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Cognitive profiles of genetic syndromes with Intellectual Disability

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Abstract

The study of similarities and differences in the cognitive profiles of persons with genetic-based Intellectual Disability is relevant to increase our understanding about the complex way in which genetic aspects affect cognitive processes.
Genetic syndromes have been mainly studied with reference to within-profile variability.
The aim of our study was to compare cognitive syndrome profiles in order to detect those cognitive variables that better characterize each syndrome.
Wechsler Intelligence Scale for Children was administered in a sample composed of 156 persons with mild or moderate Intellectual Disability, 94 males and 62 females, divided into four groups according to their genetic syndrome (Down or Trisomy-21, Williams, Prader-Willi, Fragile-X)
The groups were paired on chronological and mental ages and levels of maladaptive behaviors.
Variance analysis across syndromes, followed by a discriminant analysis, were performed for all the variables.
Results showed that the delay in cognitive functions is higher in attention-concentration and visuo-spatial constructive skills than in verbal skills.
The genetic syndromes had different profiles, with a higher level for Prader-Willi than for Down and Fragile-X; the intra-profile disharmony was lower in Down and higher in Williams syndrome.
Discriminant analysis allowed us to detect the best discriminating subtests in the classification of syndromes based on cognitive points of strength

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and weakness.
Our results supported the hypothesis that Intellectual Disability reflects the impaired functioning of a complex system in which some skills are damaged more than others.
The question of "what discriminates better among syndromes" may be answered assuming a "modular" perspective of mind in disability. To analyze what abilities are specifically impaired in each syndrome, is useful to plan specific rehabilitation procedures.

Keywords: Genetic syndromes – Intellectual Disability – Phenotype – Cognitive profiles

Introduction

Peculiar cognitive profiles of genetic syndromes, as well as intra-profile variability, have been the subject of current discussions.

The syndromes can be represented on a continuum based on the global *severity* level of the cognitive disability: namely, from the lowest level of impairment characterizing Prader-Willi Syndrome, through Williams syndrome and, finally, Down Syndrome.

On the same continuum, *stability* of IQ is also represented: more stable for Prader-Willi (Waters, 1999; Roof, Stone, MacLean, Feurer, Thompson, & Butler, 2000; Dykens, Hodapp, & Finucane, 2000), less stable for Williams Syndrome, while a progressive reduction of IQ level was found for Down syndrome (Hodapp, Evans, & Gray, 1999).

As far as the *variability* of cognitive performances across syndromes is concerned, Down Syndrome showed less variability than Williams Syndrome, which appeared to be more heterogeneous (Porter & Coltheart, 2005). Moreover, in Williams persons, a discrepancy also occurred between verbal and spatial memory (Vicari, Brizzolara, Carlesimo, Pezzini, & Volterra, 1996).

High variability was also found in Prader-Willi and Fragile-X Syndromes (Kau, Reider, Payne, Meyer, & Freund, 2000). In this latter, variability seemed to be correlated to gender-linked genetic features characterizing the syndrome. According to Cornish, Sudhalter, and Turk, (2004, p. 11), "the Fragile-X Syndrome profile is characterized by uneven abilities within and across cognitive domain".

In order to describe within-profile variability for each syndrome, many studies have focused on the differences between cognitive functions. For example, in Down and Williams Syndromes, opposite profiles seemed to emerge when matching the general intellectual levels: verbal skills turned out to be higher in the Williams syndrome, despite many atypical features in different language areas (O'Brien & Yule, 1995;Volterra, Capirci, Pezzi-

ni, Sabbadini, & Vicari, 1996; Mervis, Robinson, Bertrand, Morris, Klein-Tasman, & Armstrong, 2000; Mervis, 2003); higher visual-spatial skills were found in Down Syndrome (Lanfranchi, Cornoldi, & Vianello, 2004), typically characterized by marked deficits in language development, usually affecting more phonology and syntax than lexicon (Rondal, 2004; Chapman & Hesketh, 2001).

A few authors highlighted similarities rather than differences across profiles: according to Fisch *et al.* (2007), cognitive and adaptive profiles of children with Fragile X and Williams are "surprisingly similar".

Cognitive outcomes of genetic disorders leading to intellectual disabilities were analyzed from a number of different perspectives (Hodapp, 1997).

