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Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype

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This review critically examines the research findings which characterize the cognitive, behavioral, and neuroanatomical features of Williams syndrome (WS). This article analyzes 178 published studies in the WS literature covering the following areas: 1) General intelligence, 2) Language skills, 3) Visuospatial and face processing skills, 4) Behavior patterns and hypersociability, 5) Musical abilities, and 6) Brain structure and function. We identify methodological issues relating to small sample size, use and type of control groups, and multiple measures of task performance. Previously described 'peaks' within the cognitive profile are closely examined to assess their veracity. This review highlights the need for methodologically sound studies that utilize multiple comparison groups, developmental trajectories, and longitudinal analyses to examine the WS phenotype, as well as those that link brain structure and function to the cognitive and behavioral phenotype of WS individuals. **Keywords:** Williams syndrome, review, phenotype, cognition, language, music, social behavior.

Williams syndrome (WS) has come under increased scrutiny by cognitive neuroscientists as a model for investigating the relationship between a specific genetic defect and its cognitive and behavioral expression. WS is a rare neurodevelopmental disorder, with an estimated prevalence of 1 in 7,500 to 1 in 20,000 (Stromme, Bjornstad, & Ramstad, 2002; Wang et al., 1997) that is caused by a hemizygous deletion of approximately 26 genes on the long arm of chromosome 7 (7q11.23) (Peoples et al., 2000). One copy of the elastin gene is deleted in over 96% of individuals with WS (Lowery et al., 1995) and this deletion can now be genetically confirmed using fluorescent *in situ* hybridization (FISH). There are other individuals who have only one copy of the elastin gene, but these individuals have smaller deletions and do not display any phenotypic features of WS except for supravalvular aortic stenosis (Karmiloff-Smith et al., 2003; Tassabehji & Urban, 2006). Prior to the early 1990s, the diagnosis of WS was based only on its clinical phenotype and/or the presence of abnormal calcium metabolism, such as in the occurrence of infantile hypercalcaemia. The latter, however, is now considered to be an unpredictable feature of the syndrome (Jones & Smith, 1975; Pober & Dykens, 1996).

Individuals with WS have been characterized as possessing mild to moderate intellectual deficits, connective tissue abnormalities, cardiovascular disease, and facial dysmorphology (Bellugi, Klima, & Wang, 1996; Pober & Dykens, 1996). Muscle tone in children with WS is often decreased, but tends to increase in adulthood, and joint contractures may develop. The most common cardiovascular abnormality is supravalvular aortic stenosis, which may be found in addition to other vascular stenoses (Pober & Dykens, 1996). The distinctive facial characteristics have been described as elfin-like and include a broad brow, flat nasal bridge, a short upturned nose, wide mouth with full lips, and irregular dentition (Morris & Mervis, 1999). More recently, three-dimensional morphometric analysis has allowed for finer discrimination of facial features among individuals with WS (Hammond et al., 2005).

The majority of cognitive studies have described a fractionated cognitive profile, with relatively intact language and facial processing skills and profoundly deficient visuospatial abilities (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Schmitt, 2001). The personality of individuals with WS has been described as hypersociable (Bellugi, Mills, Jernigan, Hickok, & Galaburda, 1999b) and it has been asserted that their musical skills surpass their cognitive level and that their musical interests, musical creativity, and emotional reactions to music exceed that of normal controls (Levitin et al., 2003). In addition, most individuals with WS exhibit auditory abnormalities such as fearfulness to specific sounds (auditory allodynia) and a lowered pain threshold for loud sounds (odynacusis) (Levitin, Cole, Lincoln, & Bellugi, 2005).

The atypical cognitive, behavioral, and neuroanatomical profile of individuals with WS affords an unsurpassed opportunity to examine developmental pathways of expression of the genome as reflected in cognition, social behavior, and brain structure (Bellugi, Korenberg, & Klima, 2001; Reiss et al., 2000; Schmitt et al., 2002). To generate a thorough

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understanding of the effects of the genetic deletion, the cognitive and behavioral features of WS need to be accurately identified. In addition, the effects of the genetic deletion at the level of brain structure need to be understood through a detailed examination of brain morphology studies in individuals with WS. This comprehensive review focuses on the cognitive, behavioral, and neuroanatomical characteristics of WS, while also addressing the research that is beginning to link the genotype with the phenotypic features of WS.

There are several detailed summaries of empirical findings in WS (Bellugi et al., 2000; Braden & Obrzut, 2002; Brock, 2007; Mervis, Morris, Bertrand, & Robinson, 1999; Schmitt, 2001). Other researchers have addressed the theoretical framework surrounding the WS literature, arguing that it is important to understand the effect of neurodevelopmental disorders on developmental trajectories (Johnson, Halit, Grice, & Karmiloff-Smith, 2002; Karmiloff-Smith, 1998; Karmiloff-Smith, Scerif, & Thomas, 2002). To date, there have been few comprehensive critiques of the cognitive, behavioral, and neuroanatomical findings relating to WS, which is a critical first step on the path of clarifying genotype–phenotype relationships. Thus, in this review we examine whether the WS phenotype has been characterized with sufficient clarity and methodological soundness to set the stage for genotype–phenotype linkage studies.

Review methodology

The first documented study of WS was published in 1975 (Jones & Smith, 1975). Thus, a literature search was completed for all empirical studies published from 1975 to December, 2006. A computer search of the databases of PsycINFO, Expanded Academic, Web of Science, and PubMed was conducted using the keywords Williams syndrome. Additionally, reference lists from peer-reviewed articles were examined for other pertinent studies. The following inclusion criteria were used: (a) publication in a peer-reviewed journal, (b) original articles published in English, and (c) provision of sufficient methodological and statistical information to allow replication of the study. These criteria were chosen to examine studies with sufficient methodological detail to allow adequate interpretation of the findings.

This review includes studies with small sample sizes and unclear diagnostic criteria for WS, as these characterize much of the WS literature upon which conclusions have been drawn. The following topical areas were reviewed: 1) General intelligence, 2) Language skills, 3) Visuospatial and face processing skills, 4) Behavior patterns and hypersociability, 5) Musical abilities, and 6) Brain structure and function. Overall, 178 articles were examined that met the inclusion criteria. The number of studies critiqued in each domain is shown in Table 1.

Table 1 Number of Williams syndrome studies reviewed in each topical area

Topical area	Number of studies reviewed[a]
General intelligence (IQ)	47
Language skills	56
Visuospatial and face processing skills	53
Behavior patterns and hypersociability	31
Musical abilities	8
Brain structure and function	29

[a]The total number of studies reviewed across topical areas exceeds 178 due to several studies reporting on more than one skill domain.

Results

General intelligence

It has been commonly cited that the mean IQ of individuals with WS lies between 50 and 60, with a range of 40–100 (Bellugi et al., 1999b; Lenhoff, Wang, Greenberg, & Bellugi, 1997; Levitin & Bellugi, 1998; Reis, Schader, Milne, & Stephens, 2003). These IQ scores have been shown to remain stable with increasing age (Howlin, Davies, & Udwin, 1998; Searcy et al., 2004). Studies have described a relative verbal strength in comparison to significant visuospatial weaknesses (Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990; Mervis & Klein-Tasman, 2000), although debate continues regarding the significance and size of the discrepancy between Verbal and Performance IQ (VIQ and PIQ) scores.

Table 2 summarizes the 47 studies that evaluated the general intelligence of individuals with WS. To allow comparison, only studies which used complete tests to estimate global IQ scores, as opposed to those which used abbreviated tests or mental ages, were included. The majority of the studies utilized various forms of the Wechsler Intelligence Scales, while other studies used versions of the Stanford-Binet and other standardized intelligence tests. In 16 of the 47 studies, a majority of the participants were diagnosed with WS using FISH, as well as the clinical phenotype.

Sample sizes of the studies varied substantially, with 57% utilizing fewer than 15 participants. Five studies included overlapping participants. Importantly, a broad age range of WS individuals has been tested. Across 46 of the studies, the average global Full Scale IQ score ranged from 42 to 68 (mean = 55). The remaining study reporting a Full Scale IQ pertained to a single four-year-old participant who obtained a global IQ score of 82 after receiving two years of intensive language therapy (Capirci, Sabbadini, & Volterra, 1996). These results should be interpreted cautiously, as IQ scores

Table 2 General intellectual functioning in Williams syndrome

Author/Year	*N*	Age (yrs)	Diagnosis	Measure	FSIQ	VIQ	PIQ
Arnold et al. (1985)	22	7–12	IH	WISC-R	42 (40–72)	49	47
Bellugi et al. (1990)	6	10–17	Phenotype & CL	Not stated	50		
Bennett et al. (1978)	7	4–8	Phenotype	MSCA	53 (30–81)		
Bihrle et al. (1989)	14	9–18	Phenotype & CL	WISC-R	57 (49–77)		
Boddaert et al. (2006)	9	5–15	Phenotype & FISH (all)	WISC-III	63 (50–79)	76 (62–91)	53 (43–65)
Capirci et al. (1996)	1	2–4	Phenotype & FISH	WPPSI	82	89	78
Carlier et al. (2006)	34	8–26	Phenotype & FISH (all)	WISC-IV SB:L-M	52		
Clahsen & Almazan (1998)	4	11–15	Not stated	WISC-III	52 (44–60)		
Crisco et al. (1988)	22	4–10	Phenotype	SB:L-M	67		
Deruelle et al. (1999)	12	7–23	Phenotype	WISC-III, WPPSI-R	Not stated	58 (46–75)	48 (41–66)
Don et al. (1999)	18	8–13	WSA (US, Canada)	WISC-III	52	61 (46–81)	50 (45–62)
Frigerio et al. (2006)	21	16 (avg)	Phenotype & FISH (all)	SB:L-M	50		
Goncalves et al. (2005)	1	13	Phenotype & FISH	WISC-R	42	53	46
Greer et al. (1997)	15	4–18	Phenotype & FISH (8)	SB: IV	62		
Howlin et al. (1998)[x]	62	19–39	Phenotype	WAIS-R	60	64	60
Jackowski & Schultz (2005)	28	11–39	Phenotype & FISH (all)	WISC-III, WAIS-III	63 (40–82)		
Jernigan & Bellugi (1990)[Y]	6	10–20	Phenotype & CL	WISC-R	50		
Jernigan et al. (1993)[y]	8	10–20	Phenotype & CL	WISC-R	51		
Jones & Smith (1975)	14	3 mos – 23 yrs	Phenotype	Not stated	56 (40–80)		
Karmiloff-Smith et al. (1995)	18	9–23	Not stated	WISC-R	52 (40–65)		
Karmiloff-Smith et al. (1997) (2 studies)	20	8–34	WSA (UK)	WAIS-R, WISC-R, WISC-III	Not stated	66	54
	14	9–22	WSA(France)	WAIS-R, WISC-R	51–67		
Karmiloff-Smith et al. (1998)	8	14–34	Not stated	WISC-III, WAIS-R	Not stated	71 (51–87)	58 (46–75)
Kataria et al. (1984)	7	1–5	Phenotype	Bayley,SB	50 (28–64)		
Lenhoff et al. (2001)	4	Not stated	Phenotype & FISH (1)	Not stated	57 (51–69)		
Levitin et al. (2005)	118	20 (avg)	Phenotype, FISH (# not stated)	WAIS-R WISC-III	66		
Levy & Bechar (2003)	9	6–17	FISH (all)	WISC-R, WPPSI	61 (41–89)		
Levy & Hermon (2003)	10	12–17	Phenotype & FISH (all)	WISC-R	56 (40–92)		
Mervis et al. (2000)[Z]	84	3–46	Phenotype & FISH (50)	DAS	59		
Mervis et al. (2001)[z]	41	4–8	Phenotype & FISH (most)	DAS	59 (26–78)		
Morris et al. (1988)	17	17–34	Phenotype	Not stated	58 (17–80)		
Morris et al. (1990)	9	17–45	Phenotype	Not stated	53 (17–87)		
Nakamura et al. (2001)	5	6–10	Phenotype & FISH (4)	K-ABC	43 (37–54)		
Pagon et al. (1987)	9	10–20	Phenotype	WISC-R	42 (40–75)	54 (45–85)	52 (45–69)
Paul et al. (2002)	33	12–51	Phenotype & FISH (all)	WAIS-R	68		

Table 2 (*Continued*)

