INTERNATIONAL CONFERENCE WILLIAMS SYNDROME 2022
Clinical, genetic and social aspects

SOCIO ADAPTIVE PROFILE IN THE WILLIAMS SYNDROME (WBS)

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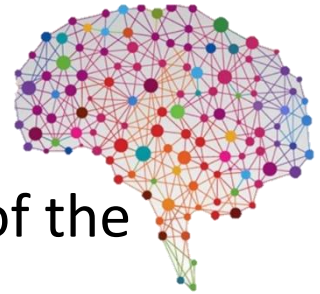
ASSOCIAZIONE ITALIANA SINDROME DI WILLIAMS

Bambino Gesù
OSPEDALE PEDIATRICO

COGNITIVE-BEHAVIORAL PHENOTYPE



- Over the last decades, a lot of researchers started to be interested to the study of the cognitive-behavioral phenotype in genetic syndromes, in order to identify the relationship between the phenotype of a syndrome (=what we see, its physical and behavioral manifestation) and the genotype (= genetic background)(Battaglia 2001)

- In the individuals with intellectual disability (ID) and genetic syndromes, the neurobehavioral profile depends to the etiology and the specyfic brain development (Vicari et al., 2001). Indeed, the emotional and cognitive developments can considerably differ from syndrome to syndrome (but also within the same syndrome).

European Journal of Human Genetics (2014) 22, 64–70

www.nature.com/ejhg

ARTICLE

Smaller and larger deletions of the Williams Beuren syndrome region implicate genes involved in mild facial phenotype, epilepsy and autistic traits

Carmela Fusco[1,6], Lucia Micale[1,6], Bartolomeo Augello[1], Maria Teresa Pellico[1], Deny Menghini[2], Paolo Alfieri[2], Maria Cristina Digilio[3], Barbara Mandriani[1,4], Massimo Carella[1], Orazio Palumbo[1], Stefano Vicari[2] and Giuseppe Merla*[,1,5]

WILLIAMS SYNDROME IDENTIKIT (?)

- **Verbal skills > Non-verbal skills (Verbal IQ > Performance IQ)**
- **Language is atypical: tangential, perseverative, repetitive, logorrheic, etc.**
- **Discontinuous eye contact → anxiety**
- **Deficits across the different attentional components (selective, sustained, divided and alternating)**
- **Hyperacusis (sensitivity to sounds)**
- **Difficulties in fine and gross motor development**
- **Over-friendly personality**
- **Anxiety disorders: generalized anxiety and specific phobias**

Bello et al., 2004

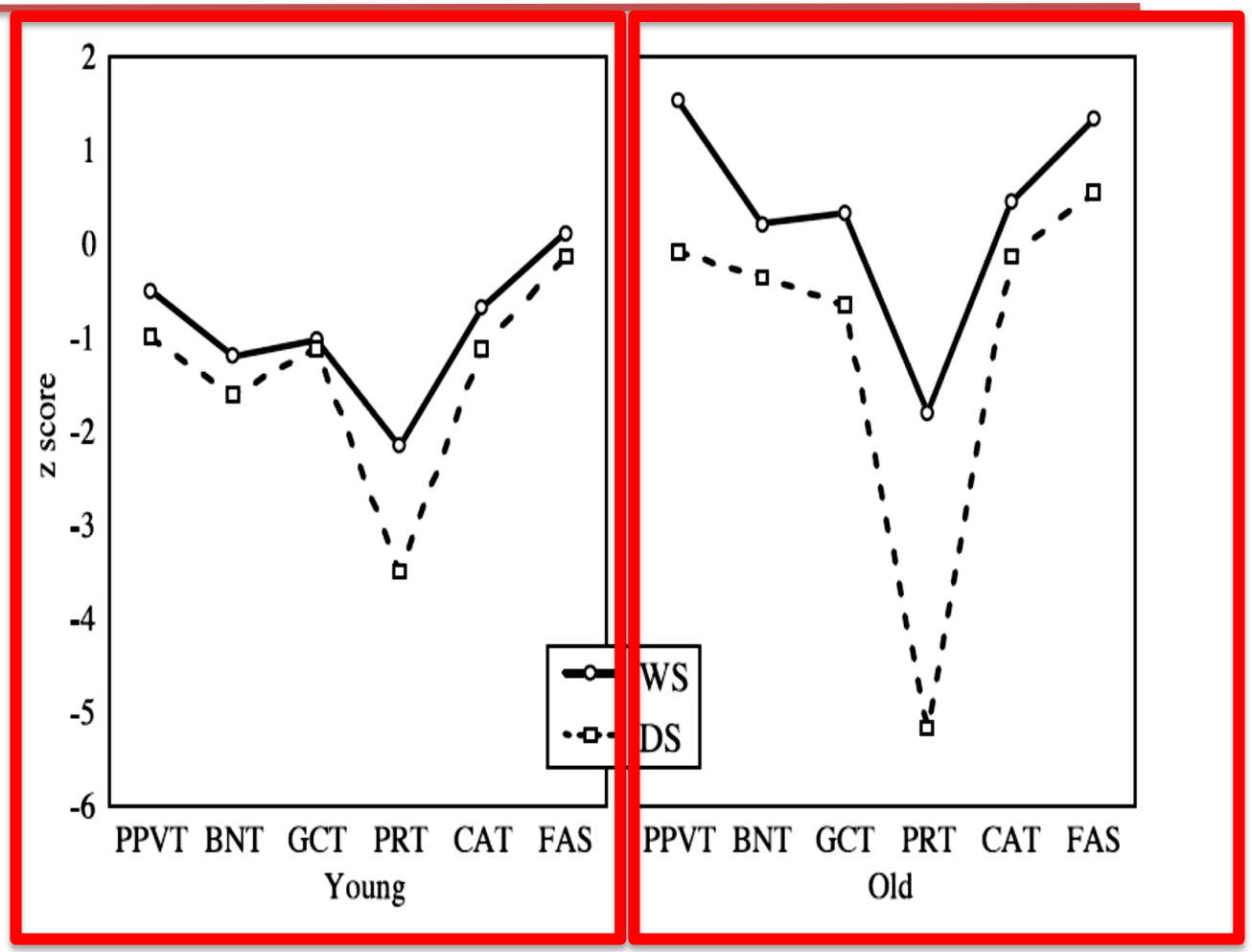
The cognitive phenotype changes over the time

