Event Related Potentials as possibile biomarker of ADHD symptoms severity in Tuberous Sclerosis complex (TSC)

Dr. Stefano Pro

Neurophysiology Unit
Bambino Gesu` Children's Hospital, IRCCS, Rome, Italy

Neurological and neuropsychiatric aspects of tuberous sclerosis complex

Paolo Curatolo, Romina Moavero, Petrus J de Vries

Tuberous sclerosis (also known as tuberous sclerosis complex [TSC]) is a multisystem genetic disorder that affects almost every organ in the body. Mutations in the *TSC1* or *TSC2* genes lead to disruption of the TSC1–TSC2 intracellular protein complex, causing overactivation of the mammalian target of rapamycin (mTOR) protein complex. The surveillance and management guidelines and clinical criteria for tuberous sclerosis were revised in 2012, and mTOR inhibitors are now recommended as treatment options for subependymal giant cell astrocytomas and renal angiomyolipomas—two common features of the disease. However, most morbidity and mortality caused by tuberous sclerosis is associated with neurological and neuropsychiatric manifestations. Treatment of epilepsy associated with tuberous sclerosis remains a major challenge, with more than 60% of patients having ongoing seizures. Tuberous-sclerosis-associated neuropsychiatric disorders (TAND) are multilevel and occur in most individuals with the disorder, but are rarely assessed and treated. Clinical trials of mTOR inhibitors to treat seizures and TAND are underway. Management of the neurological and neuropsychiatric manifestations of the disorder should be coordinated with treatment of other organ systems. In view of the age-related expression of manifestations from infancy to adulthood, continuity of clinical care and ongoing monitoring is paramount, and particular attention is needed to plan transition of patient care from childhood to adult services.

Lancet Neurol 201

Neuroscience De
Child Neurology
Division, Univers
Tor Vergata, Ron
(Prof P Curatolo M
R Moavero MD); I
Department, Chi
Division, Bambi
Children's Hospi
Rome, Italy (R M
Division of Child
Adolescent Psyc
University of Ca
Cape Town, Sout
(Prof P J de Vries I
Correspondence t

Autosomal dominant multisystem disease characterized by hamartomas in several organs and systems

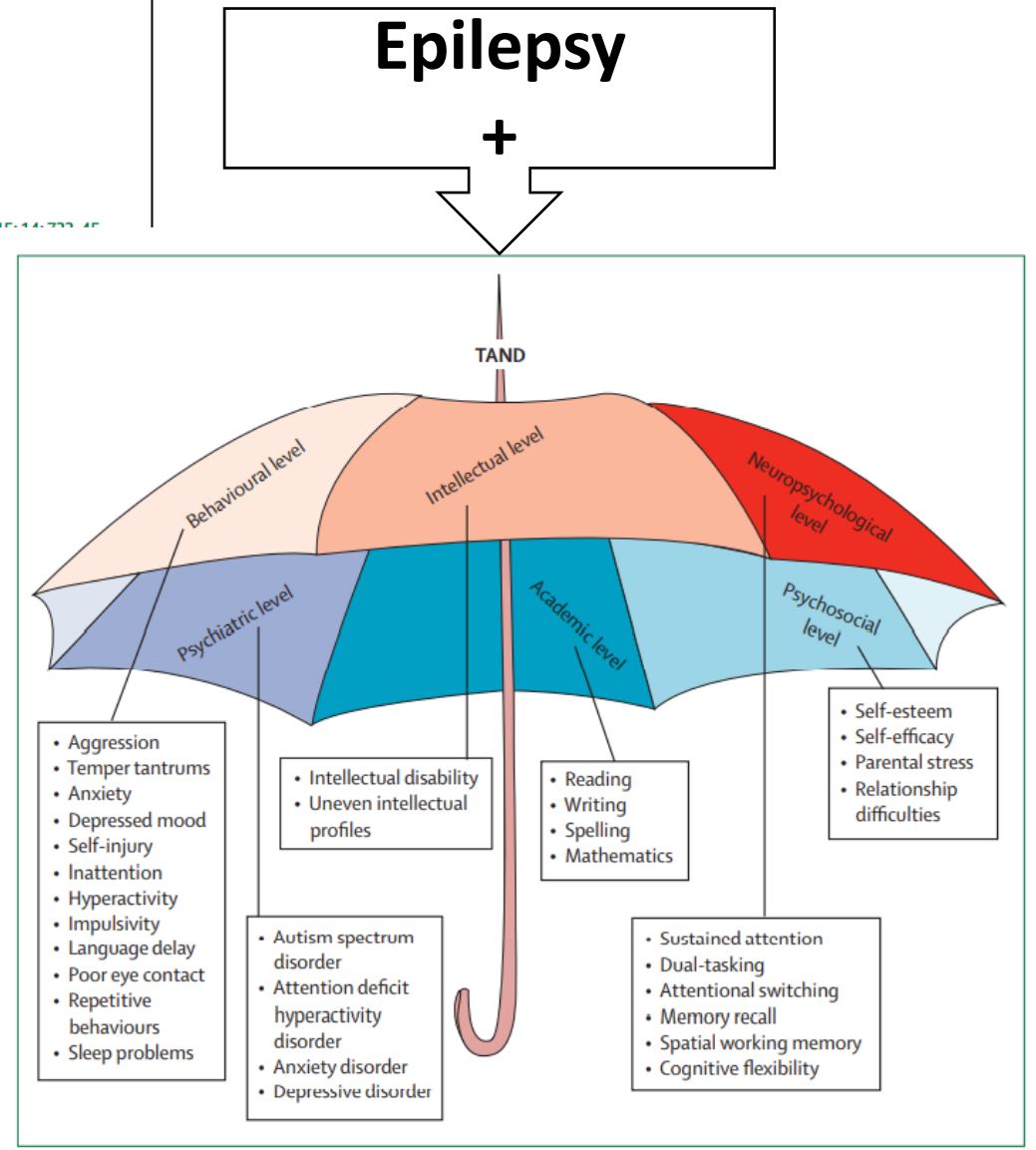


Figure 4: **TAND**
TAND is used as an umbrella term to capture the range of neuropsychiatric disorders associated with tuberous sclerosis across different levels of investigation. TAND=tuberous-sclerosis-associated neuropsychiatric disorders.

ADHD

Attention-Deficit Hyperactivity Disorder

General Population 3-7%

TSC 30-50%

Topical Review Article

Journal of Child Neurology
Volume 24 Number 10
October 2009 1282-1287
© 2009 The Author(s)
10.1177/0883073809341272
http://jcn.sagepub.com

Attention-Deficit Hyperactivity Disorder (ADHD) and Tuberous Sclerosis Complex

Elisa D'Agati, MD, Romina Moavero, MD, Caterina Cerminara, MD, and Paolo Curatolo, MD

The neurobiological basis of attention-deficit hyperactivity disorder (ADHD) in tuberous sclerosis complex is still largely unknown. Cortical tubers may disrupt several brain networks that control different types of attention. Frontal lobe dysfunction due to seizures or epileptiform electroencephalographic discharges may perturb the development of brain systems that underpin attentional and hyperactive functions during a critical early stage of brain maturation. Comorbidity of attention-deficit hyperactivity disorder (ADHD) with mental retardation and autism spectrum disorders is frequent in children with tuberous sclerosis. Attention-deficit hyperactivity disorder (ADHD) may also reflect a direct effect of the abnormal genetic program. Treatment of children with tuberous sclerosis complex with combined symptoms of attention-deficit hyperactivity disorder (ADHD) and epilepsy may represent a challenge for clinicians, because antiepileptic therapy and drugs used to treat attention-deficit hyperactivity disorder (ADHD) may aggravate the clinical picture of each other.