Author/Year	*N*	Age (yrs)	Diagnosis	Measure	FSIQ	VIQ	PIQ
Rae et al. (1998)	11	8–37	Phenotype & FISH (8)	WAIS-R, WISC-III	Not stated	71	60
Reiss et al. (2004)	43	12–50	Phenotype & FISH (all)	WISC-R, WAIS-R	68 (46–83)		
Searcy et al. (2004)	80	17–52	Phenotype & FISH (79)	WAIS-R	67	71	66
Stevens & Karmiloff-Smith (1997)	11	8–31	Not stated	WAIS-R, WISC-III	58 (48–76)		
Trauner et al. (1989)	8	16 (avg)	WSA (US)	WISC-R, WAIS	53		
Tyler et al. (1997)	12	14–30 yrs	Not stated	WAIS-R, WISC-R, WISC-III	63 (45–87)		
Udwin et al. (1987)[X]	44	6–16	IH	WISC-R	54 (40–89)	62 (45–109)	55 (45–73)
Udwin & Yule (1991)[x]	20	6–14	IH	WISC-R	57	61	59
Udwin et al. (1996)[x]	23	19–24	Phenotype, IH	WAIS-R	60	64	59
Vicari et al. (2004)	69	4–29	FISH (all)	SB: L-M	52 (33–96)		
Wang & Bellugi (1994)	9	13 (avg)	Phenotype	WISC-R	51		
Wang et al. (1995)	10	11–18	Phenotype	Not stated	48		

Bayley = Bayley Scales of Infant Development; CL = Calcium level; DAS = Differential Ability Scales; FISH = Fluorescent *in situ* hybridization; FSIQ = Full Scale IQ; IH = Infantile hypercalcaemia; K-ABC = Kaufman Assessment Battery for Children; MSCA = McCarthy Scales of Children's Abilities; PIQ = Performance IQ; SB = Stanford-Binet Intelligence Scale; SB:IV = Stanford-Binet Intelligence Scale, Fourth Edition; SB:L-M = Stanford-Binet Intelligence Scale, Form L-M; UK = United Kingdom; US = United States; VIQ = Verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale–Revised; WISC-R = Wechsler Intelligence Scale for Children–Revised; WISC-III = Wechsler Intelligence Scale for Children-Third Edition; WPPSI = Wechsler Preschool and Primary Scales of Intelligence; WSA = Williams Syndrome Association; X, Y Z= Original sample; x, y, z = Some participants from X or Y or Z.

obtained at this young age can be variable and the language therapy may have positively influenced the results on the verbal subtests of the IQ measure. The studies with smaller sample sizes (<15) reported an average Full Scale IQ score of 53 (30–82), while the average Full Scale IQ score among larger samples was 58 (26–82).

Some studies have reported differences between VIQ and PIQ. Udwin and Yule (1991) noted that only 10% of their participants obtained a VIQ below 45, in contrast to 50% who scored below 40 on PIQ. Fourteen of the studies (excluding Capirci et al., 1996) listed average VIQ and PIQ scores, with the difference in favor of VIQ ranging from 2 to 23 points. The average VIQ was 63 (45–109), while the average PIQ was 55(41–75). Howlin et al. (1998) performed one of the largest studies ($N = 62$) that reported both VIQ and PIQ scores. Howlin and colleagues observed a statistically significant four-point difference between VIQ and PIQ scores, but noted that a difference of nine points was necessary to achieve statistical significance in the general population. Searcy et al. (2004) evaluated the significance of the VIQ/PIQ difference for each participant in their study. They used Wechsler's 1981 guidelines for the age-appropriate critical value of the VIQ/PIQ difference and reported that VIQ was significantly greater than PIQ for 19 of their participants (approximately 24%), with only one participant scoring significantly higher on PIQ than VIQ. This is a particularly sound study of cognitive ability among adults with WS involving a large sample size ($N = 80$). Furthermore, in addition to reporting the Full Scale IQ, VIQ, and PIQ scores, they also report the average raw scores and age-corrected scaled scores of the Verbal and Performance subtests.

Studies with the largest VIQ/PIQ discrepancies tend to have higher VIQ scores (Boddaert et al., 2006; Karmiloff-Smith et al., 1997, 1998; Rae et al., 1998). Consistent with these findings, Jarrold, Baddeley, and Hewes (1998) found a positive linear relationship between verbal ability and the size of the verbal/nonverbal discrepancy among individuals with WS. These studies raise the issue of effect size and the importance of interpreting VIQ/PIQ differences within a clinically meaningful context, although a small effect may be relevant for characterizing the phenotype.

In summary, although the Full Scale IQ of individuals with WS has been suggested to range from 40 to 100, the average Full Scale IQ among published studies is 55, and few WS individuals score higher than 70. These results are consistent even among the studies that did not utilize FISH for a majority or all of their participants. The size, significance and prevalence of the VIQ/PIQ discrepancy

continue to be debated, with the largest discrepancies most evident in studies in which VIQ is higher than is typical for individuals with WS. While acknowledging that these published studies create an overall description of the intellectual phenotype of individuals with WS, it is also critical to remember that reporting only average IQ scores does little to reflect the variability in cognitive skills that is evident both between and within individuals with WS (Porter & Coltheart, 2005).

Language skills

Early studies with the WS population indicated that language was an area of remarkably preserved ability (Bellugi, Marks, Bihrle, & Sabo, 1988; Bellugi, Lai, & Wang, 1997; Rossen, Klima, Bellugi, Bihrle, & Jones, 1996). Bellugi et al. (1988) noted a striking dissociation between preserved linguistic functioning and severe deficits in reasoning and visuospatial processing in three adolescents with WS. In particular, it was suggested that these individuals with WS were able to understand grammatical structures and use both correct tense and appropriate syntax (Bellugi et al., 1997; Rossen et al., 1996). Pober and Dykens (1996) reported surprising strengths in the areas of syntax and semantics, although the authors acknowledged that not all individuals with WS displayed language strengths and that more studies were needed with larger numbers of participants. Receptive vocabulary has also been shown to be preserved relative to general cognitive ability (Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990). Jarrold, Baddeley, Hewes, and Phillips (2001) suggested that this 'strength' reflected a diverging developmental trajectory, whereby vocabulary levels progressed at a faster rate than pattern construction skills. Adolescents with WS have also been reported to display preserved affective language in their narratives (Reilly, Klima, & Bellugi, 1990).

Recently, researchers have investigated the language abilities of individuals with WS in more detail (for a recent review see Brock, 2007). Previously intact abilities are now thought to follow a delayed and even atypical course of development. In the current review, 55 language studies were examined and were subdivided into the most frequently researched areas: 1) Early language development, 2) Lexical, pragmatic, and grammatical skills 3) Narrative, and 4) Receptive vocabulary versus general intelligence.

Early language development. Twelve studies were reviewed that measured the language development of infants and children with WS up to the age of six years (see Table 3). Eight of the 12 studies included children with WS who had received genetic confirmation of WS using FISH. Sample sizes varied widely ranging from 1 to 54, with seven out of the 12 studies using fewer than 15 participants. Three of the studies were case studies utilizing only one or two participants.

Thal, Bates, and Bellugi (1989) studied two children with WS and reported that the development of their spontaneous language skills was similar to young normal- and late-talking children. Capirci et al. (1996) studied the language skills of one child with WS who was learning native Italian and their findings showed mixed results. The child demonstrated delayed but normal development in vocabulary, morphology, and syntax, but made atypical morphological errors in her spontaneous language. When compared to mental age-matched controls, toddlers with WS use fewer gesturing skills, which are believed to be a precursor to language development (Laing et al., 2002; Singer Harris, Bellugi, Bates, Jones, & Rossen, 1997). Nazzi, Paterson, and Karmiloff-Smith (2003) evaluated the segmentation skills of infants and toddlers with WS and found that they were able to recognize nouns (as measured by head turn preference) with a strong-weak stress pattern, but were unable to recognize words with a weak-strong emphasis, suggesting a deficit in their early phonological processing.

Children with WS have often been compared to mental age-matched children with Down syndrome (DS). On a task measuring vocabulary development in toddlers, the scores of the two groups were comparable (Paterson, Brown, Gsodl, Johnson, & Karmiloff-Smith, 1999). Singer Harris et al. (1997) used a cross-sectional study to measure the early development of language. Parents of toddlers with either WS or DS reported that their children displayed a similar two-year delay in language acquisition. During the initial period of language acquisition when the children produced fewer than 50 words, the DS group displayed an advantage over the WS group. However, this difference disappeared when both groups acquired vocabularies greater than 50 words. These findings, however, have been questioned due to possible sample bias. Singer Harris et al. (1997) used an outcome variable (expressive vocabulary size) that was the same as their inclusion criteria (children with a vocabulary of fewer than 50 words), confounding the results and making them difficult to interpret.

Mervis and Robinson (2000) found that two-year-old children with WS displayed a significantly larger expressive vocabulary than similar-aged children with DS. However, the vocabulary sizes of the children with WS were well below average for their age and 86% scored below the 10th percentile in their expressive vocabulary skills. Volterra, Caselli, Capirci, Tonucci, and Vicari (2003) found that the sentences produced by children with WS were comparable in complexity to those of typical children with similar-sized vocabulary, and more complex than those produced by children with DS. Vicari, Caselli, Gagliardi, Tonucci, and Volterra (2002) reported that toddlers with WS scored comparably to

Table 3 Early language development in Williams syndrome

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Capirci et al. (1996)	1	2–4	None	Phenotype & FISH	Morphology and syntax were delayed and atypical in WS
Laing et al. (2002)	13	1–4	13 NC matched on MA & sex	Phenotype & FISH (all)	Early stages of WS language were atypical
Levy (2004)	2	3–5	20 NC matched on MLU	Phenotype & FISH (all)	Mean length of utterance developed slowly in WS, but may underestimate grammatical development
Mervis & Robinson (2000)	24	2	28 DS matched on CA	FISH (all)	WS had a larger vocabulary than DS based on parent questionnaire
Nazzi et al. (2003)	19	1–4	None	Phenotype & FISH (all)	Toddlers with WS displayed deficits in early phonological processing
Nazzi & Karmiloff-Smith (2002)	12	2–6	None	WSA (US)	WS categorized objects according to visual rather than verbal cues
Nazzi et al. (2005)	8	5–6	34 NC 2-6 years old	WSA	WS demonstrated delay in the emergence of name-based categorization
Paterson et al. (1999)	15	2–3	22 DS matched on CA & MA 17 NC matched on MA 17 NC matched on CA	Phenotype & FISH (all)	Vocabulary development was delayed and impaired in both WS and DS
Singer Harris et al. (1997)	54	1–6	39 DS matched on CA & MA	WSA (US)	WS and DS were similarly delayed in early word acquisition, but WS was stronger in later grammar acquisition
Thal et al. (1989)	2	2–5	9 NC (14 mos) 9 NC (23 mos) 9 Late-talkers (23 mos)	Phenotype	Language development was delayed and variable in WS
Vicari et al. (2002)	12	4 (avg)	12 DS matched on MA 12 NC matched on MA	FISH (all)	WS demonstrated lexical-semantic difficulty on sentence repetition task
Volterra et al. (2003)	6	3–5	6 DS matched on CA & MA 6 NC matched on MA	Phenotype & FISH (all)	Sentence complexity in WS was similar to NC and more complex than DS

CA = Chronological age; DS = Down syndrome; FISH = Florescent *in situ* hybridization; MA = Mental age; MLU = Mean length utterance; NC = Typical (Normal) developing control; US = United States; WSA = Williams Syndrome Association.

mental age-matched normal controls on tasks of verbal comprehension and phrase repetition, although they displayed atypicalities in their substitution of articles and prepositions. The Vicari et al. (2002) study is methodologically strong because the comparison groups included both DS and normal controls, and the findings were based on both experimental tasks and parental report. Studies targeting specific language skills have shown that children with WS show a delay in their mean length utterance (Levy, 2004) and in their ability to categorize objects by name (Nazzi, Gopnik, & Karmiloff-Smith, 2005).

The results across studies have been varied, most likely reflecting the range of instruments used to test language development (parental report versus experimental task), as well as the use of differing control groups and small sample sizes in many of the studies. Results within studies have also indicated variable language development, with evidence of both typical (but delayed) and atypical language skills in vocabulary, morphology, and syntax (Capirci et al., 1996).

In summary, the early language studies have not identified a characteristic developmental trajectory in WS, with some studies showing typical (but delayed) language development and others showing atypical language development. The findings thus far suggest that verbal comprehension, phrase repetition, mean length utterance, and object categorization have been shown to be typical (but delayed), while the development of phonological processing and morphology appear to be atypical. It is somewhat difficult to delineate a clear phenotype of early language development in WS due to the range of measures and comparison groups utilized between studies. Specifically, the studies involving children with DS as the sole comparison group may lead to questionable outcomes given that the language capabilities of individuals with DS are impaired relative to their other cognitive skills (Singer Harris et al., 1997). Singer Harris et al. (1997) and Mervis

and Robinson (2000) utilized the largest samples, but their results were based solely on parental reports, which may introduce a possibility of bias. Longitudinal studies, as well as cross-sectional studies with large sample sizes and multiple comparison groups, would be helpful in teasing out the development of early language in young children with WS.

