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Neurological soft signs feature a double dissociation within the language system in Williams syndrome

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ABSTRACT

The neurocognitive profile of Williams-Beuren syndrome (WBS) is characterized by visuospatial deficits, apparently fluent language, motor soft signs, and hypersociability. We investigated the association between neuromotor soft signs and visuospatial, executive-attentive, mnestic and linguistic functions in a group of 26 children and young adults with WBS. We hypothesized that neurological soft signs could be an index of subtle neurofunctional deficits and thus provide a behavioural window into the processes underlying neurocognition in Williams-Beuren syndrome. Dysmetria and dystonic movements were selected as grouping neurological variables, indexing cerebellar and basal ganglia dysfunction, respectively. No detrimental effects on visuospatial/visuoconstructive skills were evident following the presence of either neurological variable. As for language skills, participants with dysmetria showed markedly reduced expressive syntactic and lexico-semantic skills as compared to non-affected individuals, while no difference in chronological age was evident. Participants with dystonic movements showed reduced receptive syntax and increased lexical comprehension skills as compared to non-affected individuals, the age factor being significant. In both instances, the effect size was greater for syntactic measures. We take these novel findings as suggestive of a double dissociation between expressive and receptive skills at sentence level within the WBS linguistic phenotype. The investigation of neuromotor soft signs and neuropsychological functions may provide a key to new non-cortico-centric genotype/phenotype relationships.

1. Introduction

Williams-Beuren syndrome (WBS) is a neurodevelopmental disorder linked to a hemizygous deletion of approximately 1.6 megabases on either maternal or paternal chromosome 7q11.23, as a result of meiotic mispairings (Korenberg et al., 2000; Meyer-Lindenberg, Mervis, & Berman, 2006). Prevalence estimates vary between 1/20,000 and 1/7,500 live births (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988; Strømme, Bjørnstad, & Ramstad, 2002). The microdeletion region contains ~28 genes, among which those encoding elastin (ELN) (Tassabehji et al., 1999). Haploinsufficiency for elastin has been causally linked with cardiovascular abnormalities (supravalvular aortic stenosis), connective tissue abnormalities, and dysmorphic facial appearances, which are systemic hallmarks of WBS (Beuren, Apitz, & Harmjanz, 1962; Lowery et al., 1995; Williams, Barratt-Boyes, & Lowe, 1961). Generally, children and adults with WBS present with a mild to moderate mental retardation, but normal intelligence has been documented in a small subset of individuals (Morris, Lenhoff, & Wang, 2006).

The peculiar neurocognitive profile of WBS is characterized by severe visuospatial and visuoconstructive deficits in the context of relatively preserved face processing and language skills, which are usually within the variability range of mental age controls and thus represent a relative peak of strength (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Gagliardi et al., 2003; Karmiloff-Smith et al., 2003). Children and adults with WBS typically show hypersociability with lack of inhibition and non-socially determined anxiety (Frigerio et al., 2006; Meyer-Lindenberg, Hariri et al., 2005). Neurological features such as clumsiness, coordination difficulties (hypodiadochokinesia), balance instability, hyperreflexia, choreiform and dystonic movements, and oculomotor signs (nystagmus) have been consistently described (Gagliardi, Martelli, Burt, & Borgatti, 2007; Morris et al., 2006). While cerebellar motor features have been linked to procedural and/or incidental learning difficulties (Vicari, Verucci, & Carlesimo, 2007), extrapyramidal signs have been recently discussed in light of the hypothesis of a dysfunctional dopaminergic system in the brain of individuals with

Abbreviations: WBS, Williams-Beuren syndrome; ELN, Elastin; FISH, fluorescent in situ hybridisation; WISC-R, Wechsler Intelligence Scale-Revised; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; VMI, Visuomotor Integration Test; PPVT, Peabody Picture Vocabulary Test.

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WBS, which becomes more evident with age and could be linked to accelerated aging (Cherniske et al., 2004; Gagliardi et al., 2007). The complex WBS phenotype is thus layered across different levels of higher-order cognition and sensorimotor functions.

Major efforts are being devoted to the investigation of the neural underpinnings of WBS uneven cognitive profile, with the aim of linking gene, brain and behaviour. Eckert et al. (2006) showed that the anomalous functioning of the visual system (visuospatial search and visuoconstruction deficits) in WBS is specifically related to disorders in dorsal stream anatomy and function, involving a bilateral reduction of cortical volume or density in different structures which are relevant for space-based actions: parietooccipital/intraparietal sulcus (Meyer-Lindenberg et al., 2004), superior parietal lobule, posterior thalamus, cerebellar vermis (Thompson et al., 2005). Similarly, abnormal gyrification with reduction in sulcal depth in the parietal sulcus has also been demonstrated in WBS (Shane Kippenhan et al., 2005). Visual integration deficits do not seem to have a significant impact on social abnormalities, whose neurobiological origin is likely to be due to a dysregulation of orbitofrontal cortex systems on the amygdala (Meyer-Lindenberg, Hariri et al., 2005). This could explain why people with WBS can detect negative affect faces but cannot inhibit a consequent approach response (Frigerio et al., 2006; Järvinen-Pasley et al., 2008). Impaired frontal functions involved in planning and controlling speech production may also underlie the growing evidence of a disorganized interactional pragmatic behaviour in children and adolescents with WBS, who seem unable to appropriately negotiate meaning with a conversational partner (Mervis & Becerra, 2007).