According to a "total specificity" perspective (Flynt & Yule, 1994), each genetic syndrome has unique characteristics that other syndromes have not. For example, with regard to cognitive functioning, higher visual rather than auditory receptive abilities were found only in Down syndrome (Pueschel, Gallagher, Zartler, & Pezzullo, 1987; Chapman & Hesketh, 2001); Williams syndrome subjects are typically characterized by high-level language abilities, impaired visuo-spatial functioning and low mental age (Bellugi, Wang, & Jernigan, 1994); attention, executive functions and visuo-perceptual organization are usually impaired in Prader-Willi Syndrome, as a consequence of deficits in frontal cognitive processes (Jauregi *et al.,* 2007).

In a "partial specificity" perspective, a few genetic disorders had a single outcome, differing from mixed-etiology intellectual disabilities. For example, slightly impaired sequential processing was found both in Prader-Willi and in Fragile-X Syndromes (Dykens, Hodapp, & Leckman, 1987).

In this perspective, analysis of similarities and differences in the cognitive development of persons with genetic-based Intellectual Disability appear to be of most relevance.

The above mentioned studies focused on each of the syndromes as well as on the comparisons between syndromes, or – in a few cases – on the study of the same function across syndromes: e.g., memory in Williams and Down Syndromes (Wang & Bellugi, 1994; Devenny, Krinsky-McHale, Kittler, Flory, Jenkins, & Brown, 2004; Vicari, 2004; Vicari & Carlesimo, 2006), expressive *versus* receptive vocabulary and speech production in Fragile-X and Down Syndromes (Roberts *et al.* 2007); and, finally, specific language functions across several genetic syndromes (Rondal, 2004).

In order to answer the crucial question about the disharmony of intellectual functioning in genetic syndromes – namely, specific impairments in each syndrome – we compared different profiles by pairing samples on chronological and mental ages.

Aim

The aim of our study was to compare cognitive syndrome profiles as well

as to use a discriminant analysis approach to detect those cognitive variables that better characterize each syndrome.

Method

Instruments

Wechsler Intelligence Scale for Children (suitable for 6-to-17 age ranges, and persons with < 18 years of mental age) was administered, including 11 tests, divided into two subscales, namely "verbal" (*Information, Similarities, Comprehension, Digit Span, Arithmetic* and *Vocabulary* subtests), and "performance" (*Picture Completion, Picture Arrangement, Block Design, Object Assembly* and *Coding* subtests). Scaled scores were used for each subtest.

We administered the Italian version of WISC-R (Wechsler, 1974; translated, adapted and standardized by Rubini & Padovani, 1986). The long procedure of sample recruitment (several years), due to the rarity of some genetic syndromes, did not allow us to use the most recent WISC-III version, which has only recently been translated, adapted and standardized in Italy.

Tests were administered by qualified psychologists, specifically trained in assessing persons with Intellectual Disability.

Sample

The sample (n = 156, males = 94 and females = 62), was composed of persons with mild or moderate mental retardation since WISC-R scale and other cognitive tests may be reliably administered only to people with these levels of Intellectual Disability. The sample was diagnosed according to ICD-10 (WHO, 1992) criteria.

Table 1 shows that differences in chronological age, mental age (assessed with age equivalent composite scores derived from intelligence and adaptive tests) and levels of maladaptive behaviors – measured with *Vineland Adaptive Behavior Scale* (Sparrow, Balla, & Cicchetti, 1984) – turned out to be not-significant in the subgroups selected according to each genetic syndrome considered.

The difference in composition of subgroups reflects the different prevalence of the syndromes in our regional context; for some syndromes almost all the cases existing in Sicily in last few years were recruited for the research.

Table 1 - *Genetic syndromes with Intellectual Disability. Comparison between means (± standard error) for Chronological age, mental age (in months), maladaptive behaviors (from Vineland Adaptive Behavior Scale)*

	Total	*m*	*f*	*Chronol. Age*	*Mental age*	*Malad. behav.*
Down	103	56	47	182.04 ± 9.39	81.04 ± 1.44	11.07 ± .75
Williams	12	9	3	210.00 ± 25.91	77.96 ± 5.04	10.43 ± 2.79
Prader-Willi	16	7	9	196.44 ± 19.59	83.16 ± 4.32	14.50 ± 1.97
Fragile-X	25	22	3	180.00 ± 18.12	77.63 ± 3.36	13.75 ± 1.90
	156	*94*	*62*	*F=.43, p=.73*	*F=.65 p =.59*	*F=1.47 p=.23*

Data analysis

Variance analysis across syndromes was performed for all the variables. The comparison are displayed in Figure 1, and Table 2 shows means and standard errors for each measure.