Lexical, pragmatic, and grammatical skills. Table 4 presents the results of 37 studies evaluating the lexical, pragmatic, and grammatical skills of children, adolescents, and adults with WS. Sample sizes ranged from 1 to 69, with 68% of the studies using fewer than 15 WS participants. Twenty-seven percent of the studies indicated that the majority or all of their participants had been genetically confirmed as having WS using FISH.

Some researchers have suggested that specific aspects of grammar (word fluency, syntax, irregular past tense, plurals, word roots/suffixes, and semantics) follow a typical (but delayed) developmental course in individuals with WS (Bello, Capirci, & Volterra, 2004; Burani, Bimonte, Barca, & Vicari, 2006; Gosch, Stading, & Pankau, 1994; Jarrold, Hartley, Phillips, & Baddeley, 2000; Levy & Bechar, 2003; Thomas et al., 2001; Tyler et al., 1997; Udwin & Yule, 1990; Zukowski, 2005). In these studies, individuals with WS were compared to normal controls, individuals with developmental disabilities, and those with specific speech or language impairments. Individuals with WS performed similarly to mental age-matched controls when comprehending pronouns and passive sentences (Ring & Clahsen, 2005). Losh, Bellugi, Reilly, and Anderson (2000) found that the complex syntactical skills of children with WS followed a typical (but delayed) developmental pattern. The Losh et al. (2000) study is methodologically strong because it utilized a narrower age range (5 to 10 years) and multiple comparison groups.

Other researchers have reported that recent studies of complex grammatical skills have revealed not only delays, but atypical performance in the areas of grammatical comprehension, gender agreement, morphosyntax, pragmatics, oral fluency, and semantic fluency (Clahsen & Almazan, 1998; Clahsen & Almazan, 2001; Grant, Valian, & Karmiloff-Smith, 2002; Laws & Bishop, 2004; Monnery, Seigneuric, Zagar, & Robichon, 2002; Pezzini, Vicari, Volterra, Milani, & Ossella, 1999; Stojanovik, 2006; Temple, Almazan, & Sherwood, 2002; Vicari et al., 2004; Volterra, Capirci, Pezzini, Sabbadini, & Vicari, 1996; Volterra, Longobardi, Pezzini, Vicari, & Antenore, 1999). Stojanovik, Perkins, and Howard (2001) proposed that given this atypicality, the language skills of WS individuals should no longer be considered a 'relative strength' of their cognitive profile. The Vicari et al. (2004) study is methodologically strong because they utilized multiple comparison groups. Furthermore, although Vicari and colleagues used a wide age range of participants, they analyzed their data based on chronological age, which indicated that the developmental profile of younger children with WS differed from that of older individuals with WS.

In addition to displaying atypical language when compared to others, dissociations have been reported within the language skills of WS individuals themselves. Monnery et al. (2002) found that individuals with WS used gender-agreement rules appropriately when learning native French but used an atypical approach when applying gender to nonwords, whereas Volterra et al. (1996) found atypical patterns in the spontaneous morphosyntax of Italian children and adolescents with WS. Clahsen and Almazan (1998) reported a distinction between an intact computational component (combined operations to form linguistic expressions) and an impaired lexical component (a finite list specifying parts of speech and information regarding form and meaning). A specific weakness in word-finding skills was proposed by Bello et al. (2004). Additional dissociations were suggested by Pezzini et al. (1999), who reported that individuals with WS were more impaired than mental age-matched controls on a naming task, but more proficient on a semantic fluency task.

Individuals with WS have also been found to demonstrate atypical development in various functional aspects of language. The comprehension and production of language used to describe spatial location has been shown to be impaired in individuals with WS (Landau & Hoffman, 2005; Phillips, Jarrold, Baddeley, Grant, & Karmiloff-Smith, 2004). Furthermore, individuals with WS were reported to use stereotypical conversation and initiate conversation inappropriately more often than individuals with a specific language impairment (Laws & Bishop, 2004). Stojanovik (2006) conducted a preliminary study with five children with WS and found that the children produced a higher number of extended responses, but had more difficulty maintaining a flow of conversation, than children with a speech and language impairment. The children with WS had difficulty with reciprocal communication because they failed to correctly respond to requests for information and clarification.

Variable findings across grammatical studies most likely reflect methodological issues such as differing sample sizes and the use of various language tests and comparison groups, as well as inconsistencies in language skills between and within WS individuals. Stojanovik et al. (2001 p. 237) stated that 'any attempt to generalize from group studies should be approached with extreme caution.' Despite this, generalizations frequently occur in secondary sources (Grant et al., 2002) and findings of *relative* strengths evolve into claims of *spared* language skills in WS (Bellugi, Wang, & Jernigan, 1994; Pinker, 1999).

Table 4 Lexical, pragmatic, and grammatical skills in Williams syndrome

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Bello et al. (2004)	10	9–12	10 NC matched on CA 10 NC matched on MA	Not stated	WS displayed typical lexical-semantic skills but had word-finding difficulties
Bellugi et al. (1990)	6	10–17	6 DS matched on CA & MA	Phenotype & CL	Receptive vocabulary, syntax, and semantics were higher in WS than DS
Burani et al. (2006)	12	7–26	12 NC matched on MA	Not stated	WS recognized morphemic word structure and used roots and suffixes in comprehension
Clahsen & Almazan (1998)[X]	4	11–15	11-15 SLI (6–12 yrs) 10-12 NC (5 –7 yrs) 12 NC (17 yrs+)	Not stated	Syntax and regular inflection was not impaired in WS
Clahsen & Almazan (2001)	4	11–15	23 NC matched on MA	Phenotype & FISH (# not stated)	WS adolescents demonstrated strengths in regular past tense and plurals, but had difficulty with irregular lexical forms
Gosch et al. (1994)	25	4–10	25 NDD matched on CA & MA	Phenotype	WS language was similar to controls, with more plural-singular forms
Grant et al. (2002)	14	8–30	32 NC (5–7 yrs)	WSA (UK)	WS showed delay and deviance in syntax
Jarrold et al. (2000)	13	7–27	39 MLD (7–16 yrs) matched on MA	Phenotype, IH, FISH (2)	Word fluency of WS was not atypical, but word ordering was less complex
Jones et al. (2000)	30	5–10	30 NC matched on CA & sex	Phenotype & FISH (# not stated)	WS made more morphological errors
Karmiloff-Smith et al. (1997)	18	8–34	None	WSA (US)	WS showed deficits in morphosytax
(2 studies)	14	9–22	18 NC (4–5 yrs)	WSA (France)	WS performed poorly on grammatical gender markers
Karmiloff-Smith et al. (1998)	8	14–34	18 NC (19–29 yrs)	Not stated	WS receptive syntax was not intact
Krause & Penke (2002)	2	15, 18	10 NC matched on MA	Phenotype	WS adolescents had difficulty with irregular nouns and verbs in the German language
Landau & Hoffman (2005)	23	8–64	23 NC matched on MA	Phenotype & FISH (all)	Spatial language of WS was less specific than controls and showed evidence of directionality errors
Lakusta & Landau (2005)	10	9–17	10 NC matched on MA 12 NC adults	Phenotype & FISH (all)	WS use of "to" and "from" in prepositional phrases was similar to MA-matched NC
Laws & Bishop (2004)	19	6–25	24 DS (10–22 yrs) 17 SLI (4–7 yrs) 31 NC (4–6 yrs)	WSA (UK)	WS demonstrated significant deficits in pragmatic language based on parental report
Levy & Bechar (2003)	9	6–14	7 NDD matched on CA & MA 10 NC matched on CA 10 NC matched on MA	FISH (all)	WS lexical and morpho-syntactic skills were similar to NDD controls
Levy & Hermon (2003)	10	12–17	20 NC matched on MA	Phenotype & FISH (all)	WS demonstrated knowledge of root structure but had errors in morphology
Losh et al. (2000)	30	5–10	30 NC matched on CA 24 NC matched on PPVT 4 NC matched on VMI	Phenotype & FISH (all)	WS showed morphological errors and less complex syntax
Monnery et al. (2002)	10	5–21	29 NC matched on MA	Not stated	WS were not impaired in gender agreement, but had difficulty with lexical retrieval
Phillips et al. (2004) (2 studies)	32	8–38	32 NC matched on TROG 32 MLD matched on TROG	WSA (UK) & FISH (9)	WS made more errors on items containing a spatial component
	15	19 (avg)	15 NC matched on VMA 15 MLD matched on VMA	Phenotype & FISH (3)	WS showed deficits in understanding spatial terms

Table 4 (*Continued*)

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Pléh et al. (2003)	14	5–19	29 NC matched on VMA	WSA (Hungary)	WS demonstrated difficulty producing inflected forms of irregular morphology
Ring & Clahsen (2005)	10	11–13	8 DS matched on CA 30 NC matched on MA	Not stated	The ability to interpret sentences with passives and pronouns was relatively preserved in WS
Stevens & Karmiloff-Smith (1997)	11	8–31	12 NC (3 yrs) 12 NC (9 yrs)	Not stated	WS did not use whole object or taxonomic categories to acquire vocabulary
Stojanovik et al. (2001)	4	7–12	4 SLI matched on CA	WSA (UK)	WS showed linguistic difficulties on standardized measures and in conversational speech
Stojanovik et al. (2004)	5	7–12	5 SLI (similar CA)	Phenotype & FISH (all)	WS were similar to SLI on receptive vocabulary, grammar comprehension, and morpho-syntactic production
Stojanovik (2006)	5	7–12	8 SLI matched on VMA 9 NC matched on CA	WSA (UK) & FISH (all)	Compared to SLI, WS used more extended responses but had more difficulty maintaining conversation
Temple et al. (2002)[x]	4	11–15	5-10 NC (depending on task) matched on MA	Phenotype (1) FISH (1) 2 not stated	WS displayed deficits in semantics and atypical oral fluency
Thomas et al. (2001)	21	10–53	10 NC (6 yrs) 10 NC (8 yrs) 10 NC (9 yrs) 16 NC (30 yrs)	WSA (UK)	WS ability to use irregular past tense verbs was delayed but not atypical
Tyler et al. (1997)	12	14–30	20 NC (18–40 yrs)	Not stated	WS showed normal semantic memory for individual words, but difficulty with semantic integration in WS
Udwin & Yule (1990)	43	6–15	None	IH	WS used more adult vocabulary but were not hyperverbal
Vicari et al. (2004)	69	4–29	46 NC matched on MA 56 DS matched on CA & MA	Phenotype & FISH (all)	WS demonstrated relative strengths in fluency and comprehension, and weaknesses in morphosyntax and production
Volterra et al. (1996)	17	4–15	116 NC, CA similar to MA of WS	Not stated	WS showed delayed and atypical grammatical comprehension, morphosyntax, and semantics
Volterra et al. (1999)	1	10	1 NC twin	Phenotype & FISH	WS showed preserved phonological abilities with deficits in semantics and morphosyntax
Ypsilanti et al. (2005)	6	10–17	5 DS matched on CA & MA 22 NC matched on MA	Phenotype & FISH (all)	WS made more expressive semantic errors and fewer circumlocutions than MA controls Receptive vocabulary exceeded MA in WS
Zukowski (2005)	12	8–16	12 NC matched on MA 18 NC adults	WSA	WS children and adolescents demonstrated knowledge of plurals in compounds and suppressed productive morphological rules

CA = Chronological age; DS = Down syndrome; FISH = Florescent *in situ* hybridization test; IH = Infantile hypercalcaemia; MA = Mental age; MLD = Moderate learning difficulties; NC = Typical (Normal) developing control; NDD = Non-specific developmental disability; PPVT = Peabody Picture Vocabulary Test; SLI = Specific language impairment; TROG = Test of Reception of Grammar; UK = United Kingdom; US = United States; VMA = Verbal mental age; VMI = Visuomotor Integration Test; WSA = Williams Syndrome Association; X = Original sample; x = Some participants from X.

Overall, the findings of the grammatical studies suggest both typical (but delayed) and atypical grammatical abilities within WS individuals. Such varied findings are not surprising, given the wide range of grammatical skills that have been evaluated across studies, combined with the variability of skills within the WS population and the use of varied comparison groups. Individuals with WS have been found to exhibit typical (but delayed) skills on tests of word fluency, irregular past tense, plurals, and semantics. Atypical grammatical abilities have generally been reported on tasks that measure more complex skills, such as morphosyntax and semantic integration. Future studies employing more rigorous methodological approaches, such as matching control groups based on performance on an individual measure, rather than on overall mental age, are recommended to clearly identify the grammatical features of the WS language phenotype.

Narrative. Only two studies have examined the use of emotional and linguistic expression in narratives by individuals with WS. The study by Reilly et al. (1990) included four adolescents with WS, although it is not known if these adolescents were genetically confirmed with the diagnosis. Losh et al. (2000) included a much larger sample of 30 children, all of whom were diagnosed using FISH, as well as the clinical phenotype.