Keywords: ADHD; tuberous sclerosis complex; antiepileptic drugs; methylphenidate; autism

>Cortical Tubers
>Frontal Epileptiform abnormalities
>Genetic mutation per se

Received: 6 May 2018 | Revised and accepted: 29 May 2018
DOI: 10.1002/ajmg.c.31637

WILEY AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics

RESEARCH REVIEW

A clinical update on tuberous sclerosis complex-associated neuropsychiatric disorders (TAND)

Petrus J. de Vries[1] | Lucy Wilde[2] | Magdalena C. de Vries[1] | Romina Moavero[3,4] | Deborah A. Pearson[5] | Paolo Curatolo[3]

[1]Division of Child and Adolescent Psychiatry, University of Cape Town, Cape Town, South Africa
[2]Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, United Kingdom
[3]Child Neurology and Psychiatry Unit, Systems Medicine Department, University of Rome Tor Vergata, Rome, Italy
[4]Child Neurology Unit, Neuroscience and Neurorehabilitation Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[5]Department of Psychiatry & Behavioral Sciences, McGovern Medical School, University of Texas Health Centre, Houston, Texas

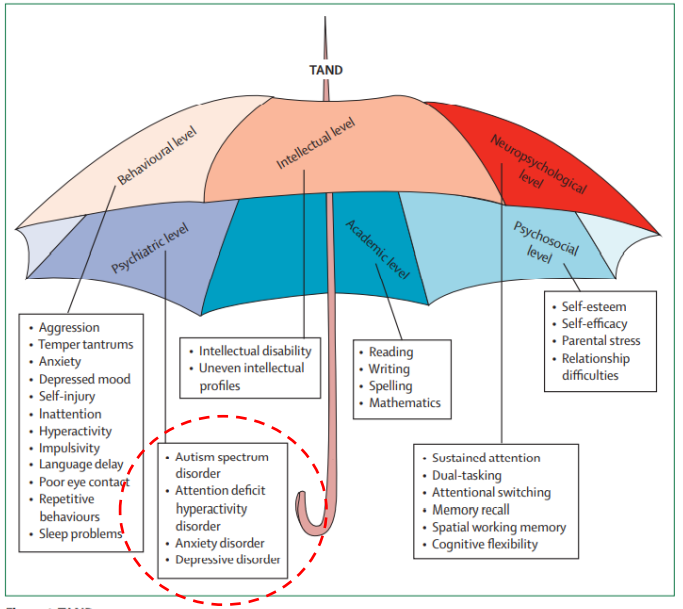
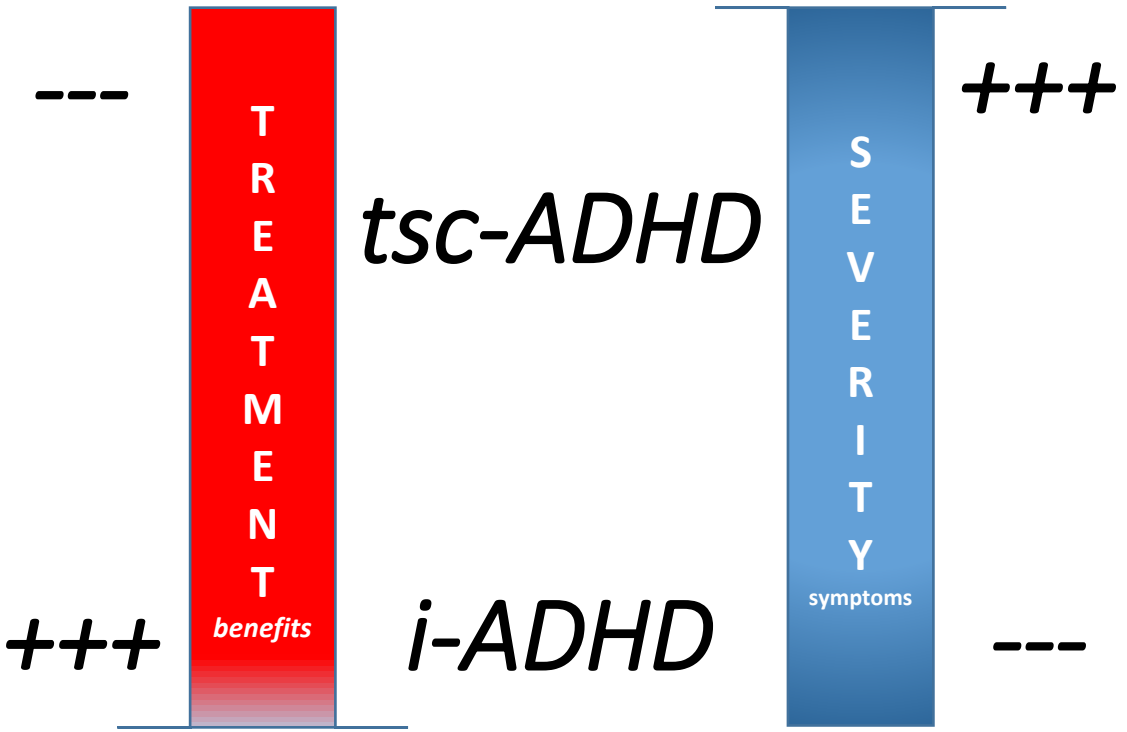


Figure 4: **TAND**
TAND is used as an umbrella term to capture the range of neuropsychiatric disorders associated with tuberous sclerosis across different levels of investigation. TAND=tuberous-sclerosis-associated neuropsychiatric disorders.

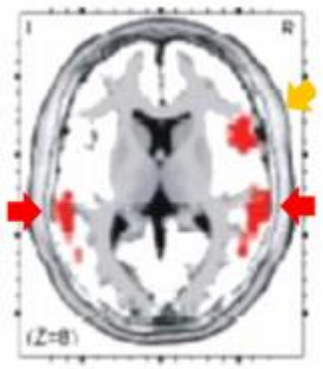


TREATMENT
benefits
+++
tsc-ADHD
i-ADHD
+++
SEVERITY
symptoms

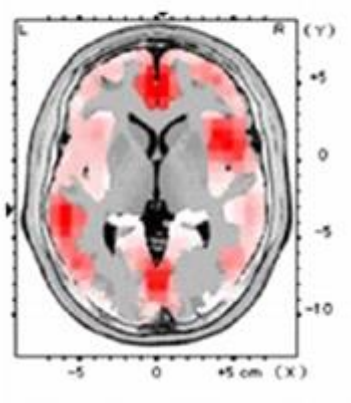
	Brief description and generators
Auditory MMN	Discriminable change in auditory stimulation without attention; bilateral auditory-cortex with the contribution of right frontal cortex
P300	Sensitive (auditory/visual) measure of the capacitiy to allocate attentional resources; multiple cortical-subcortical, relatively independent generators