(Vicari et al. 2004)

Developmental trajectories and neuroanatomical correlates

Table 2. Demographic characteristics of "young" and "old" individuals with WS, DS and typically developing controls

	Chronological age			Mental age			IQ		
	M	(*SD*)	Range	*M*	(*SD*)	Range	*M*	(*SD*)	Range
WS1 (*N* = 16)	6.8	(1.0)	5.1–8.0	4.5	(1.1)	2.7–6.7	66.7	(15.0)	40–96
DS1 (*N* = 9)	7.5	(0.6)	6.5–8.0	4.1	(0.6)	3.3–5.4	55.6	(8.0)	45–71
WS2 (*N* = 25)	17.6	(4.1)	12.5–26.8	5.8	(1.0)	2.8–7.5	41.3	(5.5)	34–50
DS2 (*N* = 25)	16.4	(2.8)	12.2–25.9	5.5	(0.7)	4.2–7.8	37.6	(4.4)	28–47



FOCUS ON WBS LANGUAGE

Language Pragmatic is particularly impaired

Some authors (Reilly et al., 2004; Philofsky et al., 2007) report **difficulties during communicative interaction**s such as:

- Inappropriate conversation's initiation
- Use of stereotyped phrases
- Difficulty on the understanding of what others are saying

Other studies (Gillberg & Rasmussen 1994; Schreiber 2002; Semel & Rosner 2003; Laws & Bishop 2004; Stojanovik et al. 2006) describe individuals with WS as:

- They talk a lot
- frequently tell personal but irrelevant experiences
- **their speech** is often tangential; they exhibit difficulty in conversational adherence, verbal perseverations and repetitive behaviors

Overall, they are interested in establishing friendly relationships but at the same time show a little understanding of the social rules that are necessary in the social interactions (Van Der Fluit et al., 2012).

Content and formal aspects represent a strength, while the usage of the functional aspects of language are a weakness, with negative consequences in the social interactions.

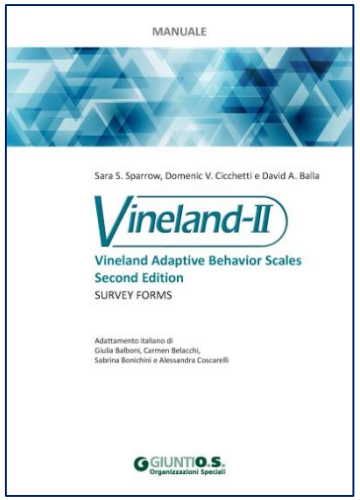
It is important non only the comparision between cognitive profiles…

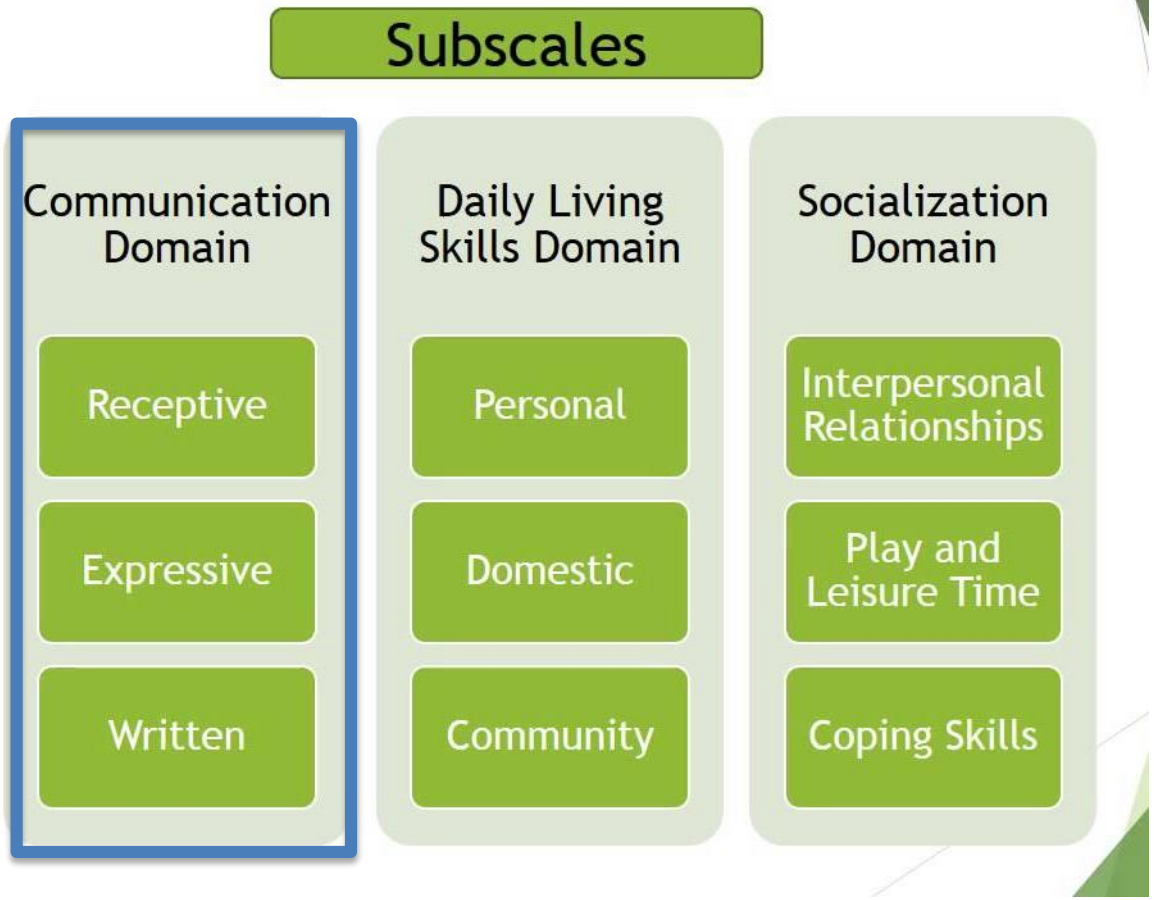
ADAPTIVE FUNCTIONING EVALUATION SHOULD BE MANDATORY(VABS)