Reilly et al. (1990) found that adolescents with WS established an orientation for their narrative and the majority began their stories with an identifiable beginning. Moreover, they used both lexical expression and vocal prosody to convey affect significantly more than mental age-matched adolescents with DS. With the exception of the use of emphatics, the participants with WS also significantly outperformed normal controls of similar mental age. Reilly and colleagues cautioned that this may represent an atypical, rather than intact, aspect of narrative skills, given that normal children use this type of emotional expressivity only when telling stories to preschool children.

Losh et al. (2000) evaluated the narrative skills of 5- to 10-year-old children with WS against three comparison groups: 1) chronological age-matched controls, 2) mental age-matched controls based on scores from the Peabody Picture Vocabulary Test-Revised (PPVT-R), and 3) mental age-matched controls based on scores from a visuomotor integration test. The children with WS used significantly more affective enhancers (such as 'Oh my, oh my!' and 'Suddenly') than the typically developing children in the three control groups. In contrast, the typical children used more cognitive inferences ('the boy thinks', 'because the boy was…'). Every child with WS used evaluative devices frequently, in sharp contrast to the typically developing children. Both Losh et al. (2000) and Reilly et al. (1990) suggested that the individuals with WS were using these devices to intentionally keep the listener engaged and postulated that this was a linguistic manifestation of their hypersociable personality. At present, however, there is no reliably established measure of such intent. Additional studies, including those with adult participants, are needed in order to more fully characterize the linguistic expressive skills of individuals with WS.

Receptive vocabulary versus general intelligence. Five studies have addressed the relationship between receptive vocabulary and general intelligence (see Table 5). Two of the studies had sample sizes greater than 15, but only one of these used FISH for genetic confirmation of WS (Pezzini et al., 1999). Receptive vocabulary has been measured using either the Peabody Picture Vocabulary Test-Revised (Dunn & Dunn, 1981) or the British Picture Vocabulary Scale (Dunn, Dunn, Whetton, & Pintilie, 1982).

It has been previously suggested that the receptive vocabulary of individuals with WS exceeds their mental age as well as that of mental age-matched controls (Bellugi et al., 1990, 1988), although no statistical data were provided in these studies. The comparison between receptive vocabulary skills and general intelligence has typically been qualitative in

Table 5 Comparison of receptive vocabulary and general intelligence in Williams syndrome

Author/Year	N	Age (yrs)	Control	Diagnosis	Findings
Bellugi et al. (1990)	6	10–17	Details not provided	Phenotype & CL	WS receptive vocabulary was at or above normal MA-matched controls
Clahsen & Almazan (1998)[X]	4	11–15	None	Not stated	WS receptive vocabulary was well above their MA
Don et al. (1999)	18	8–13	None	WSA (US, Canada)	PPVT-R scores of WS were significantly higher than VIQ and PIQ scores
Pezzini et al. (1999)	18	4–15	None	Phenotype & FISH (all)	PPVT-R scores of WS were in the expected range for MA
Temple et al. (2002)[x]	4	11–15	None	Not stated	WS receptive vocabulary was higher than MA

CL = Calcium level; FISH = Florescent *in situ* hybridization; MA = Mental age; PIQ = Performance IQ; PPVT-R = Peabody Picture Vocabulary Test-Revised; US = United States; VIQ = Verbal IQ; WSA = Williams Syndrome Association; X = Original sample; x = Some participants from X.

nature, with only one study (Don, Schellenberg, & Rourke, 1999) performing a statistical analysis of the difference. Specifically, Don et al. reported that the Peabody Picture Vocabulary Test-Revised (PPVT-R) score of individuals with WS was significantly higher than their VIQ, PIQ, and Full Scale IQ scores. In contrast, Pezzini et al. (1999) found that the PPVT-R performance of children and adolescents with WS was in the expected range for their mental age, but no statistical analysis was conducted. These contrasting results may be partly explained by the use of different measures of intelligence in the two studies, and the application of statistical testing only by Don et al.

The studies which have examined the relationship between receptive vocabulary and IQ are limited in number and only one utilized individuals who were diagnosed using both the clinical phenotypic criteria and FISH (Pezzini et al., 1999). Furthermore, only one study included a control group (Bellugi et al., 1990), which limits the discussion of whether the findings are syndrome-specific. Further studies should include larger sample sizes, hypothesis-driven control groups, and a statistical comparison of receptive vocabulary and general intelligence in order to more fully characterize the relationship between these domains.

Summary of language skills. The results of language studies in individuals with WS have yielded mixed results. Overall, the findings suggest that individuals with WS display typical (but delayed) skills in the following areas of language development: complex syntax, semantics, word fluency, expressive vocabulary, plurals, irregular past tense, and mean length utterance. Language development appears to be atypical in the following domains: grammatical comprehension, gender agreement, morphosyntax, pragmatics, oral fluency, and reciprocal conversation. These findings, however, need to be interpreted in the context of the control groups utilized in each study. A number of the researchers have matched WS with DS participants given the similarity of their global IQ scores. The language capabilities of individuals with DS, however, are impaired relative to their other cognitive skills (Singer Harris et al., 1997), affecting the validity of this comparison. The relationship between receptive vocabulary and global IQ, as well as the exploration of emotional expression in language, requires further investigation in larger groups of individuals with WS before firm conclusions can be drawn. The studies have used a variety of measures, control groups, and sample sizes, contributing to variable language findings within the WS population. One way to avoid the limitations inherent in using a control group is to use theoretically neutral developmental trajectories, as described by Karmiloff-Smith et al. (2004), which link task performance with chronological age, rather than focusing exclusively on control group comparisons. This strategy would also be advantageous in studies which employ a wide age range of participants, whereby the course of development could be viewed over time.

Visuospatial and face processing skills

Table 6 summarizes the 53 studies that have investigated visuospatial abilities and face processing skills in individuals with WS. The sample sizes range from 1 to 73, with 45% of the studies using samples larger than 15. FISH was used in 58% of the studies to genetically confirm the diagnosis of WS in a majority or all of the participants.

Initial visuospatial research, which involved copying hierarchical stimuli combining global and local features, suggested that children and adolescents with WS have a deficit in processing the global aspects of visuospatial stimuli and show a bias in processing the local features (Bihrle, Bellugi, Delis, & Marks, 1989). Farran, Jarrold, and Gathercole (2003) reported that although adults with WS also had difficulty drawing global aspects of hierarchical stimuli, they were able to detect both the global and local features. Additional studies of copying ability indicated that the performance of individuals with WS was similar to that of younger typical children, suggesting that the global deficits were indicative of delayed, rather than deviant, performance (Bertrand, Mervis, & Eisenberg, 1997; Georgopoulos, Georgopoulos, Kuz, & Landau, 2004). Dykens et al. (2001) reported no global/local distinctions on a person-drawing task and suggested that individuals with WS may be able to draw global and local features of human figures more easily than those of geometric shapes due in part to their sociable personality and their interest in human faces. The study by Dykens and colleagues is particularly sound because the researchers incorporated two control groups made up of atypical populations and had a relatively large sample. Farran (2005) noted that although individuals with WS have been shown to process visual stimuli on both a local and global level, their performance was impaired when they were asked to group stimuli by shape, orientation, and spatial features (proximity).

A particularly sound study was conducted by Porter and Coltheart (2006), who employed a relatively large number of participants with WS and included comparison groups comprised of normal controls, children with autism, and children with DS. Porter and Coltheart (2006) found that individuals with WS, as well as those with autism, demonstrated a bias in their attention to local forms, but this local bias did not extend to perception, as measured in response times. Hoffman, Landau, and Pagani (2003) suggested that the proposed deficit in global processing may reflect difficulties in planning and/or executing motor responses, rather than in visuospatial perception, based on an examination of

Table 6 Visuospatial and face processing skills in Williams syndrome

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Visuospatial					
Atkinson et al. (1997)	15	4–14	20, 30 NC (4–20 yrs)	Not stated	WS displayed deficits on dorsal processing tasks
Atkinson et al. (2001)	73	8 mos–13 yrs	None	WSA (UK)	No correlation between vision and visuospatial difficulties in WS. Small improvements in visuospatial skills over time
Atkinson et al. (2003)	45	4–15	76 NC (4–7 yrs) 64 NC (5–6 yrs) 13 NC (10 yrs) 35 NC (adults)	Not stated	Subgroup of WS performed similarly to young NC on motion (dorsal) task
Atkinson et al. (2006)	45	16–47	19 NC matched on CA	Phenotype & FISH (all)	Impairment in the detection of global motion in WS extends into adulthood
Bertrand & Mervis (1996)[x]	6	12–14	None	WSA (US), Physician	WS drawing ability was delayed but improved over time
Bertrand et al. (1997)[X]	18	9–10	18 NC matched on CA & sex 18 NC matched on MA & sex	WSA (US), Physician	WS scored lower on VMI and drawing task than controls, but errors were typical
Bihrle et al. (1989)	14	9–18	9 DS matched on CA & MA 10 NC matched on CA	Phenotype & CL	WS were impaired in global, rather than local analysis of visual stimuli
Brown et al. (2003)	13	23–37 mos.	19 DS matched on CA 17 NC matched on CA 15 NC matched on MA	FISH (all)	WS were impaired in saccade planning and visual exploration
Deruelle et al. (2006)	13	5–17	13 NC matched on CA & gender 13 NC matched on MA and gender	Phenotype & FISH (11)	Configural processing in WS was similar to MA-matched controls on visuo-perceptual task
Dykens et al. (2001)	28	4–38	28 DS matched on CA 28 MR matched on CA & MA	FISH (all)	Drawing of human figures was superior to geometric shapes in WS No local/global differences were observed in drawings of humans in WS
Farran et al. (2001)[Y]	21	9–38	21 NC (6 yrs) matched on nonverbal ability	Phenotype & FISH (6)	WS had difficulty using mental imagery on visuospatial tasks
Farran et al. (2003)[y]	21	20 (avg)	21 NC (6 yrs) matched on nonverbal ability 21 NC matched on CA	Phenotype & FISH (6)	Local/global differences on hierarchical task affected drawing but not identification in WS
Farran & Jarrold (2004)[y] (2 studies)	22	10–39	22 NC matched on RCPM	Phenotype & FISH (6)	Processing and orientation discrimination on block construction was abnormal in WS
	21	11–33	21 NC matched on RCPM	Phenotype & FISH (6)	WS performance on size transformation task was similar to NC matched on RCPM
Farran (2005)	15	6–25	15 NC matched on RCPM	Phenotype & FISH (all)	Perceptual grouping by shape, orientation, and proximity was impaired in WS
Farran & Jarrold (2005)[y]	21	21 (avg)	21 NC matched on RCPM 20 young NC with lower score on RCPM 21 NC matched on CA	Phenotype & FISH (all)	Both spatial and visual relations were impaired in WS, with atypical spatial location encoding
Georgopoulos et al. (2004)	10	6–14	10 NC (3–6 yrs) matched on non–verbal ability	Not stated	Figure copying of WS was delayed, but typical
Grice et al. (2003)	15	10–50	15 NC matched on CA & sex	Not stated	WS displayed abnormal ERPs on low-level visual processing
Hoffman et al. (2003)	8	7–13	8 NC matched on MA 8 NC adults	WSA (US)	WS showed deficiency in identification and location of spatial representations

Table 6 (*Continued*)