GENERATORS of ERPs

MMN

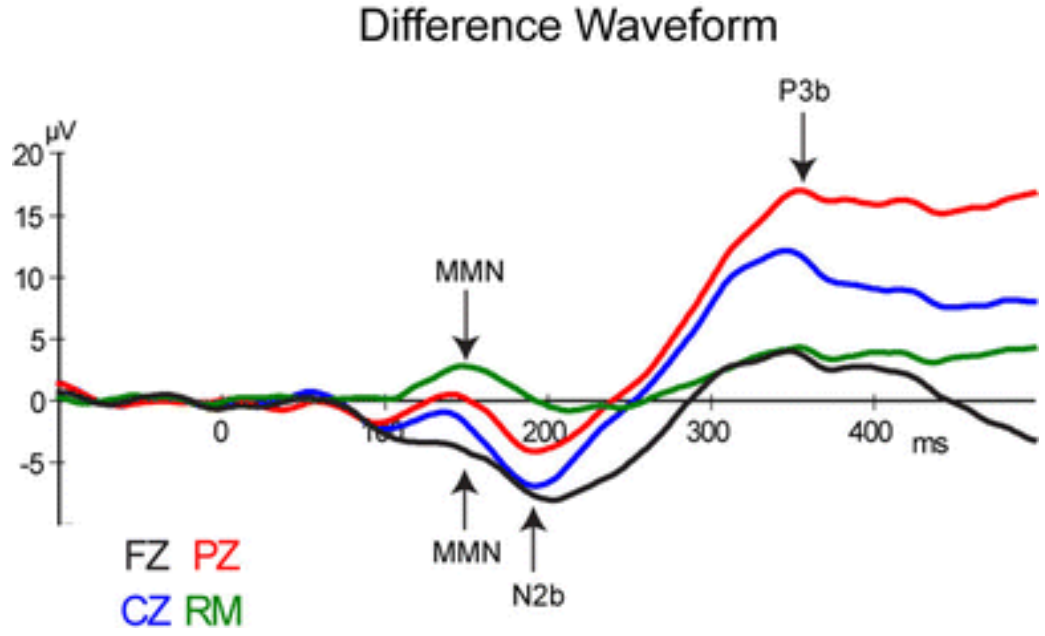


P300



Pre-Attentive

Attentive



MMN

>reflect an autonomic cerebral discrimination process not under attentive control

P300

>reflect executive and attentional function

>may reflect late-stage monitoring of outcomes related to inibitory process

Auditory Event-Related Brain Potentials in Autistic Children and Three Different Control Groups

Chantal Kemner, Marinus N. Verbaten, Juliane M. Cuperus, Gert Camfferman, and Herman van Engeland

ERPs to auditory stimuli, generated during an oddball task, were obtained in a group of autistic children and three control groups (normal, ADDH, and dyslectic children, respectively). The task included the presentation of standards, deviants, and novels and had a (between-group) passive vs. active (counting) condition. It was examined whether 1) it was possible to replicate several earlier findings, 2) autistics manifest an abnormal lateralization pattern of ERPs, 3) autistics have an abnormal mismatch negativity (MMN), and 4) differences between autistics and normals are really specific to the autistic group. The only finding that could be replicated was that autistics have a smaller A/Pcz/300. There was no evidence for abnormal lateralization or abnormal MMN; however, there was an unexpected effect of the task manipulation on the amplitude of the P3: in autistics, the occipital P3 to deviant stimuli was significantly larger in the active than in the passive condition, a finding, like the replication of the smaller A/Pcz/300,

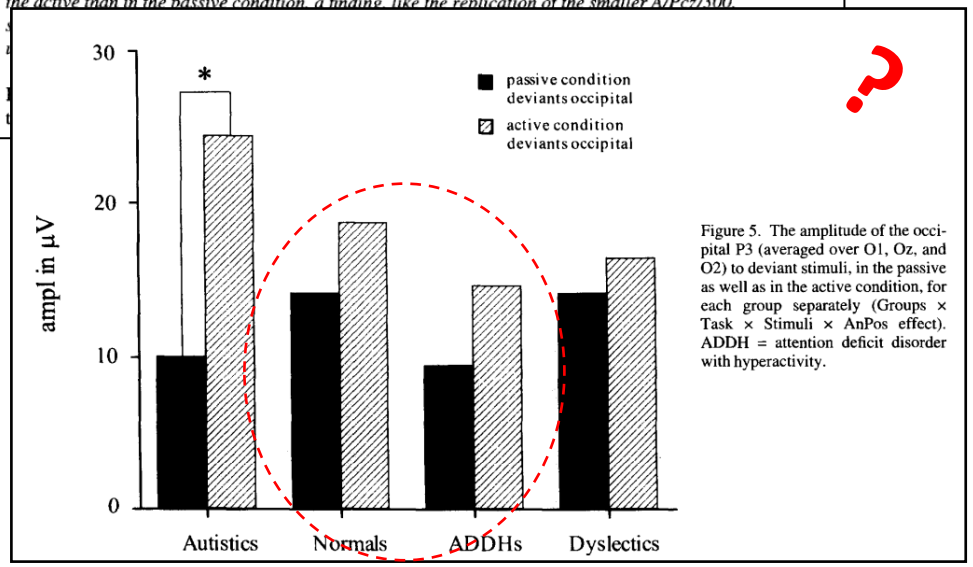


Figure 5. The amplitude of the occipital P3 (averaged over O1, Oz, and O2) to deviant stimuli, in the passive as well as in the active condition, for each group separately (Groups × Task × Stimuli × AnPos effect). ADDH = attention deficit disorder with hyperactivity.

?

MMN

↓/↑µV

↑ms

ndr

Neuropsychobiology

Original Paper

Neuropsychobiology 2016;73:131–138
DOI: 10.1159/000444490

Received: May 19, 2015
Accepted after revision: January 31, 2016
Published online: April 8, 2016

Event-Related Potentials Correlate with the Severity of Child and Adolescent Patients with Attention Deficit/Hyperactivity Disorder

Kazuhiko Yamamuro[a] Toyosaku Ota[a] Junzo Iida[b] Yoko Nakanishi[a]
Yuko Suehiro[a] Hiroki Matsuura[c] Mitsuhiro Uratani[d] Kosuke Okazaki[a]
Naoko Kishimoto[a] Shohei Tanaka[a] Hidemi Iwasaka[e] Toshifumi Kishimoto[a]

[a]Department of Psychiatry and [b]Faculty of Nursing, Nara Medical University School of Medicine, Kashihara, [c]Department of Psychiatry, Tenri Hospital, Tenri, [d]Department of Psychiatry, Nara Prefectural General Rehabilitation Center, Shiki, and [e]Department of Educat

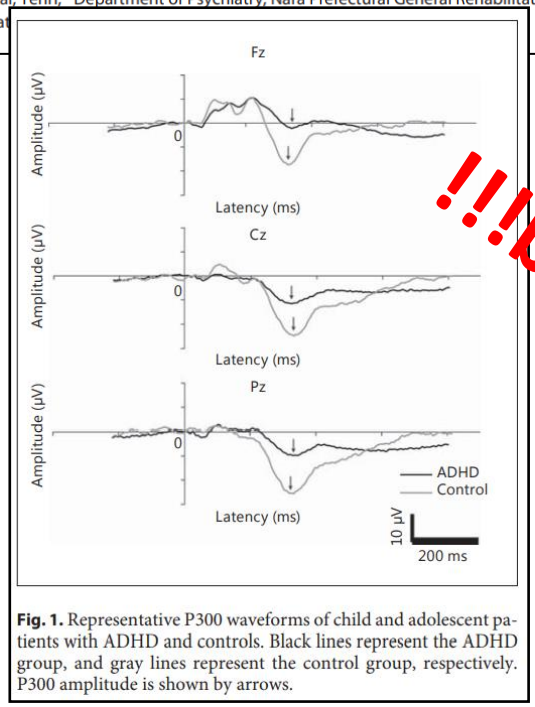


Fig. 1. Representative P300 waveforms of child and adolescent patients with ADHD and controls. Black lines represent the ADHD group, and gray lines represent the control group, respectively. P300 amplitude is shown by arrows.

!!!biomarker?