DSM 5
Intellectual Disabilty

- **Deficit in intellectual functioning (**Reasoning;Problem solving; Planning;Abstract thinking; Judgment; Academic learning; Experiential learning)
- Deficits or impairments in **adaptive functioning.** This includes skills needed to live in an independent and responsible manner.

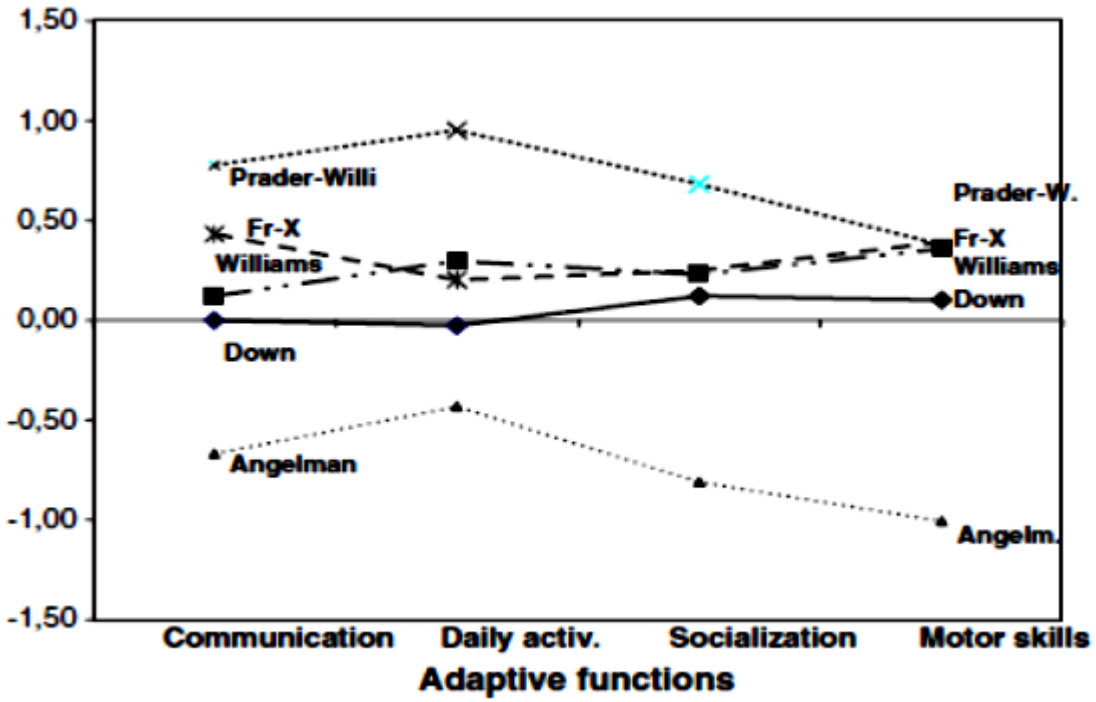
These limitations occur during the developmental period





Not only comparisons between cognitive profiles

Adaptive behavior profiles' Comparisons



Composition of the sample and differences in chronological and mental age.

Syndrome	Total	Male and %	Chronological age range (months)	Chronological age (months)[1] Mean ± s.e.	Mental age range (months)	Mental age (months)[2] Mean ± S.E.
Down	109	60 (55%)	48-468	174.94 ± 9.19	30-132	81.04 ± 1.44
Williams	12	9 (75%)	84-360	210.00 ± 27.69	36-120	77.96 ± 5.04
Angelman	16	7 (44%)	60-396	212.25 ± 23.98	12-72	24.40 ± 5.44
Prader-Willi	18	8 (44%)	36-384	178.67 ± 22.61	30-132	83.16 ± 4.32
Fragile X	26	23 (88%)	48-432	174.92 ± 18.81	30-108	77.63 ± 3.36
	181	107 (59%)				

[1] $F = 0.84$, $P = 0.50$.
[2] $F = 18.21$, $P < 0.001$ - excluding Angelman group: $F = 0.59$, $P = 0.62$.

Psychiatry Research 189 (2011) 440–445

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Psychiatry Research

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Behavioral phenotypes of genetic syndromes with intellectual disability: Comparison of adaptive profiles

Santo Di Nuovo [a,*], Serafino Buono [b]

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1. Greatest adaptive profile in Prader-Willi syndrome
2. Similar profile in Williams and X-fragile syndrome
3. Flat profile in Down syndrome
4. Worse adaptive profile in Angelman syndrome

This work confirmed the hypothesis of partial specificity --> some differences are syndrome-specific, others seem more nonspecific.

