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COGNITIVE PROFILE OF TURNER SYNDROME

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Abstract

Turner syndrome (TS) is a relatively common neurogenetic disorder characterized by complete or partial monosomy-X in a phenotypic female. TS is associated with a cognitive profile that typically includes intact intellectual function and verbal abilities with relative weaknesses in visual–spatial, executive, and social cognitive domains. In this report, we review previous and current research related to the cognitive profile of TS. We also discuss how cognitive impairments in this syndrome may reflect integrative rather than modular deficits. For example, the less commonly reported areas of verbal difficulty in TS and certain visual–spatial deficits seem significantly influenced by impairments in executive function and spatially loaded stimuli. We provide a summary of cognitive testing measures used in the assessment of visual–spatial and executive skills, which includes test domain descriptions as well as a comprehensive examination of social cognitive function in TS. This review concludes with a discussion of ecological interpretations regarding the meaning of cognitive deficits in TS at the individual level.

Keywords

Turner syndrome; X-monosomy; cognitive; visual–spatial; executive function; social cognition

Females with Turner syndrome (TS) often demonstrate a unique cognitive profile characterized by relative strengths in verbal domains and weaknesses in visual-spatial and executive areas. Several studies also suggest that girls with TS are at risk for social cognitive and emotion processing difficulties. Some posit that these social–emotional impairments are consistent with nonverbal learning disorder [Hepworth and Rovet, 2000] while others contend that nonverbal deficits do not comprehensively explain social–emotional problems in TS [Skuse et al., 2005a,b]. In this review, we will summarize and integrate previous literature regarding visual–spatial, verbal, executive, and social cognitive functioning in TS and provide clinically based, ecological interpretations regarding the meaning of deficits in these areas at the individual level.

VERBAL PROFILE IN TURNER SYNDROME

Turner syndrome is a common disorder affecting 1/2,500 women, typical symptoms include short stature, webbed neck, cardiovascular abnormalities, and endocrine problems related to ovarian dysgenesis. Turner syndrome has also been shown to have a typical neurocognitive profile characterized by average to low-average full-scale intelligence quotient (IQ) scores with a significant disjunction between verbal and performance IQ, as well as the frequent occurrence of atypical social traits.

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VERBAL IQ

The majority of early studies demonstrated that full-scale IQ is normal in these girls, but the subtest profile indicated that the performance IQ is low when compared with that of a normal or even above-average verbal IQ [Shaffer, 1962; Garron, 1977; Pennington et al., 1982; LaHood and Bacon, 1985; Rovet, 1993a,b; Temple and Carney, 1993; Silbert et al., 1977]. Although impairments in performance IQ in girls with TS have been examined extensively and generally been attributed to problems with visual–spatial skills and executive function [Temple and Carney, 1995; Ross et al., 1996a,b; Skuse et al., 1997], there is also evidence that select components of verbal performance may additionally be affected.

The development of language is a complex process involving linguistic knowledge and verbal processing skills composed of phonologic, semantic, syntactic, and pragmatic components. Generally, linguistic knowledge and phonological processing (breaking down words into basic units of speech/sound components, or phonemes, as a way to deconstruct language) appear to be a relative strength in girls with TS, including reports of hyperlexia, the ability to read and pronounce longer and unfamiliar words when compared with age-matched peers [Temple and Carney, 1996]. In contrast, girls with TS had difficulty with response speed and overall number of words generated on an oral fluency task (generating words using specific initial consonants), which also involves components of phonological processing. However, closer examination of the content of words also demonstrated a higher rate of low-frequency words when compared with peers, supporting the concept of increased receptive vocabulary skills in this group. [Murphy et al., 1993; Temple and Carney, 1996; Murphy and Mazzocco, 2008]. Semantic language in girls with TS is also demonstrated by equal or superior performance when compared with peers in receptive vocabulary and reading comprehension. Temple [2002] reports that they can outperform peers on the Peabody Picture Vocabulary Test, including a significant finding of an increased rate of low-frequency (i.e., complex) words. The performance on rapid automatized naming (RAN), which tests the aspects of decoding and transformation, has been less consistent. Studies have noted decreased fluency and speed on rapid naming in a number of categories (colors, numbers, letters) [Waber, 1979; Reiss et al., 1993; Murphy et al., 1994; Mazzocco, 2001], but Temple [2002] argues that this may be tied to atypical search mechanisms related to executive function (high-level cognitive skills critical for adaptive responses to the changing demands of the environment. Among the executive functions are abstract reasoning, self-regulation, goal-directed behavior, fluency, cognitive flexibility, response inhibition, and attention) rather than problems with lexical storage (manner in which brain stores words in memory) or decoding itself. Recently, Mazzocco examined the same task over a broader developmental range and found no differences between controls and elementary school-aged girls with TS [Temple and Carney, 1996; Temple, 2002; Murphy and Mazzocco, 2008].