P300

↓µV

↑ms

Event-related potential components can be modified by ADHD pharmacotherapies

Atomoxetine

P300

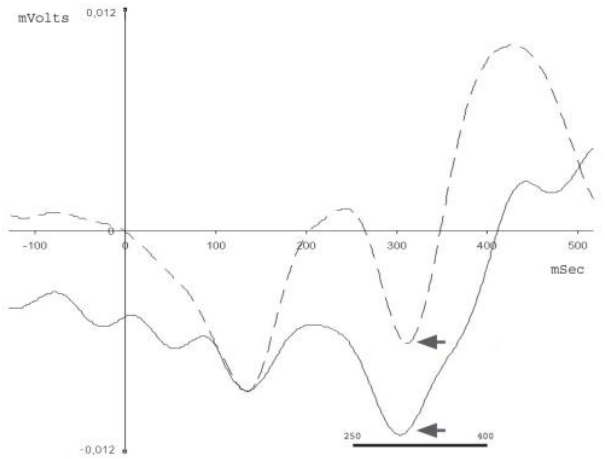


Figure 1. Grand means of ERPs from ADHD children, in conditions of medication with stimulant (continuous line) and no medication (discontinuous line). Arrows indicate the P300 potential, which has more amplitude but the same latency in medicated than in non-medicated conditions (see Fig. 2). This method showed significant effects of medication, of subject and of subject x medication interaction, indicating individual differences in response to treatment, but also a general effect of treatment in all subjects.

Methylphenidate

MMN

Psychopharmacol Bull. 1993;29(2):229-33.

Mismatch negativity in hyperactive children: effects of methylphenidate

B G Winsberg [1], D C Javitt, G S Silipo, P Doneshka

Affiliations + expand

PMID: 8290670

Abstract

This pilot study investigates electrophysiological correlates of methylphenidate (MP) treatment among hyperkinetic children who are clinical responders to therapy. Event-related potentials were obtained from a small sample (6 hyperactive and 5 controls) during an auditory "oddball" task. In the ignore condition, oddball tones elicited a frontocentral "mismatch" negativity (MMN) during the 100- to 200-msec latency range following stimulus presentation. In the attend condition, oddball target tones elicited a centroparietal P3 as well. MP significantly decreased hyperkinetic behaviors. Preliminary analyses of the electrophysiological data indicated a decreased amplitude of the P3 waveform among hyperkinetic children and a trend toward normalization on MP. Waveform abnormalities in the latency range of control MMN suggested either a decrease in MMN amplitude or an increase in MMN latency in hyperactive subjects along with a trend toward normalization by MP. The preliminary data are suggestive of information-processing abnormalities among hyperactive children that may be sensitive to MP therapy.

ERPs as possibile biomarker of ADHD symptoms severity in TSC ???

The aim of this study was to investigate ERP characteristics in patients with ADHD secondary to TSC, compared to patients with drug-naive idiopathic ADHD and healthy controls (HCs), to investigate whether distinct clinical features can be due to different pathophysiological mechanisms.

n°Pts			
13	idiopathic ADHD (iADHD)	4 females, 9 males	7 to 16 years (mean = 10.4 years, median = 9 years)
6	ADHD associated with TSC (tscADHD)	3 females, 6 males	8–15 years (mean = 12.6 years, median = 15 years)
14	age-matched healthy controls (HCs)	9 females, 5 males	8 to 16 years (mean = 11.9 years, median = 12.5 years)

No difference in age was found between the groups of subjects (one-way ANOVA: F = 0.57, P = 0.57)

Inclusion criteria

> diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and age 7–17 years.

> iADHD patients did not have to present any other neurological or medical condition associated with ADHD.

Exclusion criteria

> intelligence quotient <70, psychiatric comorbidity, and sensory deficits

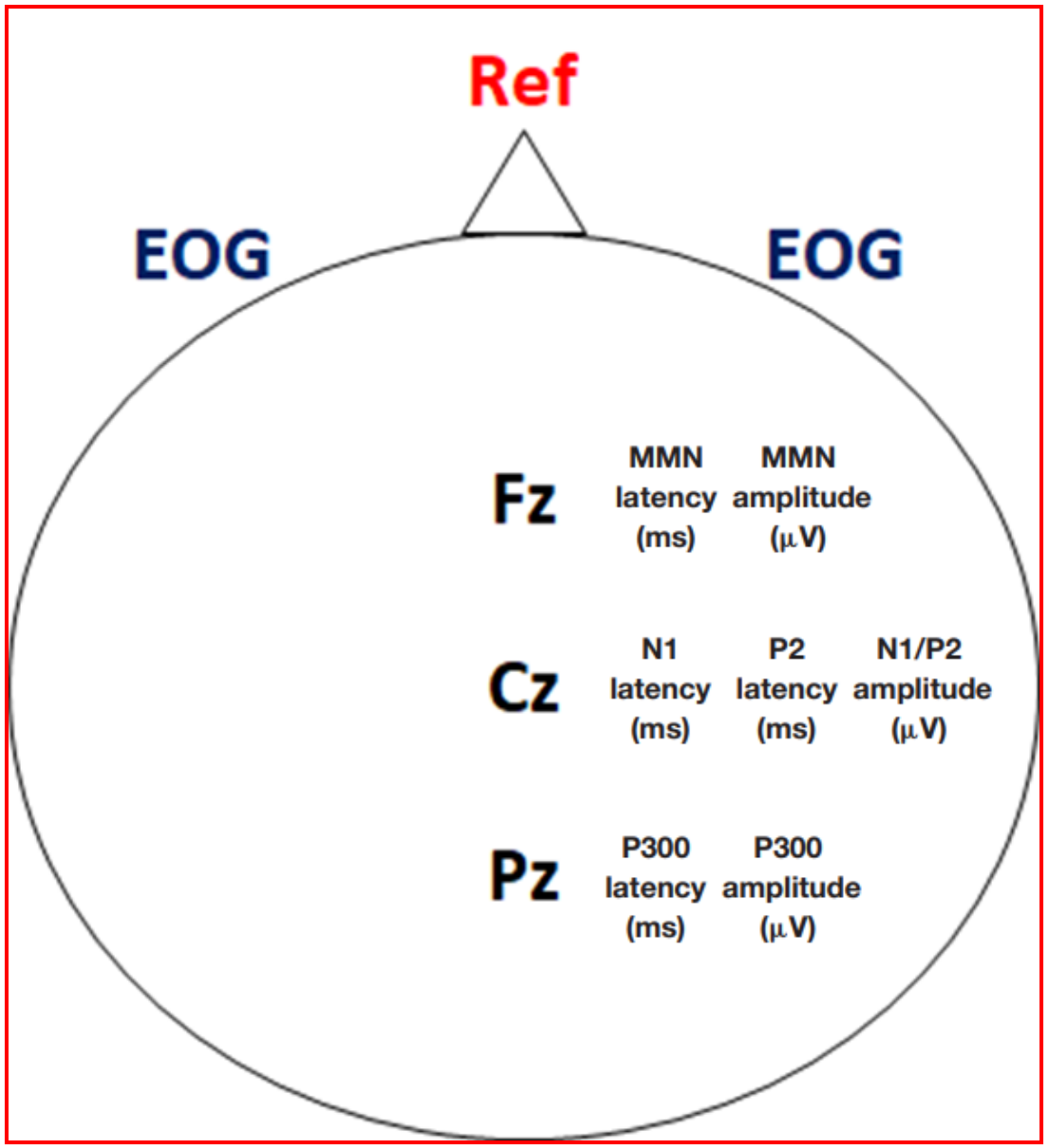
> If ADHD was pharmacologically treated, children were asked to withdraw medications for 48 h before the neurophysiological and neuropsychological examination.