Profiles and Development of Adaptive Behavior in Adolescents and Adults with Williams Syndrome

Trista Juhsin Fu

TABLE II: MEAN AGES, IQ, AND SIB-R SCORES BY AGE GROUPS (WITH STANDARD DEVIATION IN THE PARENTETHESE)

	Age Groups		
	12-20 (*n*=29)	21-35 (*n*=42)	36-53 (*n*=27)
Age	15.82 (2.61)	28.11 (4.62)	41.75 (5.04)
IQ	57.10 (11.71)	65.27 (8.19)	69.70 (8.53)
Broad Independence	48.55 (20.83)	49.14 (19.79)	46.37 (19.25)
Social Interaction and Communication	72.34 (19.87)	67.14 (17.00)	60.81 (15.23)
Personal Living	59.79 (17.84)	59.55 (16.33)	55.00 (18.00)
Community Living	49.72 (19.13)	50.83 (20.41)	49.93 (19.72)
Motor Skills	49.86 (21.39)	54.64 (17.32)	52.70 (21.85)

TABLE I: CORRELATION COEFFICIENTS BETWEEN AGE AND SIB-R SCORES FOR WS

SIB-R Scores	Pearson r	Significance
Broad Independence Score	-.024	.809
Social Interaction and Communication	-.208*	.038
Personal Living	-.079	.435
Motor Skills	.057	.574
Community Living	-.010	.924

Journal of Intellectual Disability Research doi: 10.1111/jir.12401

A comparison between linguistic skills and socio-communicative abilities in Williams syndrome

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The Communication Adaptive Profile is peculiar in WBS

Comparison between language (PPVT, PVCL, BNT), adaptive skills (Communication Scale, Vineland) and mental age in 32 children and adolescents with Williams Syndrome.
In children with Williams Syndrome, it has been described an adaptive profile with areas of strength in "Communication" and "Socialization" (Greer et al. 1997, Hahn et al., 2014, Del Cole et al., 2017) (*Greer et al. 1997, Hahn et al., 2014, Del Cole et al., 2017*)

	Whole group (n = 32)	P
Mental age Mean (range)	71.8 (40–102)	
vs.		
PPVT-r	79.5 (36–132.5)	0.04
PVCL	67.4 (46–90)	0.14
BNT	81.6 (36–150)	0.002
Communication	85 (49–132)	0.005
Receptive	52.7 (18–110)	0.01
Expressive	84.5 (42–116)	0.01
Written language	90.7 (41–177)	0.001

Comparison between mental age and Communication Domain (VABS II) over different ages

	Children (n = 15)	P	Adolescents/young adults (n = 17)	P
Mental age Mean (range)	61.7 (40–80)		80.8 (51–102)	
vs.				
PPVT-r	63.7 (36–84.5)	0.68	93.6 (53.5–132.5)	0.04
PVCL	61 (51–75)	0.53	73.5 (46–90)	0.14
BNT	69.7 (36–90)	0.09	92.1 (51–150)	0.01
Communication	79.3 (51–113)	0.01	90 (49–132)	0.14
Receptive	56.2 (18–110)	0.59	49.6 (18–110)	0.007
Expressive	83.1 (57–108)	0.004	85.5 (42–116)	0.48
Written language	75.5 (41–101)	0.02	104.4 (56–177)	0.01

In the younger children, VABS II, Receptive subdomain did not differ from MA, while in adolescents/young adults performance was significantly lower in comprehension subdomain when compared to MA

General domain seems a strength in younger children (significantly higher than MA); in older children it did not significantly differ from MA

Comparison between Receptive subscale of the Communication domain in VABSII and PPVT and PVCL over different ages

	Children (n = 15) Mean (range)	P	Adolescents/young adults (n=17) Mean (range)	P
Receptive	56.2 (18 – 110)		49.6 (18 – 110)	
vs.				
PPVT-r	63.7 (36 – 84.5)	0.39	93.6 (53.5 – 132.5)	0.002
PVCL	61.0 (51 – 75)	0.59	73.4 (46 – 90)	0.013

In younger children, VABS II Receptive subdomain did not differ significantly from instrumental comprehension PPVT and PVCL, while in adolescents/young adults a significantly lower performance in Receptive emerged in comparison to instrumental comprehension (PPVT and PVCL)
Over the time, the instrumental level comprehension increases, but receptive to Vineland does not; indeed it tends even to lower in the group of older people.