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Jordan et al. (2002)	10	9–15	10 NC matched on MA 10 NC adults	Phenotype & FISH (# not stated)	Biological motion appeared intact in WS
Mendes et al. (2005)	6	11–20	11 NC matched on MA 22 NC matched on CA	Phenotype & FISH (all)	WS demonstrated impaired motion processing of 3D surfaces
Nakamura et al. (2001)	5	6–10	None	Phenotype & FISH (4)	WS displayed deficits in visuospatial ability and spatial memory
Nakamura et al. (2002)	1	12	None	Phenotype & FISH	Visuospatial deficits in WS were linked to impaired neural groups in the dorsal stream
O'Hearn et al. (2005)	15	10–38	15 NC matched on MA 12 NC 4–7 years old	Phenotype & FISH (all)	Multiple object tracking of moving targets was impaired in WS
Pani et al. (1999)	2	19–47	12 NC matched on CA & sex	FISH (all)	WS had difficulty with global/local switching
Pezzini et al. (1999)	18	4–15	18 NC matched on MA	Phenotype & FISH (all)	WS showed impairment on visuospatial construction tasks
Porter & Coltheart (2006)	27	5–43	15 DS matched on MA 8 Autistic matched on MA 27 NC matched on CA	Phenotype & FISH (18)	WS demonstrated local (vs. global) bias in attention, but not perception, with mixed results in construction
Reiss et al. (2005)	20	9–39	10 NC matched on MA 10 NC adults	Phenotype & FISH (19)	WS displayed intact perception of motion coherence and biological motion, but were impaired on form-from-motion
Scerif et al. (2004)	8	3–4	8 FXS matched on MA & CA 8 NC matched on MA 8 MC matched on CA	WSA (UK)	WS toddlers demonstrated delays in visual search and made more distractor errors than controls
Stiles et al. (2000)	1	2, 6	None	Phenotype & FISH	Visuospatial deficits of WS improved with age, but persisted
van der Geest et al. (2004)	27	11–35	8 NC matched on CA	Phenotype & FISH (all)	Impaired saccadic eye movements were noted in WS
van der Geest et al. (2005)	33	10–39	23 NC matched on CA	Phenotype & FISH (all)	WS could judge depth perception, but had difficulty using depth information to guide movements
Vicari et al. (1996)	16	10 (avg)	16 NC matched on MA	Phenotype & FISH (all)	Short and long-term visuospatial memory deficient in WS
Vicari et al. (2003)	13	5–10	26 NC matched on MA	Phenotype & FISH (all)	WS visual memory was similar to controls, but spatial memory was significantly weaker
Vicari et al. (2005)	15	8–30	15 NC matched on MA	Phenotype & FISH (all)	WS visual-object memory was equal to MA controls, but visuospatial memory was impaired
Wang et al. (1995)	10	11–18	9 DS matched on CA & MA	Phenotype	WS displayed deficits on visuospatial tasks
Face processing					
Deruelle et al. (1999)	12	7–23	12 NC matched on CA & sex 12 NC matched on MA	Phenotype	WS face recognition was equal to MA controls, but below CA controls
Gagliardi et al. (2003)	26	5–32	26 NC matched on CA & sex 26 NC matched on MA & sex	FISH (all)	Recognition of facial expression in WS was similar to MA controls, but weaker than CA controls
Grice et al. (2001)	8	30 (avg)	8 Autistic, 8 NC matched on CA & handedness	Phenotype & FISH (all)	When viewing faces, EEG patterns in WS were atypical compared to autistic and NC
Karmiloff-Smith et al. (2004)	12	16–51	12 NC matched on CA & sex	Phenotype & FISH (all)	WS displayed deficits in upright configural face processing
(3 studies)	14	12–54	111 NC aged 2–11 years	Phenotype & FISH (all)	The face inversion effect showed an atypical developmental trajectory in WS

Table 6 (*Continued*)

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
	12	15–52	61 NC covering MA and CA age span of WS	Phenotype & FISH (all)	WS demonstrated delayed and atypical configural processing
Mills et al. (2000)	18	18–38	23 NC matched on CA	Phenotype & genetic records	Abnormal ERP results in WS suggest impaired face processing skills
Nakamura et al. (2006)	1	13	NC adults	Phenotype & FISH	Inverted faces processed more quickly in WS
Paul et al. (2002)	33	12–51	19 NC matched on MA 24 NC matched on CA	Phenotype & FISH (all)	WS performed well on face processing, but poorly on location processing tasks
Pezzini et al. (1999)	18	4–15	18 NC matched on MA	Phenotype & FISH (all)	WS showed strengths on facial recognition
Plesa-Skwerer et al. (2006a)	47	12–32	49 L/ID matched on CA & PPVT–III 58 NC matched on CA	Phenotype & FISH (all)	Emotion identification in faces and voices was similar in WS and L/ID, less proficient than NC
Plesa-Skwerer et al. (2006b) (2 studies)	43	12–36	42 L/ID matched on CA, MA, & PPVT–III	Phenotype & FISH (all)	WS similar to L/ID and worse than NC in labeling emotions from the eyes
	37	12–37	46 NC matched on CA 32 L/ID matched on CA, MA, and PPVT–III	Phenotype & FISH (all)	Emotion labeling from facial expressions is similar in WS and L/ID, worse than NC
Tager-Flusberg et al. (1998)	13	17–37	13 PWS matched on CA & MA 25 NC matched on CA	WSA (US)	WS adults demonstrated a strength in the ability to determine mental state from eyes
Tager-Flusberg & Sullivan (2000)	22	4–8	15 PWS matched on CA & MA 11 MR matched on CA & MA	WSA (US)	Discrimination of facial expression in WS was similar to PWS and MR controls
Tager-Flusberg et al. (2003)	47	12–36	39 NC matched on CA	Phenotype & FISH (all)	WS facial recognition and encoding delayed, but was similar to NC
Wang et al. (1995)	10	11–18	9 DS matched on CA & MA	Phenotype	WS displayed strengths in facial discrimination

CA = Chronological age; CL = Calcium level; DS = Down syndrome; EEG = Electroencephalogram; ERP = Event-related potential; FISH = Florescent *in situ* hybridization; FXS = Fragile X syndrome; L/ID = Learning/Intellectual Disability; MA = Mental age; MR = Mental retardation with mixed or unknown etiology; NC = Typical (normal) control; PPVT-III = Peabody Picture Vocabulary Test-III; PWS = Prader-Willi syndrome; RCPM = Raven's Coloured Progressive Matrices; UK = United Kingdom; US = United States; WSA = Williams Syndrome Association; X = Original sample; x = Some participants from X; Y = Original sample; y = Some participants from Y.

eye fixations in a small number of children with WS. Pani, Mervis, and Robinson (1999) suggested that the visuospatial construction difficulties noted among individuals with WS stemmed from a difficulty in alternating between global and local processing strategies. However, Porter and Coltheart (2006) surmised that the local bias observed on visuo-constructive tasks was not due to a construction deficit, because their study found evidence of local bias on tasks that did not include an element of construction.

Specific deficits in visuospatial processing have been reported in such aspects as perceptual grouping, orientation discrimination, mental imagery, spatial relationships, and spatial memory (Farran, Jarrold, & Gathercole, 2001; Farran & Jarrold, 2004; Farran, 2005; Hoffman et al., 2003; Vicari, Bellucci, & Carlesimo, 2003, 2005). Scerif, Cornish, Wilding, Driver, and Karmiloff-Smith (2004) noted that young children with WS have difficulty with visual search tasks, while other investigators have indicated that impaired saccadic eye movements in individuals with WS may play a part in their visuospatial deficits (Brown et al., 2003; van der Geest et al., 2004). In contrast, the visuospatial processing of biological motion has been reported to be preserved in individuals with WS (Jordan, Reiss, Hoffman, & Landau, 2002; Reiss, Hoffman, & Landau, 2005), although impairment has been noted on tasks involving the detection of form through global motion (Atkinson et al., 2003, 2006; Mendes et al., 2005; Reiss et al., 2005). Additional studies have examined the impact of visuospatial deficits on the memory skills of individuals with WS. Vicari and colleagues found that individuals with WS displayed both short and long-term visuospatial memory deficits, with spatial memory more impaired than object memory (Vicari et al., 2003, 2005).

Researchers studying visual processing have distinguished between the dorsal visual stream, which processes information about the position of objects, and the ventral stream, which is involved in face and

object recognition (Milner & Goodale, 1995). Some findings suggest that visuospatial deficits in individuals with WS reflect impaired function in the dorsal stream, with the ventral stream remaining intact (Atkinson et al., 1997; Wang, Doherty, Rourke, & Bellugi, 1995). Atkinson et al. (1997) observed significant deficiencies among individuals with WS on tasks requiring visuo-motor control, a skill involving structures within the dorsal stream. More recently, Atkinson et al. (2003) identified a subgroup of children and adolescents with WS who performed poorly on a motion coherence threshold (dorsal) task, although similarly poor performance was observed in younger typically developing children. This finding led Atkinson and colleagues (2003) to propose that the weak performance by individuals with WS may reflect a more general immaturity in visuospatial processing that is most evident in functions mediated by the dorsal stream.

The facial processing skills of individuals with WS, such as the recognition of faces and facial expressions, are reported to be equivalent to mental age-matched controls, but significantly below chronological age-matched controls (Deruelle, Mancini, Livet, Casse-Perrot, & de Schonen, 1999; Gagliardi et al., 2003). Some studies have suggested that face processing is an area of relative strength for individuals with WS because their ability to process faces holistically is similar to that of normal controls (Paul, Stiles, Passarotti, Bavar, & Bellugi, 2002; Pezzini et al., 1999; Tager-Flusberg, Plesa-Skwerer, Faja, & Joseph, 2003; Wang et al., 1995). Tager-Flusberg and Sullivan (2000) reported that children with WS discriminate facial expressions in a manner similar to children with other types of intellectual disabilities. Children and adults with WS have been found to identify and label emotions in faces similar to individuals with learning/intellectual disabilities (Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006a; Plesa-Skwerer, Verbalis, Schofield, Faja, & Tager-Flusberg, 2006b). Other studies, however, have reported that individuals with WS process faces atypically, based on neural responses using EEG, ERP, and magnetoencephalography (Grice et al., 2001; Karmiloff-Smith et al., 2004; Mills et al., 2000; Nakamura, Watanabe, Gunji, & Kakigi, 2006). As Karmiloff-Smith et al. (2004) suggests, these inconsistencies are due in part to unaccounted ceiling effects of comparison groups, as well as the tendency for studies to inaccurately interchange the face-processing terms of 'configural' (differentiating the spatial distances among facial features) and 'holistic' (viewing the facial features as a gestalt form).

Overall, the studies concur that visuospatial functions constitute a cognitive weakness in individuals with WS. The reasons for this difficulty have been debated, however, with some researchers suggesting that it stems from a motor planning deficit related to a weak dorsal stream. The results of the research investigating the local vs. global bias have been varied, in part due to the variety of tasks that have been used to measure this aspect of visuospatial processing. Farran and Jarrold (2003) performed a comprehensive review of the visuospatial processing literature and highlighted the methodological issues of floor and ceiling effects, choice of control groups (typically developing or special needs), and choice of appropriate tests when matching control groups by mental age. Farran and Jarrold (2003) also recommended that control groups be matched by their performance on an individual measure, rather than on a score averaging a range of abilities across subtests. The studies by Plesa-Skwerer et al. (2006a, 2006b) are noteworthy in that they utilize comparison groups that were matched on a measure of receptive vocabulary, rather than overall mental age.

Future studies of face processing skills in WS individuals should clarify which specific abilities are being evaluated: featural, configural, or holistic. Additional studies utilizing developmental trajectories for data analysis are also encouraged, as this will enable a more comprehensive understanding of how face-processing skills develop in individuals with WS.

Behavior patterns and hypersociability

The behavior of individuals with WS has been described anecdotally as 'friendly, loquacious' (Jones & Smith, 1975) and 'polite, open and gentle' (von Arnim & Engel, 1964). More recently, Jones et al. (2000) reported that individuals with WS may be 'unusually sociable, friendly, and empathic' (p. 30). Levine and Wharton (2000) reported that 'one of the most striking characteristics of the condition is a unique personality profile that includes a general presentation of exuding happiness' (p. 364).

Numerous studies since the 1990s, however, have revealed that individuals with WS display significant behavioral difficulties and are distressed by persistent fears. Twenty-five studies were reviewed relating to the behavioral patterns of WS individuals (see Table 7). All of the studies employed either questionnaires completed by parents and/or caregivers of individuals with WS, or interviews with the WS individuals themselves, with sample sizes ranging from 11 to 204. In seven of the studies, the majority or all of the participants were reported to have a genetic confirmation of WS using FISH.