Clinical, EEG, neuroimaging characteristics of tscADHD pts

Patient	Active epilepsy	AED treatment	IED	Brain MRI			
				Tubers	RML	SEN	SEGA
1	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
2	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
3	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
4	No	No	Yes, bilateral TO	Yes, diffuse	Yes, diffuse	Yes	No
5	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
6	No	CBZ	No	Yes, diffuse	Yes, diffuse	Yes	Yes

*Active epilepsy means epileptic seizures in the last 2 years. AED, antiepileptic drugs; IED, interictal epileptiform discharges; RML, radial migration lines; SEN, subependymal nodules; SEGA, subependymal giant cell astrocytomas; MRI, magnetic resonance imaging; CBZ, carbamazepine; TO, temporo-occipital.

Methods

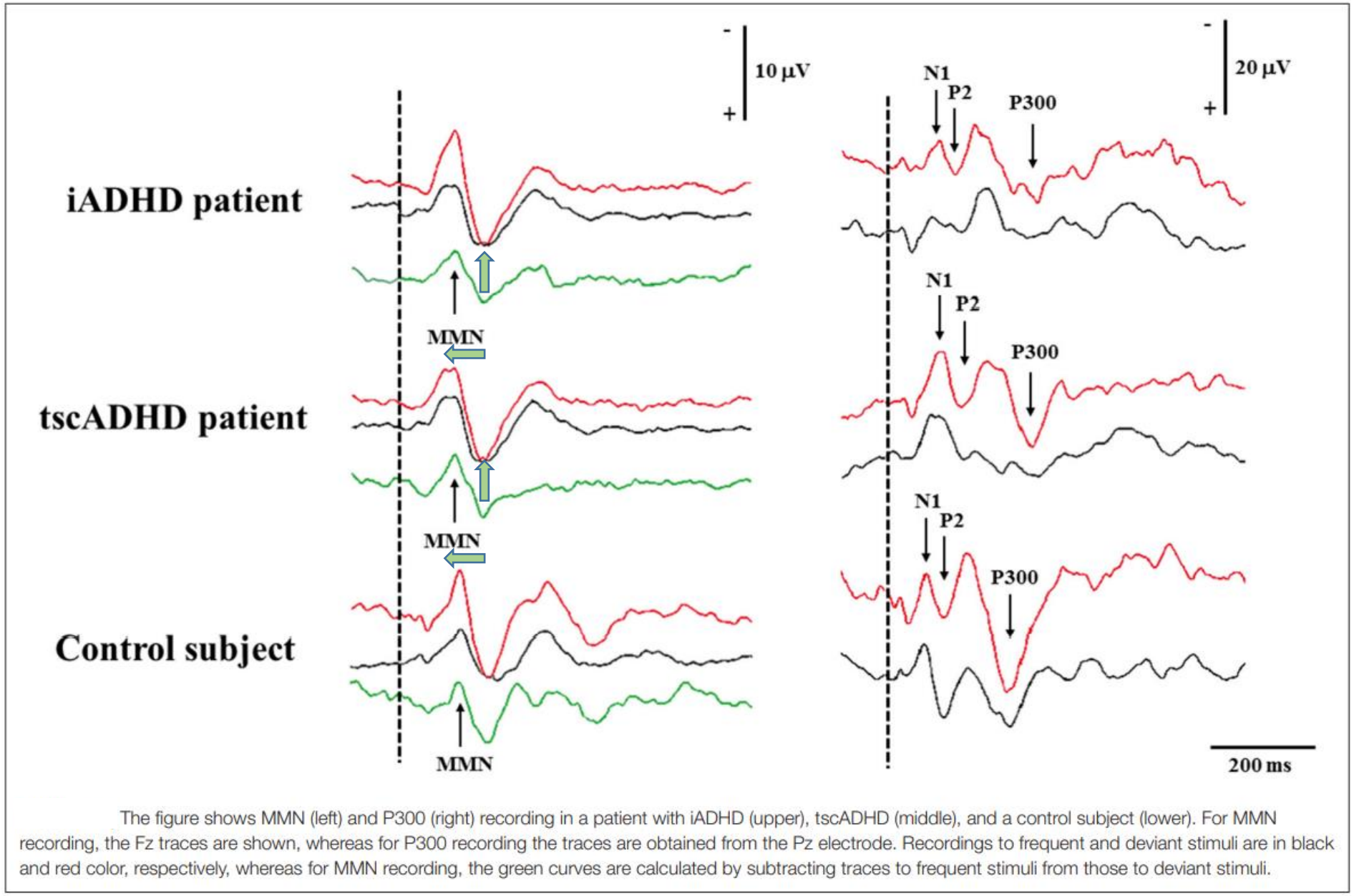


Cognitive and Neuropsychological Examination

All patients underwent the administration of an extensive battery of tests:

- Wechsler Intelligence Scale for Children for the determination of the IQ
- Tower of London test for the assessment of planning and problem solving skills and cognitive flexibility
- span of forward and backward memory numbers (DSF and DSB) for the measurement of short-term verbal memory and working memory
- Trail-Making Test Part A and Part B for the evaluation of visual search strategies, selective and divided attention
- phonological (FAS) and semantic (CAT) verbal fluency test for the evaluation of verbal ability to access vocabulary by phonological and semantic means
- Subtest ToM and ER of the NEPSY-II battery to assess the ability to recognize one's own and others' mental states and the ability to recognize facial expressions
- Physical and Neurological Assessment of Subtle Signs to evaluate minor neurological signs
- Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version, a psychodiagnostic tool for the assessment of psychopathological symptoms in children and adolescents according to DSM-IV Text Revision criteria
- Conners' Parents and Teachers Rating Scale–Revised, questionnaires to be filled in by parents and/or teachers, used for the evaluation of ADHD from 3 to 17 years, and for externalizing disorders that can be found in comorbidities; they also provide an index (ADHD Index), which is able to differentiate subjects affected by unaffected
- Child Behavior Checklist for Ages 6–18, questionnaire to be filled in by parents, which assesses the presence of internalizing and externalizing symptoms in children and adolescents aged between 6 and 18 years.

Results:



The figure shows MMN (left) and P300 (right) recording in a patient with iADHD (upper), tscADHD (middle), and a control subject (lower). For MMN recording, the Fz traces are shown, whereas for P300 recording the traces are obtained from the Pz electrode. Recordings to frequent and deviant stimuli are in black and red color, respectively, whereas for MMN recording, the green curves are calculated by subtracting traces to frequent stimuli from those to deviant stimuli.