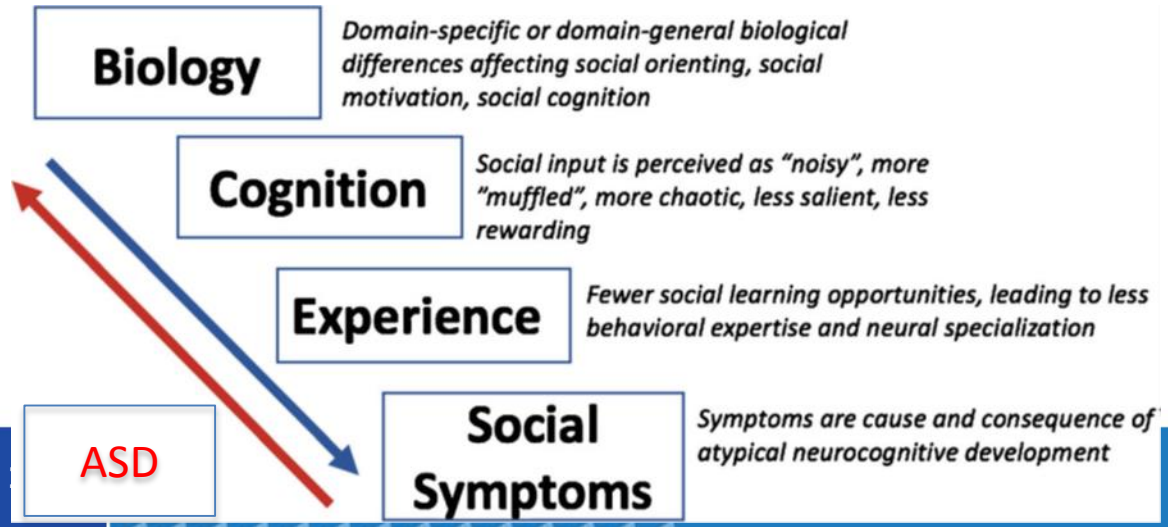
A COMPARISON WITH THE AUTISM SPECTRUM DISORDER (ASD)

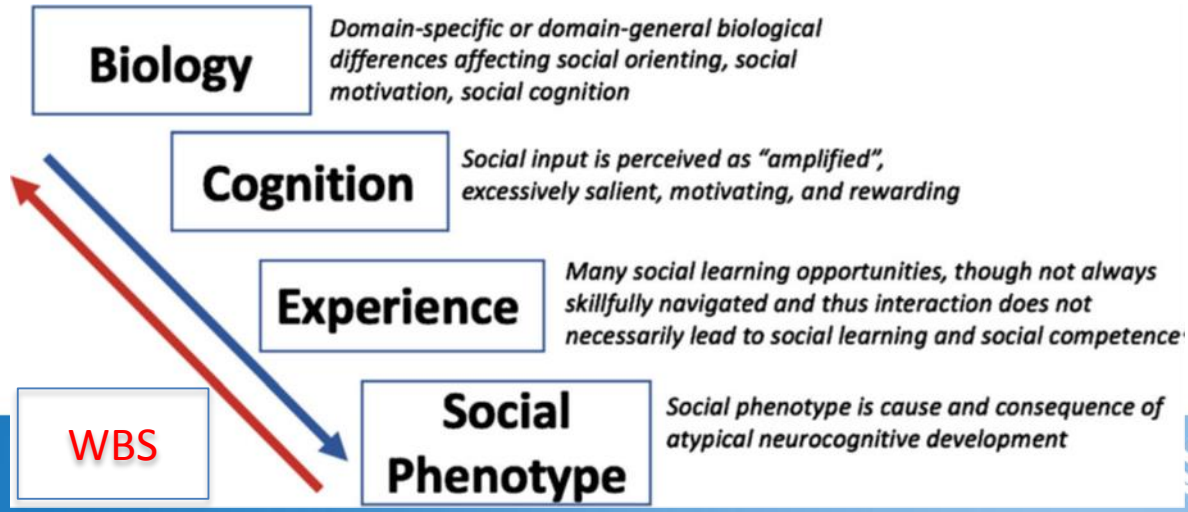
Both WBS and ASD: eye contact difficulties, difficulty in peer relationships, repetitive behaviors, need for sameness (Vivanti et al., 2018)

<u>WBS and ASD have long been treated as "the opposite poles of a condition."</u>

During preschool age, they both show difficulty in shared attention, in objects manipulation, in social relationships, in pragmatic language usage. and emotion recognition.

Approximately 30-35% of children with WBS meet the criteria for ASD on ADOS/ADOS-2 (specific tests for identifying autistic symptomatology) (Klein-Tasman 2007, 2018)





genes

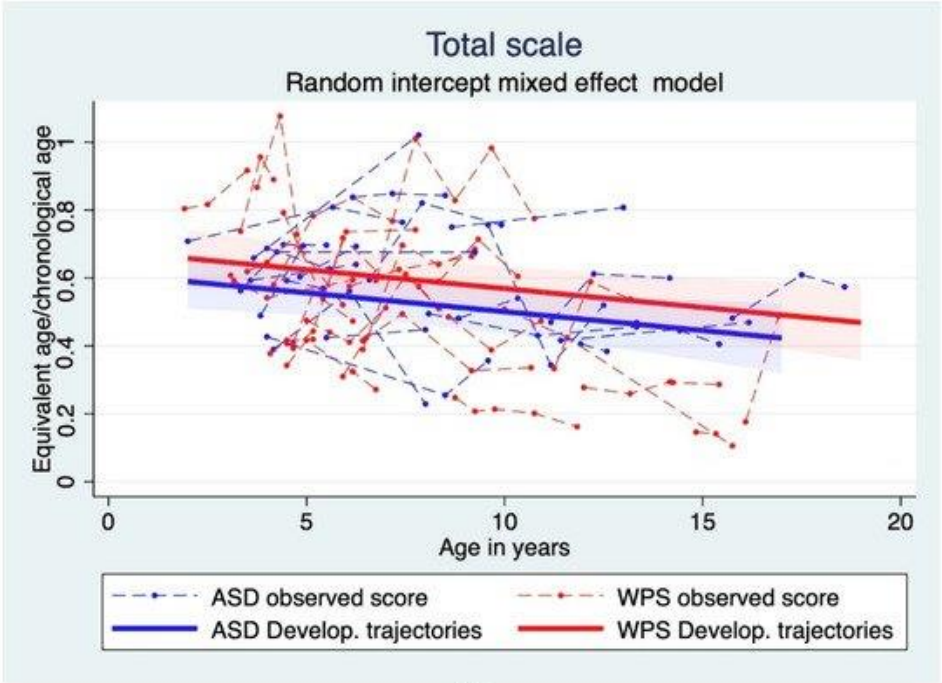
MDPI

Article

Differences and Similarities in Adaptive Functioning between Children with Autism Spectrum Disorder and Williams–Beuren Syndrome: A Longitudinal Study