Figure 1 - *Comparison of syndromes in Wechsler subtests (mean scaled scores)*

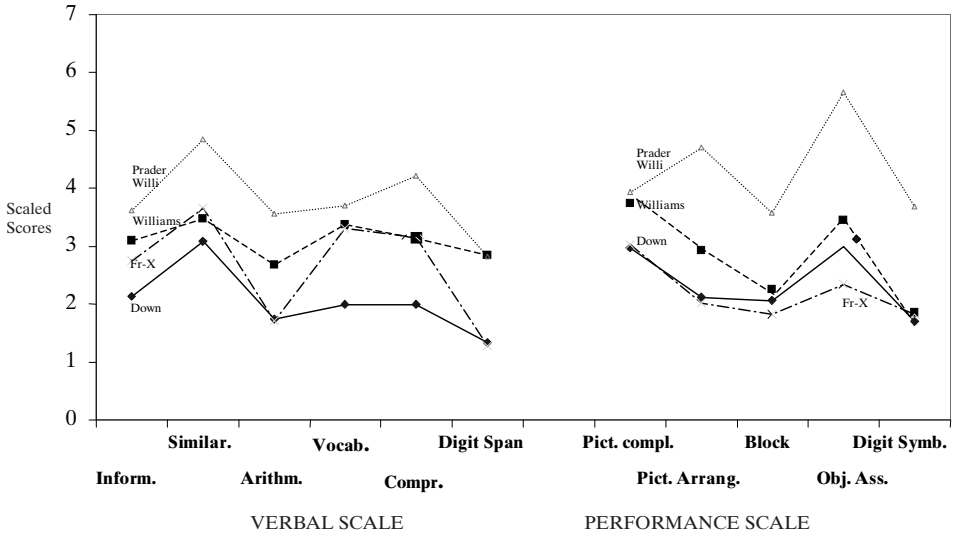

Table 2 - *Means and standard errors for each measure, and results of Analysis of Variance across syndromes*

	Down	*Williams*	*Prader-Willi*	*Fragile-X*	*F*
Information	2.13 ± .20	3.10 ± .60	3.61 ± .52	2.46 ± .41	2.85 p=.04
Similarities	3.08 ± .19	3.47 ± .55	4.85 ± .48	3.40 ± .38	3.97 p=.01
Arithmetic	1.74 ± .13	2.67 ± .37	3.55 ± .32	1.66 ± .26	10.66 p<.001
Vocabulary	1.99 ±.16	3.38 ± .48	3.69 ± .42	2.99 ± .33	7.73 p<.001
Comprehension	1.99 ± .15	3.13 ± .44	4.21 ± .38	2.87 ± .30	11.87 p<.001
Digit Span	1.33 ± .11	2.84 ± .31	2.83 ± .27	1.23 ± .22	15.25 p<.001
Picture completion	2.97 ± .16	3.74 ± .47	3.93 ± .40	2.94 ± .32	2.33 p=.08
Picture Arrangement	2.12 ± .15	2.93 ± .45	4.71 ± .39	1.92 ± .31	14.21 p<.001
Block Design	2.07 ± .14	2.26 ± .41	3.57 ± .36	1.89 ± .29	5.61 p<.001
Object Assembly	3.00 ± .20	3.45 ± .58	5.65 ± .50	2.43 ± .40	9.61 p<.001
Digit-symbol	1.71 ± .15	1.85 ± .45	3.68 ± .39	1.77 ± .31	7.41 p<.001

Overall, the syndromes showed quite similar trends, although the score levels were different and marked differences were found in some areas.

In the Verbal subscale, persons with Down Syndrome presented with the lowest profile. Those with Fragile-X had the wider within-profile variability: marked deficits were found in the subtests tapping on attentional areas (*Arithmetic* and *Digit Span*), whereas verbal profile in Williams Syndrome appeared to be rather homogeneous. Prader-Willi Syndrome showed the highest profile, despite marked decreases in attentive subtests.

Across all the syndromes, the highest score for Verbal profile was obtained in the *Similarities* subtest.

In the Performance subscale, similar profiles were found, albeit differing in score levels.

Lowest and quite overlapping profiles were found in Down and Fragile-X Syndromes, whereas improvements in *Picture Completion* and *Picture Arrangement* were detected in Williams Syndrome profiles.

Prader Willi Syndrome shows "Performance" profile rather homogenous, with a peak in *Object Assembly* and lower mean scores in *Picture Completion, Blocks* and *Digit Symbol*.