Individuals with WS are generally described as more anxious, distractible, and hyperactive and are more likely to experience difficulties with peer relationships than either chronological age-matched children or those with similar levels of mental retardation (Einfeld, Tonge, & Florio, 1997; Greer, Brown, Pai, Choudry, & Klein, 1997; Jones et al., 2000; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Tomc, Williamson, & Pauli,

Table 7 Behavior patterns and hypersociability in Williams syndrome

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Behavior					
Arnold et al. (1985)	22	7–12	NC (10 yrs) MR (10 yrs) # of controls not stated	IH	WS displayed more disturbed behavior than NC, but similar to MR controls
Davies et al. (1998)	70	19–39	None	WSA (UK), Phenotype	WS adults were described as disinhibited, distractible, socially isolated, and anxious
Dilts et al. (1990)	48	4–16	None	Phenotype	Parent questionnaire reported hyperactivity and distractibility in WS
Dykens (2003) (3 studies)	120	6–48	70 MR (6–48 yrs)	Phenotype & FISH (78)	Significantly more fears in WS than MR controls as reported by parents
(Subset of 120)	36	8–39	24 MR (8–30 yrs)	Phenotype & FISH (# not stated)	WS children described more fears than their parents reported about them
(Subset of 120)	51	5–49	None	Phenotype & FISH (all)	Parents reported that WS displayed specific phobias and symptoms of anxiety
Dykens & Rosner (1999)	35	24 (avg)	35 Prader–Willi matched on CA & sex 35 MR matched on CA & sex	Phenotype & FISH (24)	WS displayed attention-seeking behavior, empathy, and intense fears compared to control groups
Einfeld et al. (1997)	70	9 (avg)	454 MR (children & adolescents)	Phenotype	WS exhibited more anxiety, peer difficulties, and sleep disorders than MR controls
Einfeld et al. (2001)	64 ('91) 53 ('95)	9 (avg) 12 (avg)	582 MR (12 yrs avg) 454 MR (16 yrs avg)	Phenotype & FISH (# not stated)	Longitudinal analysis indicated that behavior and emotional problems persist in WS
Gosch & Pankau (1994)	19	4–10	25 MR matched on CA, MA, & sex	Phenotype	Hyperacusis and friendliness were elevated in WS compared to MR controls Other behavioral areas were similar
Gosch & Pankau (1997)	105	2–35	None	Phenotype & FISH (# not stated)	WS showed decreased acting-out behavior and increased depressive symptoms with age
Greer et al. (1997)	15	4–18	None	Phenotype & FISH (8)	Parents reported that WS displayed high levels of inattention and social difficulties
Jones et al. (2000)	20	18 (avg)	15 NC matched on CA 20 DS matched on CA 20 Autism matched on CA	Phenotype & FISH (# not stated)	WS displayed higher scores on Social-Emotional and Social-Approach subscales of questionnaire than all controls
Klein-Tasman & Mervis (2003)	22	8–10	20 DD matched on CA	FISH (all)	WS were rated as more gregarious, empathic, and tense than DD
Leyfer et al. (2006)	119	4–16	None	FISH (all)	Parents reported a high prevalence of attention problems and phobias among WS children
Mervis et al. (2001)	41	4–8	None	Phenotype & FISH (# not stated)	WS displayed strengths in language, social skills and weaknesses in daily living and motor skills
Plissart et al. (1994)	11	17–66	None	Phenotype	WS adults displayed behavioral difficulties and required supervised care

Table 7 (*Continued*)

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Rosner et al. (2004)	58	4–49	54 PWS 65 DS	Phenotype & FISH (all)	Compared to PWS and DS, WS showed greater interest in music but were less successful in job skills and visuomotor activities
Tomc et al. (1990)	204	1–12	None	Phenotype	WS showed hyperactivity, negative mood, and distractibility
Udwin et al. (1987)[X]	44	6–16	None	IH	High levels of activity, anxiety, and social isolation among WS
Udwin (1990)	119	16–38	None	IH	WS displayed excessive worrying, restlessness, and social isolation
Udwin & Yule (1991)[x]	20	6–14	20 MR matched on CA, VIQ & sex	IH	WS were more inattentive, fearful, and hyperactive than controls
Udwin et al. (1998)	70	26 (avg)	None	Phenotype & WSA (UK)	Most WS adults needed daily supervision Behavioral & emotional difficulties persisted over time
van Lieshout & De Meyer (1998)	28	2–19	39 Prader–Willi matched on CA & sex 32 Fragile–X, matched on CA & sex 28–39 NC matched on CA and sex for each group	WSA (Netherlands)	WS were found to be more agreeable than Prader-Willi or Fragile-X
Hypersociability					
Bellugi et al. (1999a)	26	23 (avg)	26 NC matched on CA & sex	Phenotype & FISH (all)	WS rated unfamiliar faces more approachable than controls
Doyle et al. (2004)	64	1–12	31 DS similar CA 27 NC similar CA	Phenotype & FISH (all)	WS were described by parents as more empathic and willing to approach strangers than DS or NC
Frigerio et al. (2006)	21	16	21 NC matched on CA & sex 21 NC matched on MA & sex	FISH (all)	Positive faces were seen by WS as more approachable, while negative faces were seen as less approachable than controls
Jones et al. (2000)	36	1–4 yrs	22 NC matched on MA & sex 22 NC matched on CA & sex	Phenotype, Diagnostic Scoresheet, & FISH (# not stated)	WS toddlers expressed fewer negative expressions during parental separation than controls
Mervis et al. (2003) (2 studies)	1	10 mos.	10 NC matched on MA & sex 10 NC matched on CA & sex	FISH (all)	WS infant gazed intensely at mother and a stranger
	31	8–43 mos	87 NC (8–43 mos) 242 DD (8–43 mos)	FISH (all)	WS infants gazed intensely at a stranger

CA = Chronological age; DD = Developmental disability; DS = Down syndrome; FISH = Florescent *in situ* hybridization; MA = Mental age; MR = Mental retardation with mixed or unknown etiology; NC = Typical (normal) control; PWS = Prader-Willi syndrome; UK = United Kingdom; VIQ: Verbal IQ; WSA = Williams Syndrome Association; X = Original sample; x = Some participants from X.

1990; Udwin, 1990; Udwin & Yule, 1991). WS individuals have also been reported to suffer from specific phobias significantly more than individuals with an intellectual disability due to mixed etiology (Dykens, 2003). Longitudinal studies and research involving adults with WS have demonstrated that these behavioral features persist into adulthood (Davies, Udwin, & Howlin, 1998; Dykens, 2003; Einfeld, Tonge, & Rees, 2001; Gosch & Pankau, 1997; Plissart, Borghgraef, Volcke, Van den Berghe, & Fryns, 1994; Udwin, Howlin, Davies, & Mannion, 1998). Leyfer et al. (2006) interviewed parents of

children with WS and found that approximately two-thirds (65%) met DSM-IV criteria for attention deficit/hyperactivity disorder (ADHD) and just over half (54%) met DSM-IV criteria for specific phobia. In addition, as the children with WS grew older, there was a significant increase in the number who met criteria for generalized anxiety disorder.

Einfeld et al. (2001) found that between the ages of 9 and 14, children with WS continued to display evidence of behavioral disturbance, such as appearing anxious and over affectionate. Einfeld and colleagues found a reduction in 'self-absorbed' behaviors, such as being a loner or appearing occupied with trivial items. The study by Einfeld et al. (2001) benefits the field by using longitudinal analysis and comparing the findings to a large number of controls with an intellectual disability. Adults with WS have been described by their parents as less active, less quarrelsome, and more reserved than children with WS, although adults with WS still display more extroverted behaviors than normal controls (Gosch & Pankau, 1997). Gosch and colleagues also found a gender effect, with female adolescents and adults with WS appearing more argumentative and less cheerful than males with WS. Rosner, Hodapp, Fidler, Sagun, and Dykens (2004) distinguished the WS behavioral phenotype from that of other specific disorders. Rosner and colleagues (2004) reported that individuals with WS were less successful in both managing household chores and acquiring job skills than individuals with either Prader–Willi syndrome or DS. Thus, research using behavioral questionnaires has supported claims of persistent anxiety and behavioral disturbance in individuals with WS.

A series of studies by Dykens (2003), however, suggests that rating scales may not adequately capture their level of behavioral disturbance. In a well-designed series of studies which took measures to control for possible acquiescence bias, Dykens (2003) was the first to conduct face-to-face interviews with WS individuals and the findings suggest a greater number of fears than reported by parents. Unbeknownst to their parents, children with WS frequently reported the following fears: being burned in a fire, getting lost, being in a fight, and being hit by a car. In addition, more common fears (failure/criticism, the unknown, and spooky things) tended to increase with advancing age, often reaching a peak when the WS individuals reached adulthood. The results of these interviews expand our understanding of the perception of fears and anxiety within this population and highlight the need for additional studies that are not solely based on proxy reports.

In summary, behavioral studies utilizing both parental ratings and individual interviews indicate that individuals with WS often display hyperactivity, peer difficulties, specific fears, and generalized anxiety. Researchers who employ self-report methodologies should be aware of the potential for response bias among individuals with WS due to their sociable personality and their below average cognitive skills (Heal & Sigelman, 1995). As noted by Dykens (2003), future research should be conducted to consider the prevalence of other psychiatric disorders within this population. It would also be beneficial to combine findings such as these with neuroimaging measures to determine if the processing of emotion is atypical among individuals with WS.

Table 7 also displays the six studies that examined hypersociability in individuals with WS, with sample sizes ranging from 1 to 36. All of the studies included participants with WS who had received genetic confirmation of their diagnosis using FISH, although the study by Jones et al. (2000) did not indicate how many of their participants with WS received FISH confirmation. The studies used several methods to measure hypersociability: gaze intensity of infants (Mervis et al., 2003), expressions of two- and three-year-olds during parental separation (Jones et al., 2000), and approachability ratings of unfamiliar faces by individuals with WS (Bellugi, Adolphs, Cassady, & Chiles, 1999a; Frigerio et al., 2006). Although a characterization of hypersociability sounds like a positive trait, Udwin et al. (1998) interviewed carers and work supervisors of adults with WS and noted that the social disinhibition displayed by WS individuals was disadvantageous, leaving them prone to exploitation.

Mervis et al. (2003) found that infants and toddlers with WS gazed at their mothers and strangers more than children of either similar developmental or chronological age. Mervis and colleagues (2003) also reported that toddlers with WS gazed more intensely at a physician during a physical examination than young children with other types of developmental delays. During a parental separation task, toddlers with WS displayed fewer negative facial expressions and a lower intensity of vocal distress than controls matched on chronological or developmental age (Jones et al., 2000).

Using the Salk Institute Sociability Questionnaire, parents rated their children with WS as more empathic, eager to please, and better able to remember names and faces than chronological age-matched normal controls and children with DS (Doyle, Bellugi, Korenberg, & Graham, 2004). The parents also rated their children with WS as more willing to approach strangers than either the normal or DS control groups. Bellugi et al. (1999a) evaluated adults with WS and reported that they rated unfamiliar faces as significantly more approachable than typical controls. Frigerio et al. (2006), using different stimuli, found that children, adolescents, and young adults with WS rated the happy faces, but not the 'non-happy' faces, as more approachable than controls. The discrepancy between the findings is likely to be related to the different facial stimuli used, with Frigerio et al. employing the facial stimuli from Ekman and Friesen (1976), while the study by

Bellugi et al. used facial stimuli from Adolphs' approachability task (Adolphs, Tranel, & Damasio, 1998). Frigerio et al. compared the ratings from both groups of facial stimuli and noted that the average approachability ratings of the Adolphs' stimuli were similar to the ratings of Ekman and Friesen's happy facial stimuli, but were significantly different from Ekman and Friesen's angry, disgusted, fearful, sad, and neutral ('non-happy') facial stimuli. Furthermore, the Bellugi et al. study utilized only adults with WS, while the Frigerio et al. study employed a wider age-span of participants with WS.

The studies assessing hypersociable behaviors do provide preliminary evidence of a hypersociability phenotype among individuals with WS that is distinguishable from the general friendliness that is observed in other populations of individuals with intellectual disabilities (Mervis et al., 2003; Doyle et al., 2004). Cross-disciplinary research has already begun to investigate the neural substrates of sociability (Meyer-Lindenberg et al., 2005a). Future researchers are encouraged to expand these investigations by including comparison groups with low degrees of sociability, such as those with autism, to further our understanding of both the neuroanatomical and behavioral features of hypersociability among individuals with WS.

Musical skills

Individuals with WS have frequently been described as having affinities with music and preserved musical skills (Hopyan, Dennis, Weksberg, & Cytrynbaum, 2001; Levitin & Bellugi, 1998; Udwin, Yule, & Martin, 1987). Levitin and Bellugi (1998) proposed that the preserved musical ability of WS individuals supports the modularity of this cognitive domain. Lenhoff (1998) stated that 'many (WS) seem to have absolute and relative pitch' (p. 34). Surprisingly, however, there has been little objective research done in this area. Since 1998, only eight studies have examined the musical skills and interests of individuals with WS, with sample sizes ranging from 5 to 118 (see Table 8). The studies with the largest number of participants (Levitin et al., 2004; Dykens, Rosner, Ly, & Sagun, 2005) were based on parental reports. Four of the studies reported that either a majority or all of their participants underwent confirmatory genetic testing using FISH. An additional functional magnetic resonance imaging (fMRI) study of activation by noise and music is included in the next section of this review (*Brain structure and function*) (Levitin et al., 2003).

A variety of musical tasks, activities, parental questionnaires, and comparison groups were used across the eight studies. Levitin and Bellugi (1998) tested the rhythmic production of eight individuals with WS and found that they scored similarly to musically trained young children. However, these individuals with WS were participants in a music camp, introducing a possible predisposition to musical interest and/or skill and potentially biasing the results. Don, Schellenberg, and Rourke (1999) found that individuals with WS display tonal and rhythmic abilities that are commensurate with their mental age. Both Levitin and Bellugi (1998) and Don et al. (1999) utilized mental age-matched normal controls as a comparison group who were chronologically much younger and would have had much less exposure to music than the WS participants. In these studies, the choice of comparison group raises questions regarding the generalizability of the findings.

Dykens, Rosner, Ly, & Sagun (2005) found that individuals with WS were more involved in musical activities based on parental report, compared with individuals with Prader–Willi or DS, while Hopyan et al. (2001) concluded that individuals with WS performed equally to normal age-matched controls on melodic imagery and phrasing, but were significantly weaker on measures of pitch, rhythm, and musical interpretation. Children and adolescents with WS have also been found to be impaired in recognizing changes in pitch directionality compared to normal age-matched controls (Deruelle, Schön, Rondan, & Mancini, 2005).