Paolo Alfieri [1,*,†], Francesco Scibelli [1,†], Federica Alice Maria Montanaro [1], Maria Cristina Digilio [2], Lucilla Ravà [3], Giovanni Valeri [1] and Stefano Vicari [1,4]

Aim: Comparison of longitudinal data of adaptive functioning measured by Vineland Adaptive Behavior Scales (VABS) between two samples of children and adolescents with ASD and WBS, matched for chronological age and cognitive/developmental level at the time of the first evaluation.



(d)

Results: no difference on the global adaptive level, both at the first evaluation and over time. However, significant differences emerged on the socialization and communication levels at the time of recruitment. **Longitudinal data show that only the socialization domain remains different over time, with individuals with WBS having better functioning than those with ASD.**

All the investigated domains in children with WBS and ASD have a descending trajectory, including global adaptive functioning → **WBS is not less severe than ASD!**

A RECENT STUDY

ORIGINAL PAPER

Williams syndrome: reduced orienting to other's eyes in a hypersocial phenotype

Johan Lundin Kleberg[1,2] · Deborah Riby[3] · Christine Fawcett[4] · Hanna Björlin Avdic[1] · Matilda A. Frick[4,5] · Karin C. Brocki[4] · Jens Högström[1] · Eva Serlachius[1] · Ann Nordgren[2,6] · Charlotte Willfors[2,6]

Accepted: 31 March 2022

Task: human faces cropped in order to include only the inner part of the face. Actors were male or female with expressions of joy, anger or neutral.

Sample: children, adolescents and adults with WBS and children, adolescents and adults with typical development

Results:

- People with WBS show lower eye preference than controls in all age groups.
- Children with WBS show lower ability to discriminate angry faces than controls.
- Adolescents and adults with WBS show a greater preference for neutral facial expressions than for joy and anger, aspect not observed in controls.

WILLIAMS SYNDROME REGION
(DELETION VS DUPLICATION 7Q11.23 REGION)

--**Deletion 7q11.23** results in reduced social anxiety, generalized anxiety/phobias, hyperverbalism, hypersociality, reduced visuospatial skills, and relatively preserved expressive competences (incidence 1:8000)

-Duplication of the same region determines deficit in expressive language, marked separation anxiety, social anxiety, aggression, schizophrenia (incidence 1:13000)

› Front Psychiatry. 2022 May 6;13:863909. doi: 10.3389/fpsyt.2022.863909. eCollection 2022.

A Comparison of Adaptive Functioning Between Children With Duplication 7 Syndrome and Williams–Beuren Syndrome: A Pilot Investigation

Paolo Alfieri [1], Francesco Scibelli [1], Federica Alice Maria Montanaro [1], Cristina Caciolo [1], Paola Bergonzini [1], Maria Lisa Dentici [2 3], Stefano Vicari [1 4 5]