On the whole, the more relevant deficits were found across all syndromes – despite their different levels – in attention-concentration subtest areas, as well as in *Block Design*, which taps on visuo-spatial and constructive skills, typically deteriorated because of the neuropsychological impairment due to the genetic disease.

A discriminant analysis was performed to find a linear combination between measures (Wechsler scores) that best classified or discriminated among the syndromes.

In consideration of the number of variables entered in the analysis, a backward stepwise method was used (alpha=.10). The Wilks' Lambda index to test homogeneity among groups (d.f. 1,3,152) was .76 (F= 16,67, p<.001).

The incidence of each of the variables on the discriminant function is shown in Table 3.

Table 3 - *Discriminant analysis for WAIS-R subtests. F-to-remove and tolerance (limit: .001)*

Subtest	*F-to-remove*	*Tolerance*
Information	4.41	0.39
Similarities	3.57	0.38
Arithmetic	2.38	0.42
Vocabulary	4.21	0.25
Comprehension	2.41	0.36
Digit Span	7.55	0.48
Picture completion*	0.44	0.54
Picture Arrangement	8.34	0.42
Block Design	4.48	0.37
Object Assembly	12.04	0.60
Digit-symbol	4.54	0.50

** Variable removed after stepwise procedure*

The best discriminating subtests in the classification of syndromes were:

- *Object assembly*: as previously shown in the analysis of mean scores (fig. 1), Prader-Willi scored the highest, whereas Fragile-X the lowest.
- *Picture arrangement*: higher mean scores in Prader-Willi than in Down and Fragile X syndromes.
- *Digit* span: higher mean scores in Prader-Willi and Williams than in Down and Fragile-X syndromes.

Picture Completion was the subtest with the lowest discrimination power, with similar mean scores across groups.

The eigenvalue for the first canonical variable (the linear combination of the variables that best discriminates among groups) was remarkably higher than subsequent combinations (.90 vs .24 and .12), showing a higher variance in the first variable (72% of the total dispersion among groups). Canonical correlations between these variables and the groups (represented as dummy variables) were quite high: .70, .44, .30.

In the "classification matrix" of the discriminant analysis, each case falls into a specific group having the largest value of its classification function. The overall percentage of correct classifications was high (82%). The high-

est percentage was found for Down syndrome (88%), the lowest for Williams syndrome (58%)

Discussion

The study of genetic syndromes with Intellectual Disability is relevant to increase our understanding about the complex way in which genetic differences affect cognitive processes.

Our study aimed to explore what is specifically retarded in each genetic syndrome, and to compare the profiles obtained from samples matched on chronological and mental ages.

Overall, results supported the hypothesis that, in genetic syndromes, the delay in cognitive functions is higher in attention-concentration and visuo-spatial constructive skills (as in *Block Design* task) than in verbal skills, as it is the case of *Similarity* and *Comprehension* tasks.

The genetic syndromes have different profiles, with a higher level for Prader-Willi than for Down and Fragile-X. As reported by Porter & Coltheart (2005), the intra-profile disharmony is lower in Down syndrome and higher in Williams syndrome, prevalently in "Performance" tasks. The highest variability was found in Fragile-X, thus confirming previous results reported by Kau *et al.* (2000) and Cornish *et al.* (2004).

The reported prevalence of verbal skills in the profile of people with Williams syndrome (e. g., Bellugi *et al.*, 1994; Volterra *et al.*, 1996; Mervis, 2003) was confirmed for receptive and semantic characteristics (*Similarities, Vocabulary, Comprehension*), but similar levels of performance were also found in the Williams sample for some visual-based tasks, such as *Picture Completion* and *Object Assembly*.

The expected highest performance in Trisomy 21 visuo-spatial skills (Hodapp, 2004; Lanfranchi *et al.*, 2004) was partially confirmed: *Picture Completion* and *Object Assembly* were the highest points of the profile, although we found at the same level *Similarities*, that is a verbal task requiring receptive language skills. This confirms that lexical aspects of language are less impaired in Down syndrome; while phonological and syntactic aspects (more damaged according to Rondal, 2004) are not assessed by Wechsler subtests.

Deficits in sequential thinking found both in Prader-Willi and in Fragile-X by Dykens *et al.* (1987) was confirmed in our sample only for the latter syndrome: *Picture Arrangement* task, requiring sequential processing of information, was a point of strength for Prader-Willi cognitive profile.