MMN

Literature data iADHD:
↓/↑µV
↑ms
ndr

Our data i/tscADHD:
↑µV
↓ms

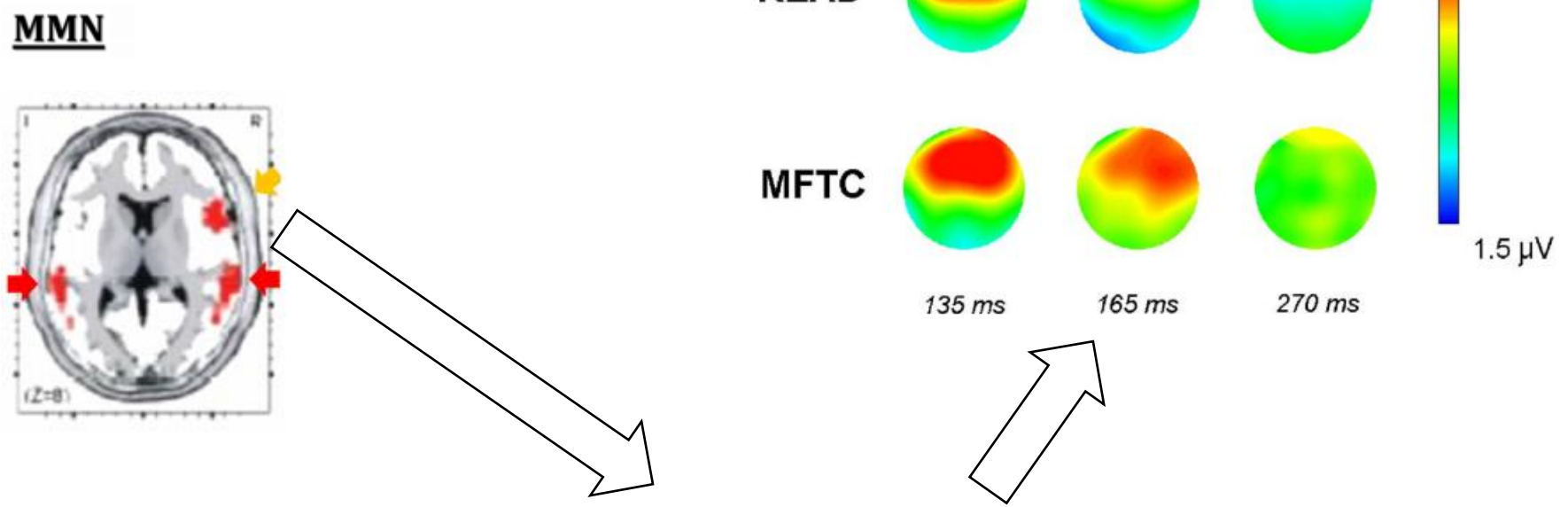
Available online at www.sciencedirect.com
SCIENCE DIRECT
Cognitive Brain Research 25 (2005) 891 – 899
ELSEVIER
COGNITIVE BRAIN RESEARCH
www.elsevier.com/locate/cogbrainres

Research Report

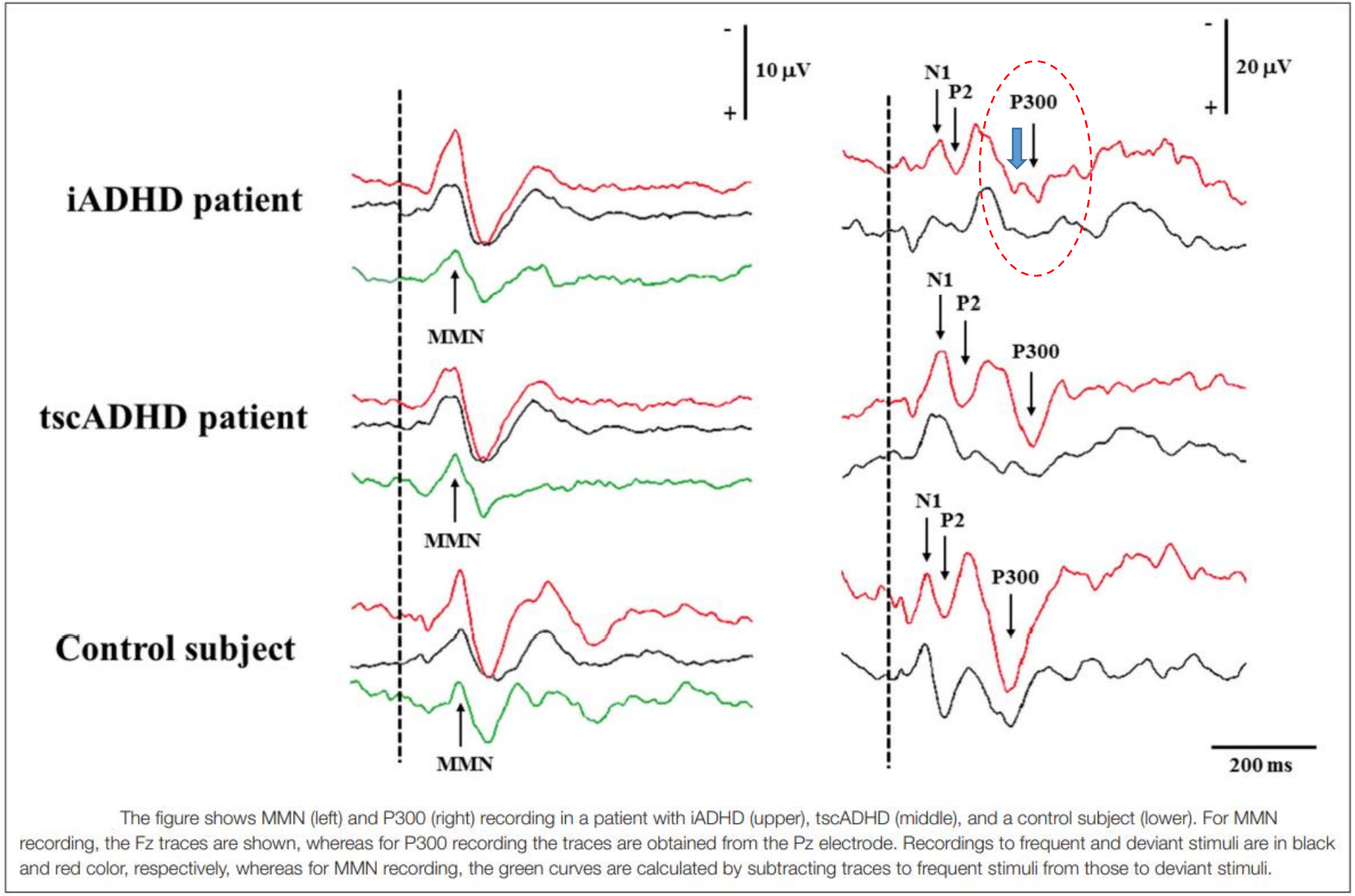
Attentional load of the primary task influences the frontal but not the temporal generators of mismatch negativity

Domenico Restuccia [a,b,*], Giacomo Della Marca [a], Camillo Marra [a], Marco Rubino [a], Massimiliano Valeriani [c]

[a]Department of Neurosciences, Catholic University, Policlinico A. Gemelli, L.go A. Gemelli 8, 00168 Rome, Italy
[b]Scientific Institute "E. Medea"—Regional Scientific Research Center of San Vito al Tagliamento and Pasian di Prato, Italy
[c]Division of Neurology, Pediatric Hospital "Bambino Gesù", IRCCS, Rome, Italy



Concomitant highly demanding task
*→ Bilateral Auditory cortex + **Frontal source ?***