Although a love of music has been described as a characteristic of WS (Levitin et al., 2003; von Arnim & Engel, 1964), Don et al. (1999) noted that 15% of their sample were either indifferent or displayed an intense dislike of music. The results of Hopyan et al. (2001) and Levitin et al. (2004) suggest that individuals with WS may demonstrate emotional responsiveness to music that is similar to normal age-matched controls. Dykens et al. (2005), however, noted atypical associations between reported affect, anxiety, and music. Specifically, in contrast to others with mental retardation, individuals with WS reported a positive emotional state, but increased anxiety, in response to music that conveys negative emotions such as sadness.

It has been suggested that individuals with WS possess absolute pitch – the ability to name notes without use of a reference tone – at a higher rate than the general population. In a music camp setting, Lenhoff, Peral, and Hickok (2001) identified five individuals with WS who demonstrated absolute pitch. Lenhoff and colleagues suggested that the incidence was higher than expected in the general population, but a matched control group was not studied. Furthermore, at least one of the individuals demonstrated this skill after being taught the notes and their corresponding names over a period of two years. Comparison with individuals in the general population is questionable, therefore, because this skill is typically not taught before being evaluated. In addition, only one of the five individuals received genetic confirmation of WS using FISH. So in addition to finding a way to better evaluate absolute pitch among individuals with WS, it would be important to

Table 8 Musical abilities in Williams syndrome

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Deruelle et al. (2005)	16	8–19	16 NC matched on CA, sex, & musical experience	Phenotype & FISH (14)	WS performed below NC on musical task and did not show typical advantage for global properties of music
Don et al. (1999)	19	8–13	19 NC matched on receptive vocabulary (avg 7 yrs)	WSA (US & Canada)	Music performance of WS similar to receptive vocabulary, but below CA WS discriminated pitch better than rhythm and showed emotional responsiveness to music
Dykens et al. (2005) (2 studies)	31	10 (avg)	26 PWS 32 DS (similar age to WS)	Phenotype & FISH (all)	WS were described as anxious and tended to play musical instruments more frequently than controls Involvement in musical activities was negatively correlated with anxiety
	26	20 (avg)	16 PWS 25 DS (similar age to WS)	Phenotype & FISH (all)	WS reported more fears than controls Involvement with music was associated with decreased anxiety, fears, and aggression A positive emotional response to negative music was associated with increased anxiety
Hopyan et al. (2001)	14	12 (avg)	14 NC matched on CA	Phenotype & FISH (all)	WS were similar to CA controls in musical expressiveness, but scored lower on tests of pitch, rhythm, and interpretation
Lenhoff et al. (2001)	5	Not stated	None	Phenotype & FISH (1)	WS participants displayed absolute pitch
Levitin & Bellugi (1998)	8	9–20	8 NC (5–7 yrs) musically trained	Phenotype & Music camp	WS did as well as NC on echo clapping task and errors were more rhythmically compatible
Levitin et al. (2004)	118	20 (avg)	30 autistic (avg 18 yrs) 40 DS (avg 17 yrs) 118 NC matched on CA	Phenotype & FISH (# not stated)	Parents reported increased musical interests and heightened emotional responsiveness to music in WS

CA = Chronological age; DS = Down syndrome; FISH = Florescent *in situ* hybridization; NC = Normal (typical) control; PWS = Prader-Willi syndrome; US – United States; WSA = Williams Syndrome Association.

determine if similar results are found in more individuals that have been genetically confirmed as having WS.

In general, ascertainment bias and variations in control groups hinders the ability to make generalizations from the research findings to date. Additional studies using objective measures of musical ability and unbiased samples are required to determine whether musicality constitutes a specific WS phenotype. Furthermore, the use of a developmental trajectory approach would help determine whether musical ability develops atypically among individuals with WS.

Brain structure and function

Table 9 presents the results of 29 studies that examined the brain morphology and neuroanatomical functioning of individuals with WS. Four of the studies used cytoarchitectonic evaluation of autopsy specimens, 21 used structural magnetic resonance imaging (MRI), and 4 used a combination of MRI, functional MRI (fMRI), and/or Positron Emission Tomography (PET). The size of the samples ranged from 1 to 43 and 4 initial studies (Galaburda, Wang, Bellugi, & Rossen, 1994; Jernigan & Bellugi, 1990; Meyer-Lindenberg et al., 2004; Reiss et al., 2000) formed the basis of the participant pool for 17 subsequent studies. Accordingly, while the total sample size across studies from 1990 to 2006 is 477, the results are based on data gathered from 184 individuals with WS. Twenty-two of the studies (76%) had samples in which all of the participants with WS had obtained genetic confirmation using FISH, but only 12 studies (41%) included more than 15 participants. The initial neuroanatomical studies

Table 9 Brain structure and function in Williams syndrome

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Boddaert et al. (2006)	9	5–15	11 NC matched on CA	Phenotype & FISH (all)	Left parieto-occipital regions showed significant decrease in gray matter compared to controls
Eckert et al. (2005)	17	28 (avg)	17 NC matched on CA & sex	Phenotype & FISH (all)	Gray matter was significantly reduced in the superior parietal region of WS
Eckert et al. (2006)[z]	42	12–50	40 NC matched on CA	Phenotype & FISH (all)	Right planum temporale was significantly larger in WS than controls, resulting in reduced leftward asymmetry
Galaburda et al. (1994)[X]	1	31	None	Phenotype	Abnormal neuronal layering in the primary visual cortex, and volume of the posterior forebrain diminished in WS
Galaburda & Bellugi (2000)[x]	4	8 mos–53 yrs	None	Not stated	Abnormal neuronal size in primary visual cortex, short central sulcus, reduced amygdala and lack of planum temporale asymmetry in some specimens
Galaburda et al. (2001)[z]	21	19–44	21 NC matched on CA & sex	Phenotype & FISH (all)	WS central sulcus was less likely to reach the interhemispheric fissure
Galaburda et al. (2002)[x]	3	44 (avg)	3 NC matched on CA & sex	Phenotype & FISH (all)	Cells in some layers of left peripheral visual cortex were densely packed and significantly smaller in WS
Gaser et al. (2006)[z]	42	12–50	40 NC matched on CA	Phenotype & FISH (all)	Gyrification was increased bilaterally in occipital and cuneus regions in WS
Holinger et al. (2005)[x]	3	44 (avg)	3 NC matched on CA & sex	Phenotype & FISH (all)	Larger neurons were noted in primary auditory cortex of WS
Jackowski & Schultz (2005)	28	11–39	22 NC matched on CA & sex 20 lower IQ matched on IQ, CA, & sex	Phenotype & FISH (all)	The dorsal end of the central sulcus was shortened in WS compared to NC and lower IQ groups
Jernigan & Bellugi (1990)[Y]	6	10–20	3 DS (14–17 yrs) 14 NC (8–32 yrs)	Phenotype, Calcium level	Reduced cerebral, but normal cerebellar size in WS Significantly increased size of neocerebellar lobules in WS
Jernigan et al. (1993)[y]	9	10–20	6 DS (10–20 yrs) 21 NC (10–24 yrs)	Phenotype, Calcium level	Cerebral volume reduced, but frontal cortex in WS proportional to posterior cortex Limbic volume preserved
Jones et al. (2002)	9	7–43 months	9 NC matched on CA & sex 2 DD (6 & 41months)	Phenotype & FISH (all)	Raters noted large cerebellum on MRI scans of WS children
Kippenhan et al. (2005)	14	27 (avg)	13 NC matched on CA, IQ, sex & handedness	Phenotype & FISH (all)	WS showed reduced sulcal depth in the intraparietal/occipitoparietal sulcus and the left collateral sulcus and orbitofrontal region
Levitin et al. (2003)	5	28 (avg)	5 NC matched on CA, sex, handedness, & musical experience	Phenotype & FISH (all)	Activation in response to music and noise was more widespread in WS than in controls
Meyer-Lindenberg et al. (2004)[W]	13	29 (avg)	11 NC matched on CA, IQ, & sex	Phenotype & FISH (all)	Reduction of gray matter in the parietooccipital/intraparietal sulcus and hypoactivation in the dorsal visual stream was reported in WS
Meyer-Lindenberg et al. (2005a)[w]	13	28	13 NC matched on CA, IQ & sex	Phenotype & FISH (all)	Amygdala activation and neural circuitry in WS were abnormal in response to threatening stimuli

Table 9 (*Continued*)

Author/Year	*N*	Age (yrs)	Control	Diagnosis	Findings
Meyer-Lindenberg et al. (2005b)[w]	12	29 (avg)	12 NC matched on CA, IQ, & sex	Phenotype & FISH (all)	The hippocampus of WS showed shape alterations, reduced cerebral blood flow, and decreased NAA/Cre ratio
Reiss et al. (2000)[Z]	14	19–44	14 NC matched on CA & sex	Phenotype & FISH (all)	WS showed decreased volume of the brainstem and cerebrum, but preserved volume of the cerebellum and superior temporal gyrus Preservation of gray, and reduction of white matter in WS
Reiss et al. (2004)[z]	43	12–50	40 NC matched on CA & sex	Phenotype & FISH (all)	WS showed reduced gray matter in visual-spatial regions and increased gray matter in emotion and face processing areas
Schmitt et al. (2001a)[z]	20	19–44	20 NC matched on CA & sex	Phenotype & FISH (all)	Abnormal morphology of the cerebral hemispheres and corpus callosum in WS
Schmitt et al. (2001b)[z]	20	19–44	20 NC matched on CA & sex	Phenotype & FISH (all)	The splenium and isthmus of the corpus callosum in WS was significantly reduced
Schmitt et al. (2001c)[z]	20	19–44	20 NC matched on CA, sex, & ethnicity	Phenotype & FISH (all)	The posterior vermis of the cerebellum was significantly larger in WS than controls
Schmitt et al. (2002)[z]	17	19–44	17 NC matched on CA & sex	Phenotype & FISH (all)	Increased gyrification in the right parietal and occipital, and left frontal lobes in WS
Thompson et al. (2005)[z]	42	12–50	40 NC matched on CA	Phenotype & FISH (all)	Cortical thickness in WS was increased in right perisylvian and inferior temporal regions
Tomaiuolo et al. (2002)	12	13–30	12 NC matched on CA & sex	Phenotype & FISH (all)	The corpus callosum was smaller in the splenium and caudal sections in WS, with less water content in the mid-section and caudal section
Van Essen et al. (2006)	16	13–52	37 NC young adults matched on sex	Phenotype & FISH (all)	Cortical folding abnormalities in WS noted from dorsoposterior to ventroanterior regions bilaterally
Wang et al. (1992a)[y]	11	10–20	17 NC matched on CA 7 DS matched on CA	Phenotype	Typical morphology of corpus callosum in WS compared to NC
Wang et al. (1992b)[y]	11	10–20	18 NC matched on CA 7 DS matched on CA	Phenotype	WS neocerebellar tonsils were equal in size to NC

CA = Chronological age; DD = Developmental delay; DS = Down syndrome; FISH = Florescent *in situ* hybridization; MRI = Magnetic resonance imaging; NAA/Cre = N-acetylaspartate/Creatine; NC = Normal (typical) control; W, X, Y, Z = Original sample; w, x, y, z = Some participants from W, X, Y, Z.

utilized DS individuals matched for chronological age as a comparison group. The majority of studies conducted since 1993 have used normal chronological age and gender-matched controls, which has removed the ambiguity of whether differences in brain morphology were due to WS or DS.

Individuals with WS have consistently shown a reduction in cerebral volume with preservation of cerebellar volume (Jernigan & Bellugi, 1990; Jones et al., 2002; Reiss et al., 2000; Reiss et al., 2004; Schmitt, Eliez, Bellugi, & Reiss, 2001a; Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001b; Wang, Hesselink, Jernigan, Doherty, & Bellugi, 1992b). Reiss et al. (2000) found that relative to controls, the cerebral gray matter volume of individuals with WS was preserved compared to a reduction in cerebral white matter volume. Reiss et al. (2004) found that gray matter volume was proportionally increased in individuals with WS in the orbital and medial prefrontal cortex and the amygdala.

The ratio of frontal lobe volume to combined parietal and occipital lobe volume has also been found to be higher in individuals with WS than controls (Reiss et al., 2000). Although gray matter has been found to

be relatively preserved overall in WS, a reduction of gray matter volume has been documented in the superior parietal cortex of both children and adults with WS (Boddaert et al., 2006; Eckert et al., 2005; Meyer-Lindenberg et al., 2004; Reiss et al., 2004) as well as the occipital cortex, thalamus, and parahippocampal gyri (Reiss et al., 2004). There have been inconsistencies in the voxel-based morphometry findings, with Meyer-Lindenberg et al. (2004) reporting that the orbitofrontal region has reduced gray matter, while Reiss et al. (2004) observed increased gray matter in this region when compared to controls. Eckert et al. (2006) suggests that these differing findings are due to methodological differences including whether or not the images were transformed into standard space using Jacobian modulation.