Despite these relative strengths in receptive vocabulary, phonemic processing, and lexical storage, other components such as syntactic processing (interpretation of underlying structure of words to represent a larger message or meaning, rather than simple linear interpretation of sequential words) may be impaired in TS. Specifically, content incorporating spatial relationships is a particular area of vulnerability, which is not surprising with given dominant deficits of visual–spatial problems. This includes poor performance on tasks involving spatial relationships, such as navigating a figure on a map based on verbal directions, or processing left–right orientation [Inozemtseva et al., 2002]. However, of greater interest is the authors' finding that girls with TS also perform more poorly on nonspatially related temporal relationships and lexical comparisons as well (describing how family members are related to each other). Although these questions do not contain spatial words per se, they still require a degree of sequencing and ordering of events and/or relationships. The authors note that this may be confounded by difficulties

maintaining attention throughout the task, which is a known deficit in TS [Romans et al., 1998; Ross et al., 2000], but they argue that differential performance on these tasks represents impaired syntactic processing. Given the relative spatial and organizational nature of these tasks, the results also suggest that verbal tasks requiring significant elements of visual-spatial or executive processing will be correspondingly impaired.

Pragmatic language (incorporation of speaker's intent in use of language, and implicit or suggested meaning in words that may go beyond literal definition) in TS has not been well studied. Mazzocco et al. [2006a,b] noted that girls with TS were able to initiate and maintain conversation in an interview-based format as well as controls and better than females with fragile X syndrome. Although this suggests a certain facility with social reciprocity and utilization of conversational cues, there have been no other studies explicitly examining the use of other complex pragmatic language components, such as the use of irony, humor, or sarcasm.

Girls with TS also demonstrate difficulty with verbal tasks involving configural processing [processing that accounts for overall "gestalt" or relationships between individual components as a whole concept, rather than processing each component separately (local processing)] skills as a whole. Temple [2002] reports temporal deficits in narrative tasks in girls with TS who produce a significantly more simplistic descriptions when asked to recount events of the previous day when compared with a hypothetical description of how they would plan a party. Reiss et al. [1993] also describes a twin pair, where the twin affected with TS has a significantly abridged version of events when describing a visit to the zoo when compared with the unaffected twin. Hepworth and Rovet [2000] also describes global processing deficits in a case report of a girl with TS who has difficulty in the description of a scene and instead focuses on local details. These processes are more complex than single word retrieval and likely require recruitment of executive domains of sequencing, working memory, planning, attention, and inhibitory control. Although planning and possibly verbal working memory tend to be relatively spared, other domains such as integration and flexibility, particularly in regard to temporal–spatial relationships appear to be significantly affected in TS [Romans et al., 1996; Temple et al., 1996; Buchanan et al., 1998]. In an analysis of the Boston Naming Task, Temple [2002] examined the content and cognitive flexibility of subjects by identifying the number of switches between clusters of words with shared characteristics and found that girls with TS had a significantly decreased rate of shifting, which they suggest may represent different executive processes in retrieval of lexical stores in TS. In conjunction with known deficits in frontal lobe-mediated inhibitory control of irrelevant stimuli, this supports the concept of atypical executive processing in a number of characteristic domains in the TS population.