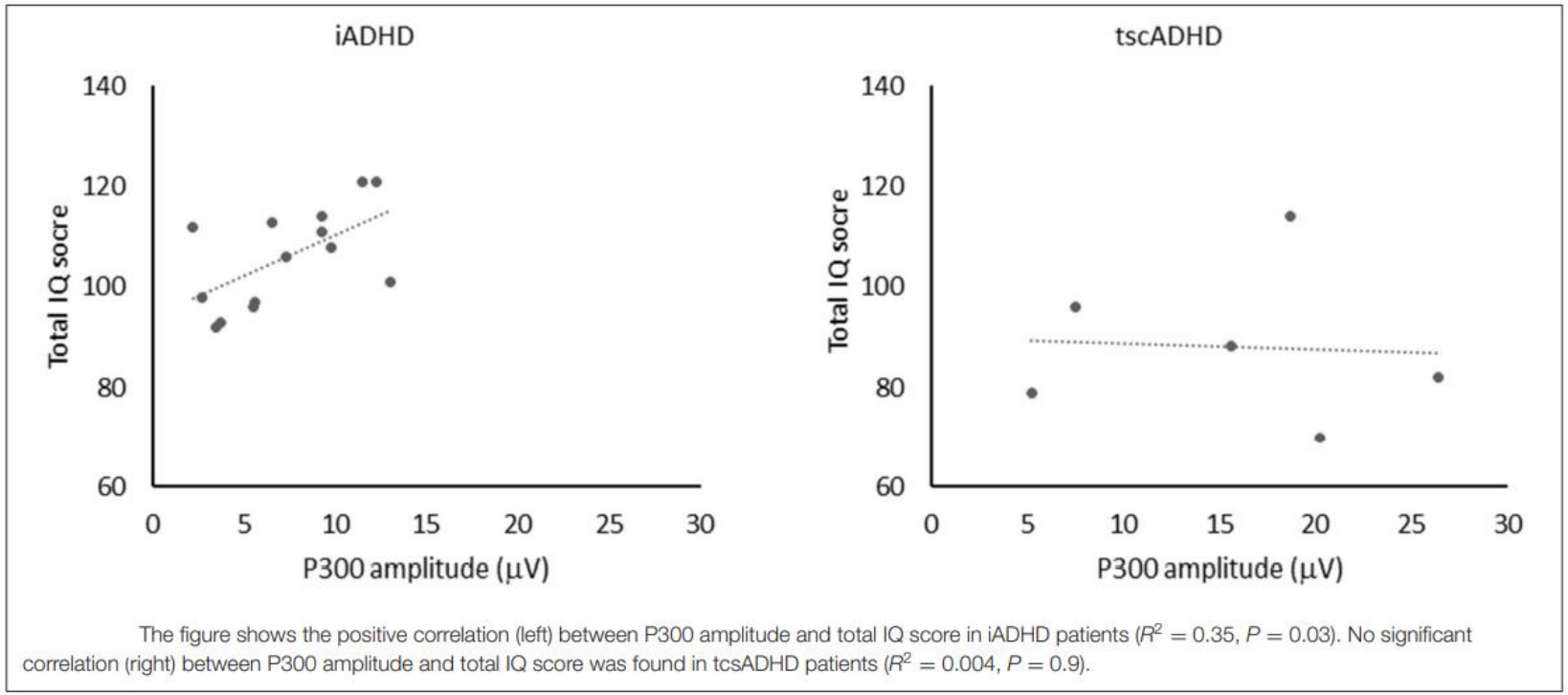


The figure shows MMN (left) and P300 (right) recording in a patient with iADHD (upper), tscADHD (middle), and a control subject (lower). For MMN recording, the Fz traces are shown, whereas for P300 recording the traces are obtained from the Pz electrode. Recordings to frequent and deviant stimuli are in black and red color, respectively, whereas for MMN recording, the green curves are calculated by subtracting traces to frequent stimuli from those to deviant stimuli.

Mean values of total (TIQ), verbal (VIQ), and performance (PIQ) intelligent quotient in patients with idiopathic ADHD compared to patients to ADHD associated with TSC.

	iADHD	tscADHD	*P*
TIQ	105.9	85.8	0.004
VIQ	113.9	92.2	0.016
PIQ	109.1	91.3	0.032

Total QI



The figure shows the positive correlation (left) between P300 amplitude and total IQ score in iADHD patients ($R^2 = 0.35$, $P = 0.03$). No significant correlation (right) between P300 amplitude and total IQ score was found in tcsADHD patients ($R^2 = 0.004$, $P = 0.9$).

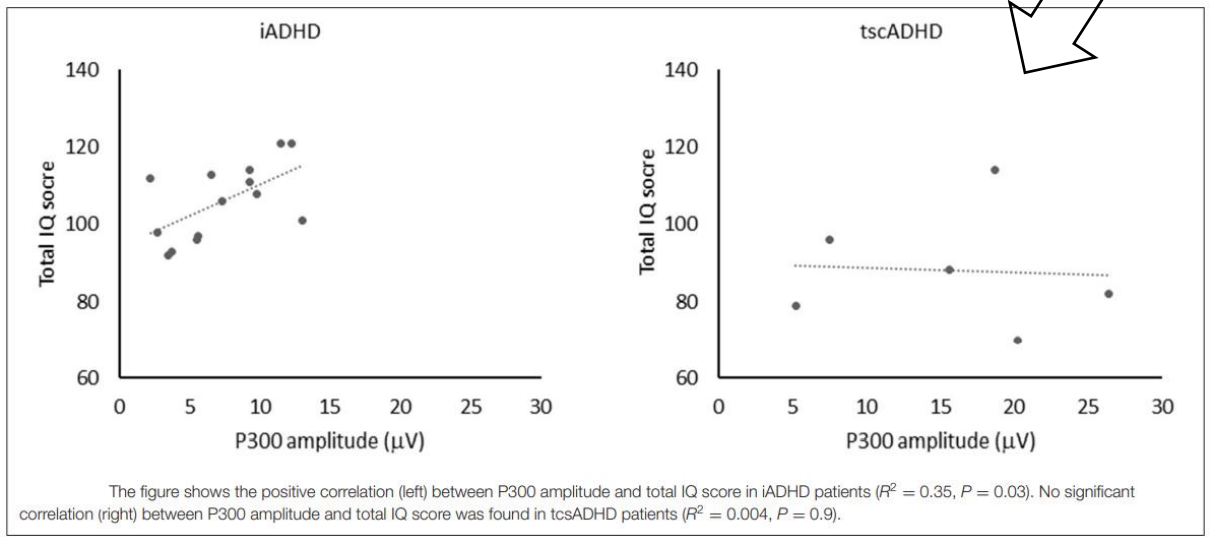
P300 amplitude

P300 µV iADHD<HCs

- *Reduced attention orienting to warning stimuli*
- *Faliure to allocate sufficient attentional resources to stimulus evalutation process due to reduced attentional capacity*

P300 µV tscADHD≈HCs ???

P300 amplitude might be influenced by different variables, especially by cognitive factors



The figure shows the positive correlation (left) between P300 amplitude and total IQ score in iADHD patients ($R^2 = 0.35$, $P = 0.03$). No significant correlation (right) between P300 amplitude and total IQ score was found in tcsADHD patients ($R^2 = 0.004$, $P = 0.9$).

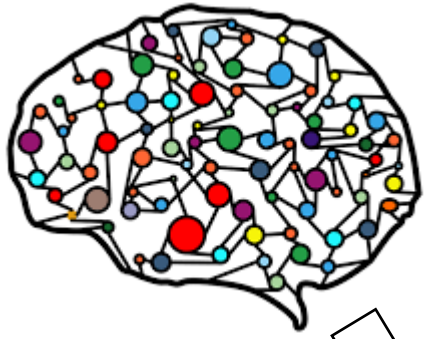
Mean values of the results obtained in neuropsychological tests administered in subjects with idiopathic ADHD and ADHD with TSC.

	iADHD	tscADHD	*P*
ToL (z)	−0.7	−1.22	0.08
DSF	−0.43	−2.15	**0.006**
DSB	−0.05	−1.22	0.05
FAS	−1.2	−1.24	0.87
CAT	−1.7	−3.51	**0.018**
TMTA (s)	62.4	81.33	0.47
TMTB (s)	148.3	114	0.32
CPRS- opp	60.76	66.83	0.43
CPRS-inatt	74.61	80.33	0.5
CPRS-hyper	68.53	70.16	0.83
CPRS-ADHD index	76.61	78.66	0.75

Significant P values in bold. ToL, Tower of London; DSF, direct number span; DSB, span of inverse numbers; FAS, phonemic fluence; CAT, categorical fluency; CAT TMTA, Trail-Making Test Part A; TMTB, Trail-Making Test Part B.

