review

Shari L. Hutchison, Jaswinder K. Ghuman, Harinder S. Ghuman, Irina Karpov
and James M. Schuster

Ther Adv Psychopharmacol

2016, Vol. 6(5) 317–334

DOI: 10.1177/
2045125316647686

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youth with ADHD and

n = 118 ATX and n = 58 Pla

Limited evidences

improvements related to dyslexia in

- **Word recognition**
- **Word comprehension**
- **Reading ability**

**attention
deficit ?**

Tannock R, Frijters JC, Martinussen R, White EJ, Ickowicz A, Benson NJ, Lovett MW,

Combined Modality Intervention for ADHD With Comorbid Reading Disorders:

A Proof of Concept Study. J Learn Disabil. 2016 Nov 28.. [Epub ahead of print]

efficacy of 2 reading programs with and without adjunctive **stimulant medication**

65 children with ADHD+RD (7-11 years in age)

intensive remedial academic programs

- phonologically or strategy-based reading instruction
- general academic strategy
- social skills training

+

immediate-release
methylphenidate

placebo

Stimulant medication alone produced expected beneficial effects on hyperactive/impulsive behavioral symptoms (reported by classroom teachers) **but none on reading.**

Children receiving a combined treatment showed greater gains than controls on standardized measures of reading and related skills

"thus"
이^그는^는 그^그므로^{므로},
그^그는^는 Free^{Free}
Freeever



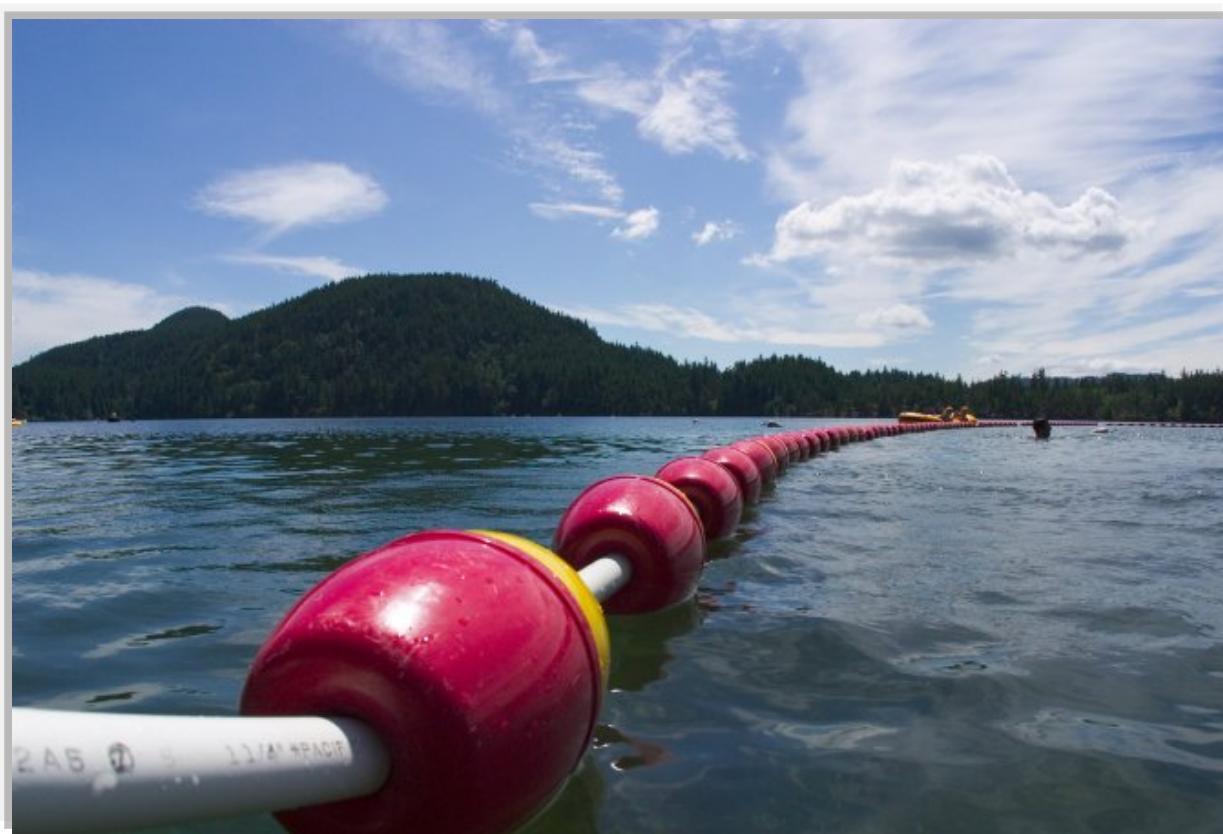
Identificare un DISTURBO potrebbe significare individuare...