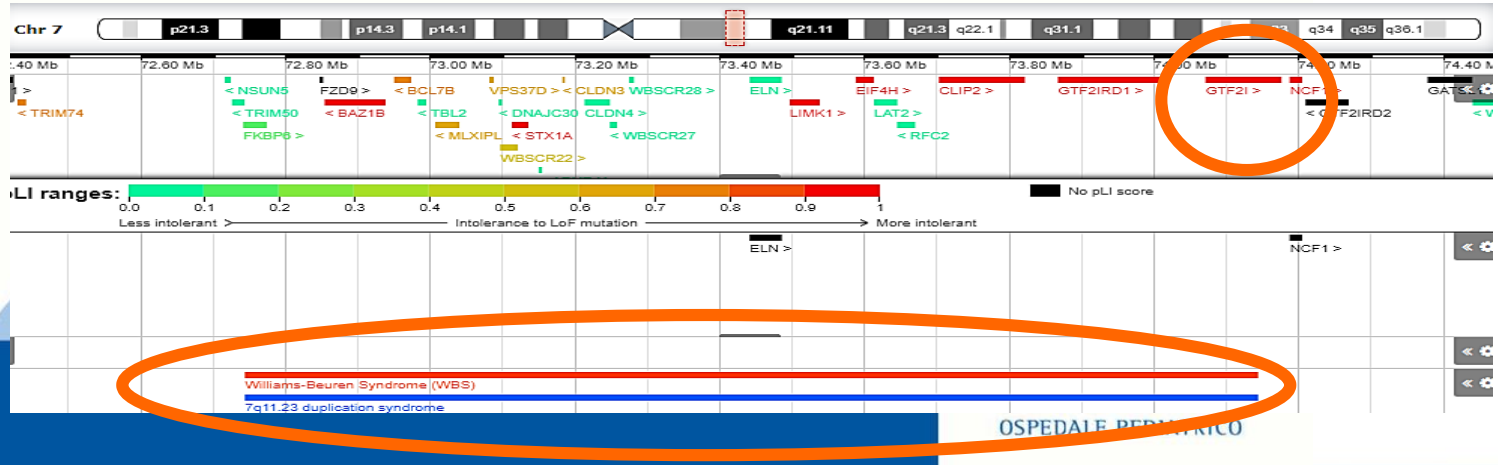
Affiliations + expand

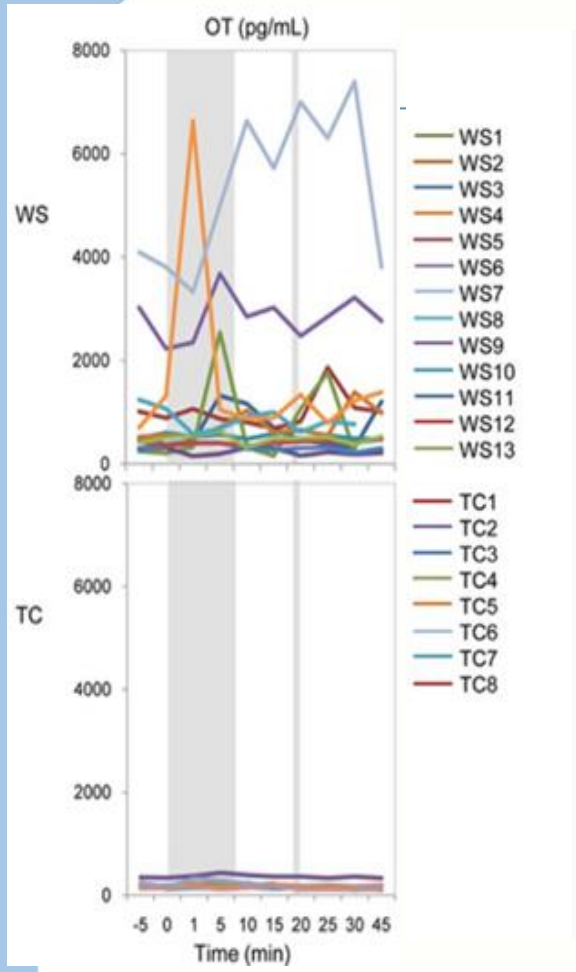
PMID: 35599769 PMCID: PMC9120542 DOI: 10.3389/fpsyt.2022.863909

Free PMC article

Abstract

Interstitial deletions of 7q11.23 cause the well-known Williams-Beuren Syndrome (WBS), while duplication of the same region leads to duplication 7 syndrome (Dup7). Children with WBS share a distinct neurobehavioral phenotype including mild to severe intellectual disability, severely impaired visual spatial abilities, relatively preserved verbal expressive skills, anxiety problems, enhanced social motivation (i.e., hypersociable behaviors) and socio-communicative problems. Children with Dup7 syndrome exhibit some "inverted" features when compared to those of individuals with WBS, such as reduced social motivation and impairment of expressive language. Direct comparison of WBS and Dup7 represents a unique opportunity for the neurobehavioral characterization of the 7q11.23 section. However, most of the available data come from qualitative analysis between different studies. To the best of our knowledge, there are no studies directly comparing features of two matched samples of individuals with WBS and Dup7 syndromes. In this pilot study, we compare the adaptive





(Dai et al., 2012)

Neuroscience and Biobehavioral Reviews 79 (2017) 14–26

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Review article

Williams syndrome deletions and duplications: Genetic windows to understanding anxiety, sociality, autism, and schizophrenia

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Elevated oxytocin levels in WBS if compared with controls.
-Evidences of 'reverse' behaviors in the two reciprocal syndromes.
(WBS vs duplication 7q11.23) and that these differences can be explained based on elevated oxytocin levels in WBS (and in duplication?).
-Evidences of GTF2I Gene implication on behavior (if deletion: greater Hypersociality) and its link to oxytocin
-In WBS: positive association between elevated oxytocin levels and hypersociality and negative association with adaptive functioning -Socialization subdomain
- In WBS: autism subtype "active but odd"?

brain sciences

MDPI

Article

Cooperative Parent-Mediated Therapy in Children with Fragile X Syndrome and Williams Beuren Syndrome: A Pilot RCT Study of a Transdiagnostic Intervention-Preliminary Data

Paolo Alfieri [1,*,†], Francesco Scibelli [1,†], Laura Casula [1], Simone Piga [2], Eleonora Napoli [1], Giovanni Valeri [1] and Stefano Vicari [1,3]

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† These authors contributed equally.

Abstract: Children with fragile X syndrome and William Beuren syndrome share several socio-communicative deficits. In both populations, around 30/35% of individuals meets criteria for autism spectrum disorder on gold standard instruments. Notwithstanding, few studies have explored feasibility and validity of therapy for socio-communicative deficits in individuals with these genetic conditions. In this study, we present preliminary data on a pilot RCT aimed to verify the effectiveness of cooperative parent-mediated therapy for socio-communicative deficits in a transdiagnostic perspective in a small sample of 12 participants. Our preliminary data showed that the experimental group had significant improvement in one socio-communicative skill (responsivity) and in clinical global impression, while the control group in an adaptive measure of socialization and word production. Implications of these results are then discussed.

Keywords: parent-mediated therapy; RCT; autism spectrum disorders; fragile X syndrome; William Beuren syndrome; transdiagnostic intervention

check for updates

Citation: Alfieri, P.; Scibelli, F.; Casula, L.; Piga, S.; Napoli, E.; Valeri, G.; Vicari, S. Cooperative Parent-Mediated Therapy in Children with Fragile X Syndrome and Williams Beuren Syndrome: A Pilot RCT Study of a Transdiagnostic Intervention-Preliminary Data. *Brain Sci.* **2022**, *12*, 8. https://doi.org/10.3390/brainsci12010008

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1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous complex neurodevelopmental disorder characterized by socio-communicative deficits and restricted, repetitive patterns of behaviors and interests [1]. ASD occurs in approximately 1:100 in the world [2] and in 1:54 in USA [3]. In approximately 10–15% of cases, ASD shows some genetic conditions [4,5], including tuberous sclerosis complex, fragile X syndrome (FXS), Down syndrome, Angelman syndrome, Rett syndrome, and, most recently considered, William Beuren Syndrome (WBS) [6–10].