Marked Network dysregulation in TSC

Corticali Tubers
Frontal Epileptiform abnormalities
Genetic mutation *per se*



P300 amplitude does not really reflect symptom severity in TSC

Patient	Active epilepsy	AED treatment	IED	Brain MRI			
				Tubers	RML	SEN	SEGA
1	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
2	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
3	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
4	No	No	Yes, bilateral TO	Yes, diffuse	Yes, diffuse	Yes	No
5	No	No	No	Yes, diffuse	Yes, diffuse	Yes	No
6	No	CBZ	No	Yes, diffuse	Yes, diffuse	Yes	Yes

**Active epilepsy means epileptic seizures in the last 2 years. AED, antiepileptic drugs; IED, interictal epileptiform discharges; RML, radial migration lines; SEN, subependymal nodules; SEGA, subependymal giant cell astrocytomas; MRI, magnetic resonance imaging; CBZ, carbamazepine; TO, temporo-occipital.*

I = tsc

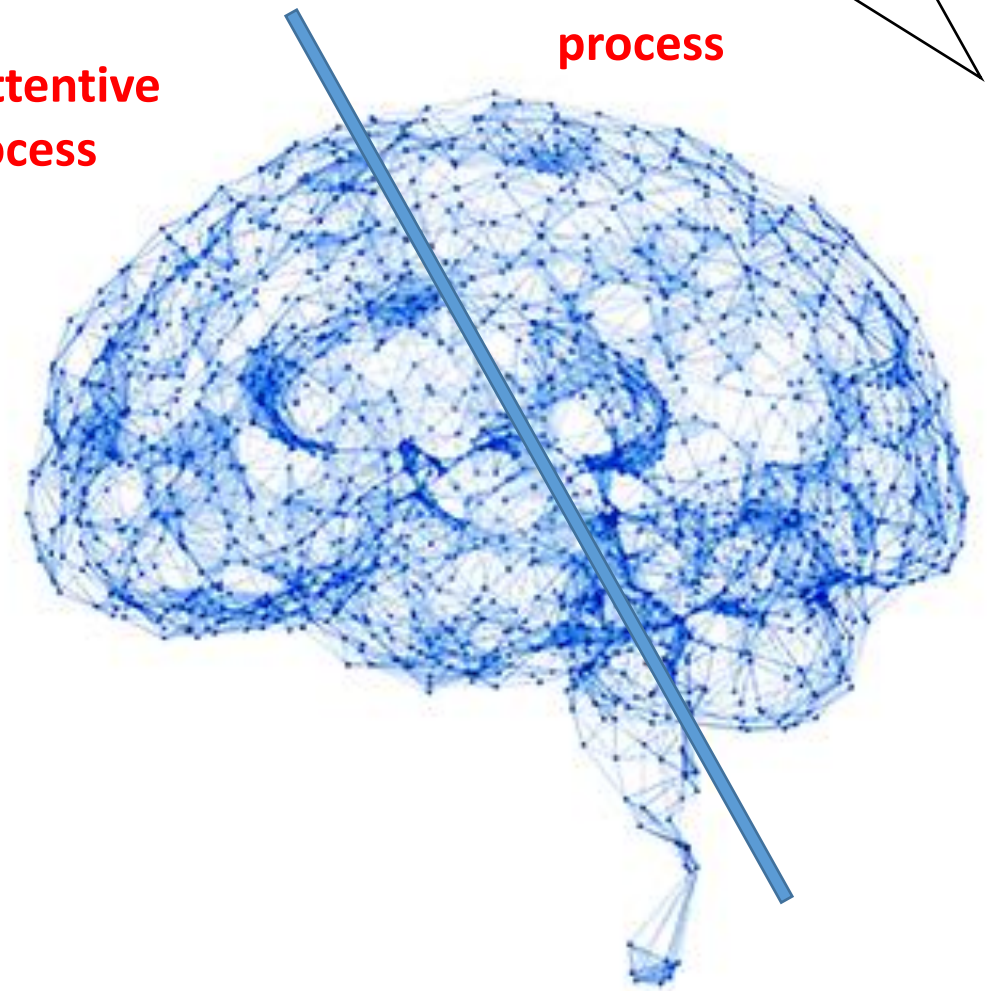
ADHD phenotype

I ≠ tsc

ADHD etiology

Attentive process

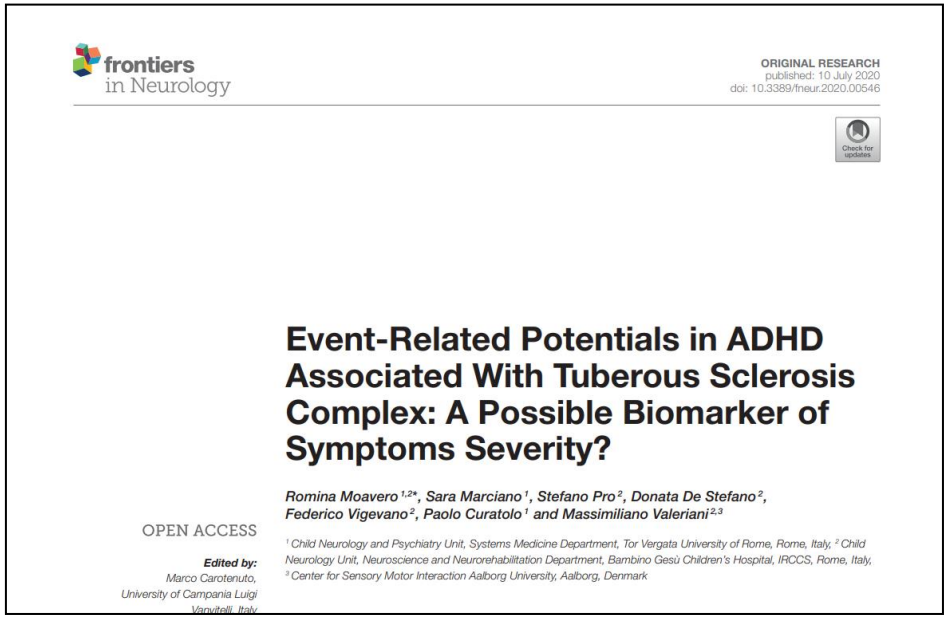
Pre-Attentive process



Bambino Gesù
OSPEDALE PEDIATRICO

PTV
FONDAZIONE PTV
POLICLINICO TOR VERGATA

Thanks



frontiers in Neurology

ORIGINAL RESEARCH
published: 10 July 2020
doi: 10.3389/fneur.2020.00546

Check for updates

Event-Related Potentials in ADHD Associated With Tuberous Sclerosis Complex: A Possible Biomarker of Symptoms Severity?

Romina Moavero[1,2], Sara Marciano[1], Stefano Pro[2], Donata De Stefano[2], Federico Vigevano[2], Paolo Curatolo[1] and Massimiliano Valeriani[2,3]*

[1] Child Neurology and Psychiatry Unit, Systems Medicine Department, Tor Vergata University of Rome, Rome, Italy, [2] Child Neurology Unit, Neuroscience and Neurorehabilitation Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [3] Center for Sensory Motor Interaction Aalborg University, Aalborg, Denmark

OPEN ACCESS

Edited by:
Marco Carotenuto,
University of Campania Luigi
Vanvitelli, Italy