...quale diagnosi categoriale meglio descrive l'esofenotipo....



... che è a sua volta funzione di una peculiare costellazione endofenotipica in interazione con l'ambiente...

Delimitare ciò che è difficilmente delimitabile ...

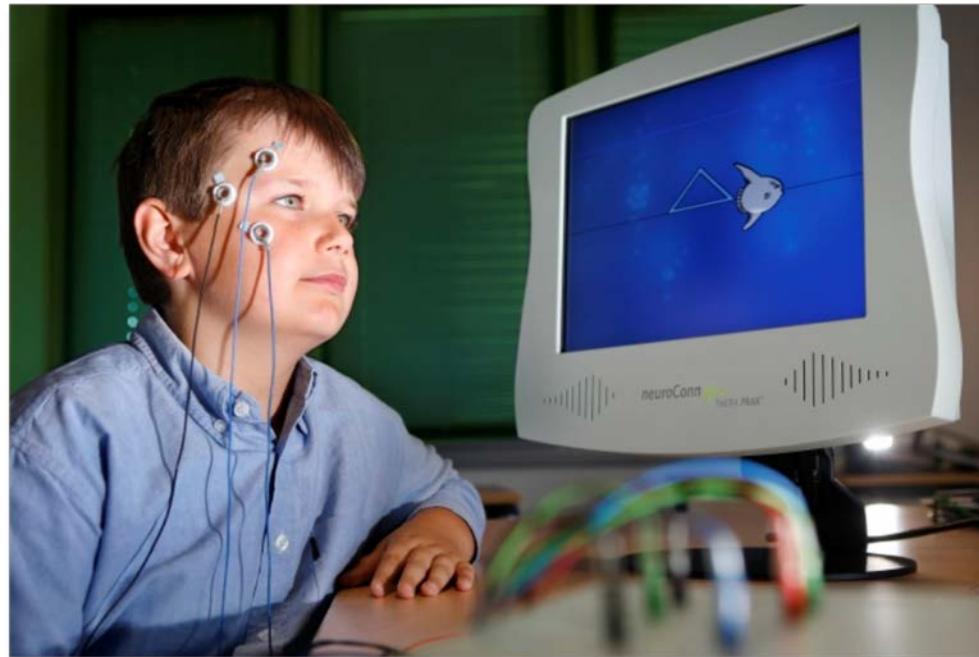


...parlare in categoriale e pensare in dimensionale

Marzbani, H., Marateb, H. R., & Mansourian, M. (2016). Neurofeedback: a comprehensive review on system design, methodology and clinical applications. *Basic and Clinical Neuroscience*, 7(2), 143-158.

neurofeedback is known as a complementary and alternative treatment of both ADHD and Dyslexia

Limits : it is expensive, time-consuming and its benefits are not long-lasting



current research does not support conclusive results about its efficacy

specific deficits ADHD/DYS

- 1. Working Memory**
- 2. rapid automatized naming (RAN)**
- 3. processing speed**

(Willcutt, Pennington et al., 2005; Shanahan et al., 2006).

Take home message

fenotipo ADHD/Dys

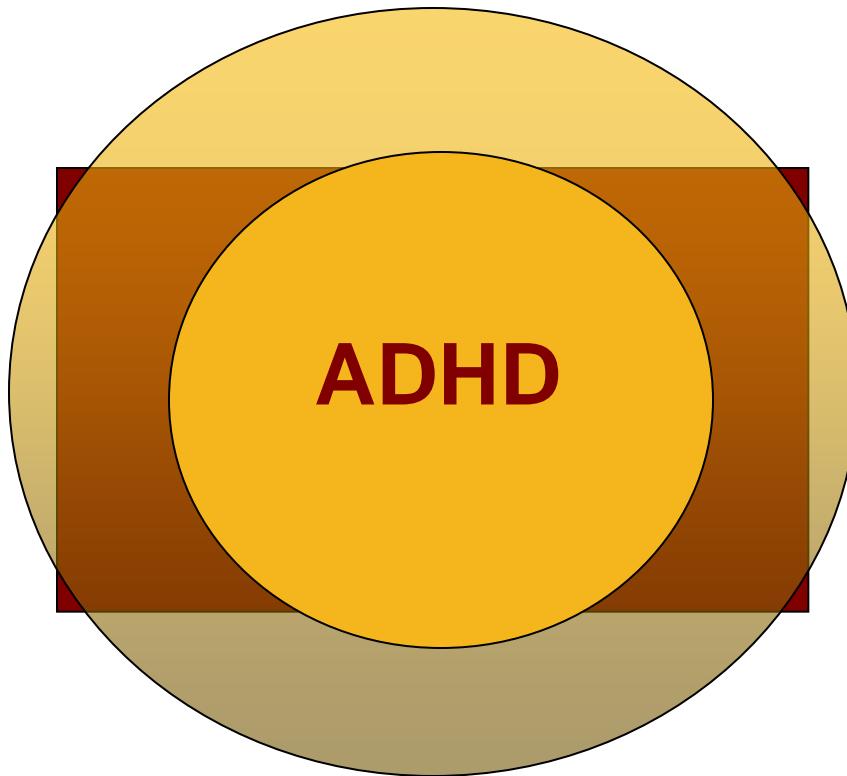
- i disturbi dell'apprendimento combinati con l'ADHD favoriscono il fallimento accademico
- l'outcome scolastico è peggiore
- c'è un più alto rischio di presentare sintomi esternalizzanti, disturbo oppositivo- provocatorio e disturbo della condotta