Discriminant analysis allowed us to detect the best discriminating subtests in the classification of syndromes based on cognitive points of strength and weakness.

Object assembly was the subtest that best represented performances in Prader-Willi syndrome; this is a task – similar to puzzles assembly – which

requires an ability that is unusually high in this syndrome, and considered as a common feature of the syndrome (Dykens *et al.* 2000).

Picture arrangement, that requires logical and sequential thinking, was particularly low in Down and Fragile-X Syndromes.

Digit span, i.e. verbal immediate memory, positively characterized Prader-Willi and Williams, and negatively Down and Fragile-X Syndromes.

Our results supported Detterman's (1987, 2002) hypothesis that "intellectual disability reflects the defective functioning of a complex system in which some competencies may be disrupted more than others" (Vicari *et al.*, 1996, p. 503).

To answer the question of "what discriminates better among syndromes", we need to refer to some modularity of mind in the field of disability (e.g., "category-specific deficits": Santos & Caramazza, 2002), although it is not possible to assume that modules related to specific abilities start out either intact or impaired (Paterson, Brown, Gsödl, Johnson, & Karmiloff-Smith 1999). A mild and non massive modular perspective may be useful in order to explain differences in genetic syndromes, and to analyze in detail which abilities are expected to be impaired, thus obtaining a relevant information for planning early and specific rehabilitation interventions.

References.

Bellugi, U., Wang, P., & Jernigan, T. L. (1994). Williams syndrome: An unusual neuropsychological profile. In S. H. Browman, & J. Grafram (Eds), *Atypical cognitive deficits in developmental disorders*, 23-56. Mahwah, N.J.: Lawrence Erlbaum.

Chapman, R. S., & Hesketh, L. J. (2001). Language, cognition, and short-term memory in individuals with Down syndrome. *Downs Syndrome Research & Practice*, *7*, 1-7.

Cornish, K., Sudhalter, V., & Turk, J. (2004). Attention and language in fragile X. *Mental Retardation and Developmental Disabilities Research Reviews*, *10*, 11-16.

Detterman, D. K. (1987). Theoretical notions of intelligence and mental retardation. *American Journal of Mental Deficiency*, *92*, 2-11.

Detterman, D. K. (2002). General intelligence: Cognitive and biological explanations. In R. J. Sternberg & E. L. Grigorenko (Eds.), *The general factor of intelligence* (pp. 151-182). Mahwah, N.J.: Lawrence Erlbaum.

Devenny, D. A., Krinsky-McHale, S. J., Kittler, P. M., Flory, M., Jenkins, E., & Brown W. T. (2004). Age-associated memory changes in adults with Williams syndrome. *Developmental Neuropsychology, 26*, 691–706.

Dykens, E. M., Hodapp, R. M., & Leckman, J. F. (1987). Strengths and weaknesses in intellectual functioning of males with fragile X syndrome. *American Journal of Mental Deficiency*, *92,* 234-236.

Dykens, E. M., Hodapp, R. M., & Finucane, B. M. (2000). *Genetics and Mental Retardation Syndromes. A New Look at Behavior and Intervention*. Baltimore: Paul H. Brookes Publishing.

Fisch, G. S., Carpenter, N., Howard-Peebles, P. N., Holden, J. J., Tarleton, J., Simensen, R., & Nance, W. (2007). Studies of age-correlated features of cognitive-behavioral development in children and adolescents with genetic disorders. *American Journal of Medical Genetics, 143*, 2478-2489.

Flynt, J., & Yule, W. (1994). Behavioral phenotypes. In M. Rutter, E. Taylor, & L. Hersov (Eds), *Child and adolescent psychiatry: Modern approaches* (3rd ed.) (pp. 666-686). London: Blackwell.

Hodapp, R. M. (1997). Direct and indirect behavioural effects of different genetic disorders of mental retardation. *American Journal of Mental Retardation*, *102*, 67-79.

Hodapp, R. M., Evans, D. W., & Gray, F. L. (1999). Intellectual development in children with Down syndrome. In J. Rondal, J. Perera, & L. Nadel (Eds.), *Down syndrome: A review of current knowledge* (pp. 124-132). London: Whurr.

Hodapp, R. M. (2004). Behavioral phenotypes: Going beyond the two-group approach. *International Review of Research in Mental Retardation, 29*, 1-30.