A narrowing of the corpus callosum in the splenium and isthmus has also been reported in individuals with WS (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001b; Tomaiuolo et al., 2002), as well as a shortening of the dorsal extent of the central sulcus (Galaburda & Bellugi, 2000; Galaburda et al., 2001; Jackowski & Schultz, 2005). Abnormal cell density in the primary visual cortex of WS autopsy specimens has been documented (Galaburda et al., 1994; Galaburda & Bellugi, 2000; Galaburda, Holinger, Bellugi, & Sherman, 2002), while enhanced neuronal size in the primary auditory cortex of these autopsy specimens has been recently reported (Holinger et al., 2005). Eckert et al. (2006) noted that the surface area of the planum temporale showed reduced leftward asymmetry due to the tendency of the Sylvian fissure within the right hemisphere to extend horizontally, rather than coursing upward into the parietal lobe.

It has been suggested that the atypical cognitive and behavioral profile of individuals with WS may be related to their atypical brain morphology. Apparent sparing of limbic structures (Reiss et al., 2000), in contrast to significant volume reductions in parietal and occipital cortex (Galaburda & Bellugi, 2000; Schmitt et al., 2001a), has prompted suggestions that the exaggerated hypersociability and deficient visuospatial skills of individuals with WS may be linked to a morphological dorsal-ventral dissociation. Jernigan, Bellugi, Sowell, Doherty, and Hesselink (1993) hypothesized that the preserved limbic structures may underlie the affective functions that have been characterized as relative strengths within individuals with WS.

The intraparietal/occipitoparietal sulcus has been shown to have reduced sulcal depth in individuals with WS (Kippenhan et al., 2005), providing further evidence of atypical neuroanatomy in brain regions that support visuospatial processing. Increased gyrification in the cuneus, precuneus, and occipital regions of individuals with WS has also been linked to the visuospatial abnormalities noted in this population (Gaser et al., 2006). Conversely, enhanced cortical thickness in the perisylvian and inferior temporal regions of WS individuals has been reported by Thompson et al. (2005), and may underpin the relatively preserved aspects of language and music in the WS phenotype. Van Essen et al. (2006) documented cortical folding abnormalities in individuals with WS that spread from the dorsoposterior to the ventroanterior regions bilaterally and proposed that these abnormalities may be related to the visuospatial deficits, as well as relative strengths in language and music, that are noted in this population.

Recent studies utilizing functional neuroimaging have also begun to examine the neural pathways associated with specific phenotypic features of individuals with WS. In comparison to normal controls, musical stimuli resulted in widespread cortical and subcortical activation in individuals with WS, as well as increased activation of the right amygdala (Levitin et al., 2003). The latter finding was linked to the heightened emotional responsiveness of these individuals to music. Meyer-Lindenberg et al. (2005a) reported increased amygdalar activation in individuals with WS in response to viewing threatening scenes, whereas viewing threatening faces was associated with reduced amygdalar activation. Meyer-Lindenberg and colleagues (2005a) also noted abnormal connectivity between the amygdala and the orbitofrontal cortex when individuals with WS were viewing threatening stimuli. They proposed that this abnormal circuitry may underlie the hypersociable and anxious characteristics of many individuals with WS. Lastly, the anterior hippocampal formation and the intraparietal/occipital sulcus have shown reduced resting blood flow (Meyer-Lindenberg et al., 2005b), while the parietal region of the dorsal stream has shown hypoactivation during tasks of visual processing (Meyer-Lindenberg et al., 2004). These changes have also been linked to the visuospatial deficits that are common among individuals with WS.

The studies within the neuroanatomical domain do show methodological strengths in comparison to the studies within the other domains. Specifically, the vast majority employed samples in which all of the individuals with WS were diagnosed using both the clinical phenotype and FISH confirmation. This is in part due to the fact that most of the studies were conducted within the past 10 years, well after FISH had begun to be routinely used to genetically confirm the diagnosis of WS. In addition, many of the studies have employed sophisticated neuroimaging techniques and statistical analyses to investigate the structural and functional characteristics of the WS brain.

There are some methodological concerns, however, that need to be addressed. Firstly, the vast majority of individuals with WS typically demonstrate IQ scores that are mildly to moderately below average. Meyer-Lindenberg et al. (2004, 2005a, 2005b),

however, employed an atypical sample of individuals with WS who have IQ scores within the average range and compared the findings to a normal IQ control group. Meyer-Lindenberg et al. (2004) justified their use of this atypical WS sample to avoid the following possible confounds: 1) comparing a typical WS sample to a low IQ control group raises the question of neuroanatomical pathology within the control group; 2) comparing a typical WS sample to a normal IQ control group raises questions as to whether group differences are related to overall IQ level rather than being specific to WS; and 3) utilizing a typical WS sample increases the risk of difficulty tolerating the MRI scan. Although the methodology employed by Meyer-Lindenberg et al. (2004) does address these possible confounds, it would be important to verify the findings in a typical sample of WS individuals with below average intellectual functioning in order to generalize the neuroanatomical findings to the WS population as a whole.

Secondly, the studies reporting size variations of particular structures need to be replicated using additional techniques to verify the findings. Eckert et al. (2006) reported that the right planum temporale was significantly larger in individuals with WS than in controls, and they based their findings on surface measurements. It would be important to verify if these findings can be replicated using volumetric measurements of the planum temporale.

Thirdly, the neuroanatomical studies have generally used only normal controls as a contrast group, leading one to question whether the findings are also observed in other conditions that encompass cognitive and developmental delay. Additional studies that employ multiple control groups with various aspects of developmental delay, such as the study by Grice et al. (2001) who employed a comparison group made up of individuals with autism, would significantly enhance the characterization of the neuroanatomical features of WS, particularly as these relate to specific aspects of the WS phenotype.

Lastly, seventeen of the studies employed participants with WS who had been a part of previously published studies. Studies that utilized additional participants with WS, such as those conducted by Boddaert et al. (2006), Kippenhan et al. (2005), and Van Essen et al. (2006), are particularly advantageous to help broaden the participant pool and increase the generalizability of the findings.

Discussion

Three decades of WS research have yielded a considerable amount of information on the cognitive and behavioral features of this disorder. Studies to date have pointed toward disturbances in language, behavior, and visuospatial function. Given the identified genetic abnormality, this makes WS an attractive candidate for exploring the genetic basis of human characteristics. This critical review of published data, however, has revealed a number of limitations in research methodology that currently hamper the characterization of the WS phenotype.

Methodological issues

Recurring methodological shortcomings can be identified across research domains. The first relates to sample size. With the exception of studies assessing parental reports of behavioral disturbance and hypersociability in WS, the median sample size across domains has ranged from 6 to 17 participants, limiting the generalizability of the findings. Smaller sample sizes have been a particular concern in the studies prior to 2000. The use of overlapping samples between studies further confounds this issue and is particularly problematic in the neuroanatomical domain. As stated previously, this review excluded studies that were published exclusively in book chapters. It should be noted that some of these studies used larger sample sizes (Bellugi et al., 1999b; Mervis et al., 1999), but they lacked sufficient methodological detail to allow a thorough evaluation.

The second issue relates to the methods used to diagnose WS. FISH has been used in some of the studies to genetically confirm the presence of WS in their participants, although it should be noted that this method of diagnosis has only been available since the 1990s. Across the domains reviewed, there was variability in the percentage of studies that utilized both clinical phenotype and genetic FISH testing to diagnosis WS in a majority or all of the study participants. Although there is no clear evidence from the studies reviewed that there were any significant differences in findings between those with a FISH confirmation and those without, the scientific rigor of WS research would be enhanced if future studies continued to make every effort to employ participants who have a genetic confirmation of WS, as well as the clinical phenotype.

The final two methodological issues relate to the types of control groups and tests used across the studies. The performance of WS individuals has been compared to typically developing individuals of varying ages, as well as to those with developmental disorders ranging from specific language disorders to global mental retardation. Few longitudinal studies have been conducted to examine the developmental trajectories of the various domains. Furthermore, a broad number of tests have been employed with these individuals, ranging from complete batteries of standardized test to versions of tasks that have been adapted for use with WS individuals. These issues might impede the development of a clear picture of the WS phenotype because it can be difficult to interpret the findings of various tasks across studies. However, if a consistent result is found using several methodologies, this might highlight a critical

aspect of the WS phenotype that might prove fruitful for phenotype–genotype research.

Profile of the WS phenotype

The WS cognitive profile has typically been characterized as an extreme dissociation between preserved expressive language and facial processing skills, and significantly impaired visuospatial skills. WS individuals have also been described as hypersociable and musically inclined. However, a closer examination of supposedly intact abilities reveals an atypical developmental trajectory (Karmiloff-Smith et al., 2002). As an example, language abnormalities (Karmiloff-Smith et al., 1997, 1998; Paterson et al., 1999) and atypical electrophysiological responses on face processing tasks (Grice et al., 2001; Mills et al., 2000) have now been demonstrated. Early WS studies that supported intact language and face processing were often based on small sample sizes or were published without sufficient methodological detail to be replicated.

In summary, the evidence lends support to the following description of the WS cognitive, behavioral, and neuroanatomical phenotype. The Full Scale IQ score of most individuals with WS is in the range of 50–60. Language development appears to be typical (but delayed) in the areas of syntax, semantics, word fluency, and expressive vocabulary, while atypical language skills have been noted in grammatical comprehension, gender agreement, pragmatics, and oral fluency. Visuospatial deficits among individuals with WS have been confirmed across studies. Individuals with WS typically display hyperactivity, peer difficulties, and anxiety, as well as hypersociability. They have been shown to display a heightened interest in music, as well as an increased emotional responsiveness to music. The neuroanatomical findings do support evidence for structural and functional abnormalities that could form the basis for the hypersociability, as well as the visuospatial deficits, that are evident in individuals with WS.

There are aspects of the WS phenotype which are distinctive in comparison to other syndromes and developmental disabilities. In contrast to individuals with WS, those with DS are described as social, but not overly so, and they do not generally display hyperactivity or phobias. Individuals with fragile X and autism tend to display social withdrawal and poor social eye gaze (Feinstein & Singh, 2007). Individuals with Prader–Willi often display underactivity, stubbornness, tantrums, and compulsive behaviors (Dykens & Cassidy, 1995), as well as solitary behavior and social withdrawal (Greenswag, 1989), which appears in direct contrast to the hypersociability noted in individuals with WS.

It would be important to keep in mind that variability still exists within the WS phenotype. As noted by Tager-Flusberg (1999), a phenotype should be considered in terms of a 'heightened probability of a behavior or cognitive feature that characterizes a particular syndrome' (p. 6). Porter and Coltheart (2005, 2006) noted variability within both the cognitive and the visuospatial domains among individuals with WS. It is also important to remember that the adult phenotype may differ from the phenotype observed in a child because developmental trajectories are impacted in various ways from genetic deletion disorders (Karmiloff-Smith, 1997).

Conclusions

To more thoroughly characterize the WS phenotype, future efforts should be focused on increasing the number of independent observations of individuals with both the clinical phenotype and genetic confirmation of WS. Studies which utilize a wide age range of participants should include analyses of age and sex in order to fully investigate the trends within a particular domain. Specifically, the use of task-specific developmental trajectories will allow researchers to view the development of a skill over time, which may shed light on specific abilities that develop atypically. Although time-consuming, longitudinal studies would be extremely beneficial in elucidating the development of the WS phenotype. If control groups are used, researchers are encouraged to use multiple control groups within a study (normal controls, specific syndrome, and mixed etiology). Comparison groups should also be matched not only on IQ, but also on task-specific performance, such as language or non-verbal ability, depending upon the focus of the study.

Furthermore, although WS is being used as a model to elucidate the links between genotype and phenotype, only a few recent studies have attempted to examine the relationship between the genetic abnormality, structural and functional changes within the brain, and the cognitive and behavioral phenotype. The most fruitful approach is likely to involve the use of specific and objective measures of cognition and behavior linked to identifiable brain structures. Future neuroanatomical studies should control for sex and handedness and every effort should be made to include 'typical' individuals with WS in functional MRI studies. Electrophysiological studies may elucidate the neural underpinnings of the heightened affective response to music and the hypersociability noted in individuals with WS. Individuals with reported high sociability have shown increased electrophysiological activity within the left frontal lobe (Schmidt, 1999) and it would be enlightening to determine if similar responses were obtained in individuals with WS. Lastly, the size of particular neuroanatomical structures should be measured using manual segmentation rather than surface analysis, which allows for a more thorough examination of structure size by using simultaneous images of the coronal, sagittal, and axial views.

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