Although girls with TS have normal composite verbal IQ, it appears that there is evidence for a characteristically uneven profile while accounting for different subsets of verbal processing. It is unclear if this verbal profile is due to underlying neuroanatomical differences in TS or rather developmental compensation for core deficits in visual–spatial and executive functions. Skuse et al. [2005a,b] have posited that these discrepancies may partly be due to the influence of absent growth and sex hormones critical to brain development, as the authors argue that hormone receptors are highly distributed in the hippocampus, a known anatomical region for working memory. Furthermore, studies of supplemental exogenous estrogen have demonstrated increased processing speed on cognitive tasks [Ross et al., 1998] as well as improved memory function [Ross et al., 2003], but this has not been clearly replicated with androgen supplementation, particularly in the involvement of the hippocampus [Ross et al., 2003]. Lastly, the administration of growth hormone in this population has been less studied, but has shown little effect on cognitive performance, despite correlation with improved psychosocial function [Ross et al., 1997;

Siegel et al., 1998]. Overall, there is evidence for characteristic verbal strengths with preserved regions of phonological and semantic processing (specifically in reference to language, the study of meaning, including the meaning of words, phrases, punctuation, etc., in a largely context-independent manner) and deficits in fluency and syntactic processing particularly with regard to verbal content that recruits visual–spatial and executive domains.

VISUAL-SPATIAL AND EXECUTIVE DEFICITS

Visual–spatial and executive deficits are the most commonly and consistently observed impairments among individuals with TS. These impairments tend to persist despite estrogen or androgen treatments/levels [Ross et al., 2002, 2003], suggesting that they stem primarily from other, nonhormonal factors. In fact, one study suggests that visual–spatial/perceptual/motor and executive deficits in TS may map to genes located at Xp22.3 [Zinn et al., 2007]. Additionally, neuroimaging studies suggest that spatial/executive difficulties are related to frontal–parietal structural, functional, and biochemical abnormalities [Brown et al., 2004; Kesler et al., 2004, 2006; Cutter et al., 2006; Holzapfel et al., 2006]. It is likely that haploinsufficiency of several inactivation-escaping X-chromosome genes interacts with other genetic and environmental factors to increase the risk for neurodevelopmental alterations and related cognitive impairments. Thus, while females with TS are at significant risk for visual–spatial and executive deficits, TS does not “cause” these impairments. The specific causal factors are likely highly complex and currently unknown.

One issue contributing to the complexity of determining specific genetic or other causes of visual–spatial or executive impairments in TS is the significant inconsistency across studies in terms of the specific visual–spatial and/or executive deficits observed. This inconsistency stems partly from a combination of methodological variations including differences in cognitive assessment batteries, age ranges, comparison groups, sample sizes, and genotype (e.g., mosaic, nonmosaic). Females with TS represent a more homogeneous group than, for example, individuals with dyslexia or attention-deficit hyperactivity disorder given that TS is associated with a particular genetic abnormality (i.e., complete or partial X-monosomy). However, significant individual variation exists in the TS cognitive profile among individuals with TS due to the interaction of this X-monosomy genetic liability with other genetic liabilities and endowments (e.g., cognitive reserve) as well as unique environmental, educational, and sex hormonal factors [Ross et al., 2006].

The various visual–spatial and/or executive deficits demonstrated by approximately 50 years of TS research are summarized in Table 1. Deficits in Wechsler Performance IQ (PIQ) or Perceptual Organization Index (POI) score appear to be the most consistent finding, whether the deficit refers to a score that is significantly lower than normative or control means and/or significantly lower than the verbal index score. Thus, PIQ/POI might be one of the most sensitive measures to cognitive deficits in TS. The PIQ/POI score is derived from several subtest scores, which vary somewhat depending on which Wechsler battery is administered (and the battery depends on the age of the subject). The Wechsler IQ battery versions primarily used in TS research to date, including the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), WPPSI-Revised (WPPSI-R), Wechsler Intelligence Scale for Children (WISC), WISC-R, Wechsler Adult Intelligence Scale (WAIS), WAIS-R, and WAIS-III, include measures of speeded performance and motor skill in the PIQ/POI [Wechsler, 1949, 1955, 1967, 1974, 1981, 1989]. Thus, it is difficult to determine if PIQ/POI deficits relate to fluid intelligence/perceptual reasoning, processing speed, motor skills, or a combination of these. The most recent Wechsler battery for children, the WISC-IV, replaces the PIQ/POI with a Perceptual Reasoning Index (PRI) that reduces the emphasis on processing speed and motor skill in the “nonverbal” or performance domain [Wechsler, 2003]. One study used both the WISC-IV and the WISC-III to assess cognitive function in

TS and demonstrated impairments when compared with controls on both the POI and the PRI [Simon et al., 2008], suggesting fluid-reasoning deficits independent of processing speed and motor skills impairments.