Formal language abilities such as lexico-semantic knowledge and grammatical skills, a relative strength peak against the visuospatial deficit valley (Järvinen-Pasley et al., 2008), are far from age appropriate and are usually within the normal range for mental-age-matched peers. Impaired spatial abilities may be causally related to the marked difficulties of children with WBS to use language for describing spatial locations, an instance of the interdependence between language and cognition (Phillips, Jarrold, Baddeley, Grant, & Karmiloff-Smith, 2004). As for grammar (syntax, morphology and phonology), an interesting finding concerns the excessive reliance on working memory skills of children and adolescents with WBS vs. typically developing participants in receptive grammar comprehension tasks (Robinson, Mervis, & Robinson, 2003). This finding can be interpreted as a difficulty in processing regular (rule-based) structural language knowledge procedurally and thus effortlessly. Accordingly, working memory performance in children with WBS correlates with both regular and irregular plural markers and case features in a highly inflected language such as Hungarian, while in typically developing children a correlation is significant only for irregular features, which are supposed to be declaratively processed and stored (Mervis & Becerra, 2007; Pléh, Lukács, & Racsmány, 2002). Such findings may be related to an impairment in the wiring or reduction in size of appropriate frontostriatal and interhemispheric white matter connections (Marenco et al., 2007; Meyer-Lindenberg, Mervis et al., 2005; Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001; Ullman, 2004).

An important, yet underdeveloped, issue concerns the evolution in time of the different phenotypical features of WBS. It is becoming apparent that the process of development itself is a major key to the understanding of genotype/phenotype correlations in human behaviour (Karmiloff-Smith, 2007). For example, it has been shown that while hypersociability is an age-independent marker feature of children with WBS (Doyle, Bellugi, Korenberg, & Graham, 2004), their processing strategy for facial features becomes less efficient as they grow older (Gagliardi et al., 2003). At a more general level, it has been shown that cerebellar signs are marker features in WBS, i.e. they manifest early in life and show no consistent pattern of increase with age (Jones et al., 2002). In contrast, extrapyramidal soft signs generally increase with age (Gagliardi et al., 2007). This finding may have a revealing potential in light of the evidence of a role for the cerebellum and basal ganglia in determining higher-order cognitive and linguistic impairments (Casey, Epstein, Buhle, Liston, & Davidson, 2007; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Tavano, Grasso et al., 2007; Vicari et al., 2007).

We investigated the relationship between neurological soft signs and the WBS neurocognitive and neurolinguistic profile. Our main aim was to use motor soft signs as indices to verify the existence of yet unspecified brain-cognition associative patterns (Chapman, du Plessis, & Pober, 1996; Gagliardi et al., 2007; Hocking, Bradshaw, & Rinehart, 2008; Reiss et al., 2000). We hypothesized that WBS participants for whom the presence of a neurological soft sign could be detected would obtain lower scores than non-affected participants.

2. Materials and method

2.1. Participants

A sample of 26 Italian children and young adults with WBS participated in the study (14 females, 12 males; mean chronological age 11.71, SD 6.42 years; range 5.10–29.11 years; mean mental age at Stanford Binet Scale-Revised 5.07, SD 1.37; range 2.80–8.40). WBS children comprised 8 participants aged $\leq$8 years, 12 adolescents aged 9–14 years, and 6 WBS young adults aged $\geq$15 years. The patients were recruited from a residential program for genetic syndromes at our Institute in Bosisio Parini (Lecco, Italy). Chromosome analysis was performed on the probands' blood using standard high resolution techniques. Fluorescent in situ hybridisation (FISH) with the commercially available probe WSR (Vysis Inc., Downers Grove, IL) was performed on the probands' metaphase spreads. Selection criteria were as follows: positive FISH test for elastin deletion (a gene consistently found in the critical deletion region 7q11.23 associated with WBS, Korenberg et al., 2000), and clinical features typical of WBS; absence of neurosensory deficits such as hypoacusia or severe visual impairment; absence of epilepsy and clinically relevant psychopathological disorders.

The WISC-R and WPPSI scales (Wechsler, 1973, 1986) were administered to all patients to fulfil the residential program requirements. Intellectual level performances were used to document the presence of a typical Williams syndrome cognitive profile: full IQ scores approximating the average of 55 among published studies; VIQ > PIQ; block design as a subtest of specific difficulty (Martens, Wilson, & Reutens, 2008).

26 Italian typically developing children participated in the study as one-to-one gender and mental-age-matched controls (14 females, 12 males; mean chronological age 5.09, SD 1.23 years; range 3.00–8.60 years; mean mental age at Stanford Binet Scale-Revised 5.17, SD 1.20; range 3.10–8.00). Control participants were included in the study if referred by both teachers and parents as normally developing with respect to emotional and cognitive skills. Further, none of them presented with neurologic, sensory or learning difficulties.

We aimed at obtaining comparable scores for the different neuropsychological tests in the WBS group, in order to detect the differential impact of the presence vs. absence of neurological soft signs with respect to the overall neurocognitive profile. The inclusion of a control group was motivated by the lack of complete neuropsychological normative data for the Italian adaptation of the neurolinguistic tests. Therefore, for each WBS participant we calculated a sample version of the z score, using the control sample participants' mean and standard deviation for all tests, except for the Token Test, for which the results for controls were not available and therefore the percentages of correct sentences given by WBS