FXS is the most known inherited form of intellectual disability, and it is considered the most common monogenic cause of ASD [11], accounting for an estimated 1% to 6% of all cases of ASD [12]. The estimated prevalence of FXS is ~1/4000 to 1/5000 in males and ~1/6000 to 1/8000 in females [13,14]. FXS is due to an expanded CGG repeat sequence (>200 repeats), termed "full mutation," in the 5′ untranslated region of the FMR1 gene located at Xq27.3. Most males with full mutation have mild to moderate Intellectual Disability (ID), while the phenotype of females is considered milder (one third of females with the full mutation have normal intellectual function) [12]. A large portion of individuals with FXS shares difficulties in socio-communicative skills, such as modulation of non-verbal communication and difficulties in relationships with peers, as well as social withdrawal, and repetitive and restricted behaviors and interests [12,15]. Studies on males with FXS have showed that 30% to 54% met criteria for ASD, while this percentage is reduced in

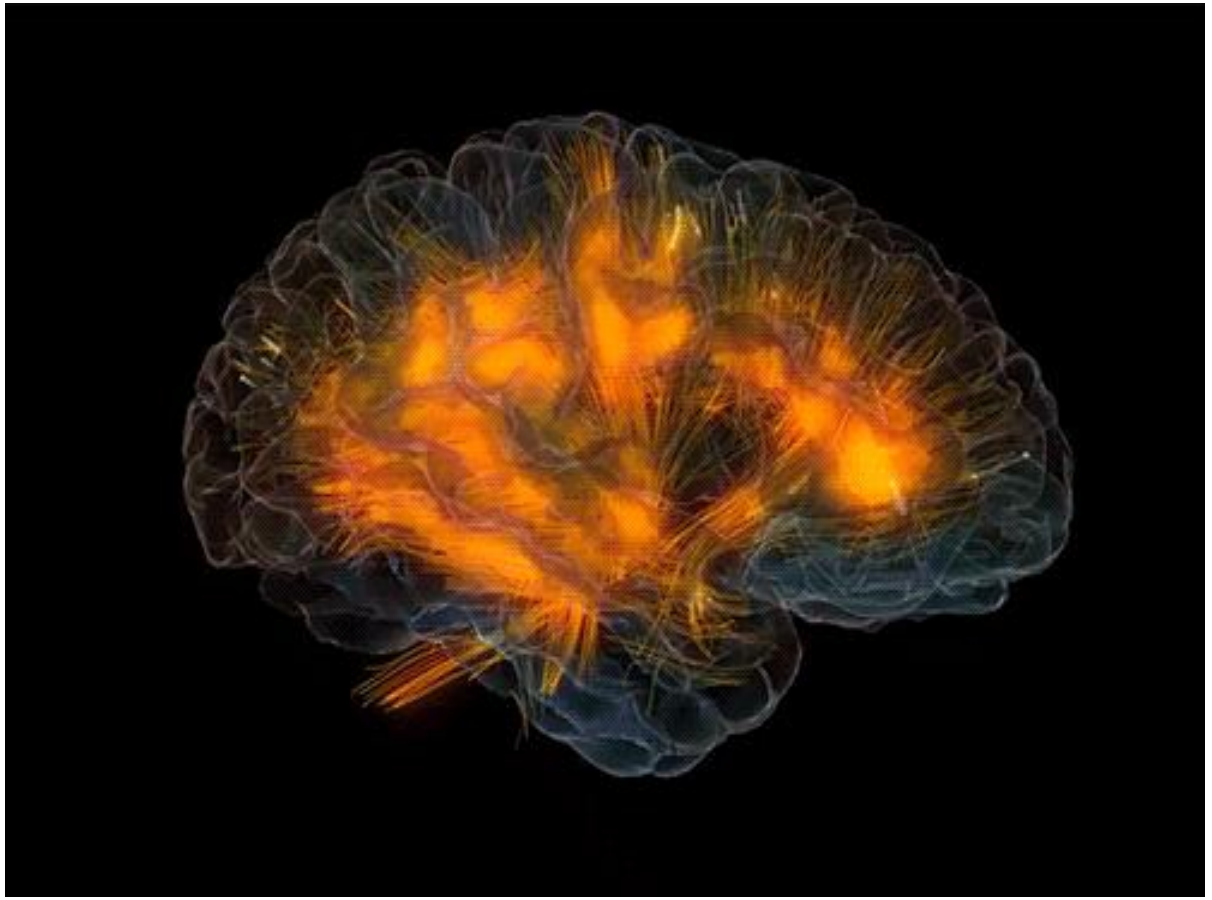
COOPERATIVE PARENT MEDIATED THERAPY IN WBS AT BAMBINO GESU' HOSPITAL

AIM: To evaluate the effectiveness of TMGC in children aged 1 to 7 years in improving the social-communicative and interpersonal skills (joint attention, assertiveness, responsiveness, expressive and receptive vocabulary) of children with WBS - compared with children with Fragile X Syndrome (FXS). The primary outcome is assessed both with child direct assessment and with parents-report questionnaires.

METHODS: 15 Parent Coaching sessions, during which parents are involved as active participants in their child's treatment.

Scientific research shows that when parents interact with their children in specific ways that motivate, encourage, and support communication, they can significantly increase language and communication development (Bearss et a., 2015; Bradshaw et al., 2017).

Our study showed an improvement in social responsiveness and a decrease in illness severity in both children with WBS and FXS.



THANK YOU