C.Gillberg, DAMP: A Brief Review, Arc Dis Child, 2003; 88: 904-910



Moduli o continuum ?

Errore diagnostico da effetto alone...

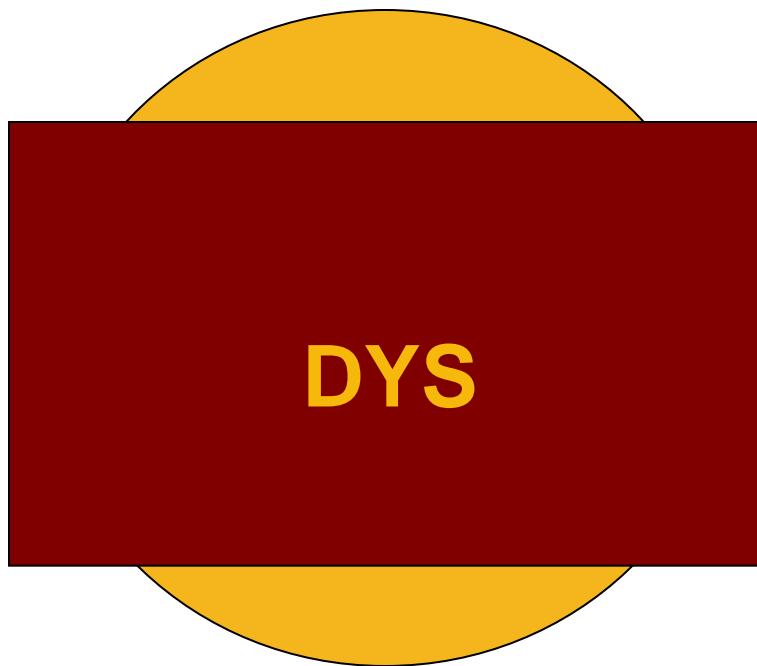


L'ADHD spiega la difficoltà scolastica

La Dislessia viene “appannata” dall'alone creato dall'ADHD

Practice Parameter for the Assessment and Treatment of
Children and Adolescents With ADHD, (AACAP), 2007

Errore opposto... ...



Rischio soprattutto per il sottotipo inattentivo

Practice Parameter for the Assessment and Treatment of
Children and Adolescents With ADHD, **(AACAP), 2007**

ADHD and Dys condividono caratteristiche comportamentali e deficit neuropsicologici

“shared aetiology” hypothesis

(De Jong et al., 2006)

“cognitive subtype” hypothesis in which cognitive deficits are different, or more severe, than those apparent in either ADHD or dys alone

(Rucklidge & Tannock, 2002)

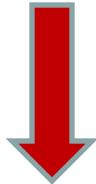
Coinvolgimento di più domini cognitivi

- velocità processamento informazione
- memoria fonologica a breve termine
- velocità di denominazione
- WM verbale

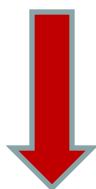


effetto di rinforzo reciproco che porta a quadri a maggiore severità e a più ampia compromissione funzionale

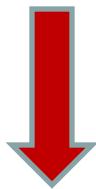
central auditory processing disorders (CAPD)



dysfunction in the central nervous system



difficulties in recognizing and interpreting acoustic patterns



- attention (Sergeant et al., 2003)
- language and literacy (Dawes et al., 2009)

30–50% of children with Dyslexia are affected by auditory problems

responses of AC to unexpected deviations in basic sound features (amplitudes of the mismatch negativity) are correlated to phonological processing and letter-naming skills at the kindergarten-age and to word reading fluency at the primary school age

(Lovio et al., 2010, Hämäläinen et al., 2015, van Zuijen et al., 2013).

Similarly...

ADHD involves a core deficit in auditory, visual and motor timing (sensorimotor synchronization, duration discrimination, and time-interval reproduction)

(Barkley et al., 2001; Smith et al., 2002; McInerney and Kerns, 2003; Falter and Noreika, 2011; Noreika et al., 2013; Lesiuk, 2014)