Jauregi, J., Arias, C., Vegas, O., Alén, F., Martinez, S., Copet, P., & Thuilleaux, D. (2007). A neuropsychological assessment of frontal cognitive functions in Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *51*, 350-365

Kau, A. S. M., Reider, E. E., Payne, L., Meyer, W. A., & Freund, L. (2000). Early behavior signs of psychiatric phenotypes in fragile X syndrome. *American Journal on Mental Retardation, 105*, 286-299.

Lanfranchi, S., Cornoldi, C., & Vianello, R. (2004). Verbal and Visuospatial Working Memory Deficits in Children With Down Syndrome. *American Journal on Mental Retardation, 109*, 456–466.

Mervis, C. B. (2003). Williams syndrome: 15 years of psychological research. *Developmental Neuropsychology*, *23* (1-2), 1-12.

Mervis, C. B., Robinson, B. F., Bertrand, J., Morris, C. A., Klein-Tasman, B. P., & Armstrong, S. C. (2000). The Williams syndrome cognitive profile. *Brain Cognition, 44*, 604-28.

O'Brien, G., & Yule, W. (Eds.). (1995). *Behavioural Phenotypes.* London: MacKeith Press.

Porter, M. A., & Coltheart, M. (2005). Cognitive Heterogeneity in Williams Syndrome. *Developmental Neuropsychology, 27*, 275-306.

Paterson, S. J., Brown, J. H., Gsödl, M. K., Johnson, M. H., & Karmiloff-Smith, A. (1999). Cognitive modularity and genetic disorders, S*cience*, *286*, n5448, 2355 - 2358.

Pueschel, S. M., Gallagher, P., Zartler, A., & Pezzullo, J. (1987). Cognitive and learning processes in children with Down syndrome. *Research in Developmental Disabilities*, *8*, 21-37.

Roberts, J., Price, J., Barnes, E., Nelson, L., Burchinal, M., Hennon, E. A., Moskowitz, L., Edwards, A., Malkin, C., Anderson, K., Misenheimer, J., & Hooper, S. R. (2007). Receptive vocabulary, expressive vocabulary, and speech production of boys with fragile X syndrome in comparison to boys with down syndrome. *American Journal of Mental Retardation, 112*, 177-193.

Roff, O., Stone, W., MacLean, W., Feurer, I. D., Thompson, T., & Butler, M. G. (2000). Intellectual characteristics of Prader–Willi syndrome: comparison of genetic subtypes. *Journal of Intellectual Disability Research*, *44*, 25-30.

Rondal, J. A. (2004). Intersyndrome and intrasyndrome language differences? In J. A. Rondal, R. M. Hodapp, S. Soresi, E. M. Dykens, & L. Nota. (Eds), *Intellectual Disabilities. Genetics, Behaviour and Inclusion*. London: Whurr.

Santos, L. R., & Caramazza, A. (2002). The domain-specific hypothesis: a developmental and comparative perspective on category-specific deficits. In E. M. E. Forde, & G. W. Humphreys (Eds), *Category specificity in brain and mind.* Howe: Psychology Press.

Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). *Vineland Adaptive Behavior Scales.* American Guidance Service: Circle Pines.

Vicari, S., Brizzolara, D., Carlesimo, G. A., Pezzini, G., & Volterra, V. (1996). Memory abilities in children with Williams syndrome. *Cortex, 32*, 503-514.

Vicari, S., & Carlesimo, G. A. (2006). Short-term memory deficits are not uniform in Down and Williams syndromes, *Neuropsychological Review*, *16*, 87-94.

Vicari, S. (2004). Memory development and intellectual disabilities. *Acta Paediatrica Supplement, 93*, 60-63

Volterra, V., Capirci, O., Pezzini, G., Sabbadini, L., & Vicari, S. (1996). Linguistic abilities in Italian children with Williams sindrome. *Cortex*, *32*, 663-77.

W.H.O. (1992). *The ICD-10 Classification of mental and behavioural disorders: clinical description and diagnostic guidelines.* Geneva: World Health Organization.

Wang, P. P., & Bellugi, U. (1994). Evidence from two genetic syndromes for a dissociation between verbal and visual-spatial short-term memory. *Journal of Clinical and Experimental Neuropsychology, 16*, 317–322.

Waters, J. (1999). *Prader-Willi Syndrome. A Pratical Guide.* London: David Fulton.

Wechsler, D. (1974). *Wechsler Intelligence Scale for children - Revised.* New York: The Psychological Corporation,. Translation and italian adaptation by V. Rubini & F. Padovani, *WISC-R Scala di intelligenza Wechsler per bambini - Riveduta*, Firenze: O.S., 1986.