Deficits in PIQ/POI/PRI in addition to the examination of other cognitive findings in TS as illustrated in Table 1 might suggest that it is the combination of visual–spatial and executive skills that tends to be most difficult for individuals with TS. As illustrated in Table 1, studies that examined subtest in addition to index score differences seem to suggest that timed tests (which rely on processing speed, an executive skills) within the PIQ/POI represent areas of increased vulnerability in TS. These include Object Assembly, Block Design, and Coding. These tests contain a motor component but performance among TS females is also relatively impaired on tests that do not involve motor skills (or processing speed) but instead combine visual perception and executive abstract reasoning and mental flexibility. Examples include Wisconsin Card Sorting Test (WCST), Contingency Naming Test (CNT), and Raven's Progressive Matrices (RPM). Scores on tests of visual–spatial processing that have no motor or speeded performance components are often deficient in females with TS as well. These include the Motor-Free Visual Perception Test (MVPT), Embedded Figures Test (EFT), Spatial Relations Test (SRT), and Mental Rotation Test (MRT). However, these and similar tests also require other executive skills including working memory and visual attention. Individuals with TS appear to demonstrate impairments on drawing tests that assess visual–motor/visual–spatial skills such as the Beery Visual-Motor Integration (VMI), Draw a Person (DAP), and Bender Visual Motor Gestalt Test (BVMGT). These tests frequently involve an executive, organizational factor, particularly those involving more complex stimuli, such as the Rey Osterrieth Complex Figure (ROCF) [Watanabe et al., 2005]. Females with TS have been shown to have impairments on the classic cube stimulus mental rotation task [Rovet and Netley, 1982]. Mental rotation is a visual–spatial skill that also relies heavily on working memory. Alternatively, another study indicated normal performance on mental rotation in the TS group using letters, a more verbally loaded stimulus [Murphy et al., 1994]. Thus, individuals with TS may be able to compensate for certain spatial-executive weaknesses by relying on verbally based strategies.

However, executive impairments in females with TS may negatively impact certain skills within the verbal domain. For example, oral fluency has been shown to be impaired in TS [Waber, 1979]. Temple [2002] examined oral fluency performance more closely in TS and observed that the TS group made fewer switches between subcategories, which were less likely to switch back to a previous subcategory and listed more uncommon words when compared with controls. They also struggled with narrative production that involved maintenance of a temporal framework [Temple, 2002]. Additionally, although many studies suggest average to above-average verbal performance in TS including certain reading-based skills, several studies have demonstrated impairments among individuals with TS in basic reading decoding [Bender et al., 1993; Rovet, 1993; Romans et al., 1998; Rae et al., 2004]. Reading is a complex skill that involves executive working memory and attention as well as phonologic awareness and rapid naming (which relies to some extent on executive processing speed). All of the studies demonstrating reading deficits in TS also showed concomitant impairments in executive skills including working memory, attention, and processing speed.

SOCIAL FUNCTION IN TURNER SYNDROME

Psychosocial difficulties and adaptive function are commonly reported problems in women with TS. Although there is no clear increase in incidence of psychiatric disorders when compared with general norms, numerous studies indicate increased self-report of anxiety, depression, low self-esteem, and impaired social competence when compared with peers

[McCauley et al., 1987; Rovet and Ireland, 1994; McCauley et al., 1995; Skuse et al., 1997; Skuse et al., 1999; McCauley et al., 2001; Lagrou et al., 2006]. Women with TS have an increased likelihood of living with parents in adulthood and a lower rate of attainment of employment than might be expected by the level of education. [Bender et al., 1984; McCauley et al., 1987; Downey et al., 1989; McCauley et al., 2001; Ross et al., 2002] Studies on sexual function also show that women with TS are less likely to be in a partnered relationship and have a later age of onset of sexual activity, although those with partners tend to have comparable degrees of sexual satisfaction and function when compared with peers [Downey et al., 1989; Pavlidis et al., 1995; Sheaffer et al., 2008]. Psychosocial status pertaining to fertility issues due to premature ovarian failure has not been examined. Impact of premature hearing loss in middle age has also been noted, with significant effect on social function [Hultcrantz and Sylven, 1997; Bergamaschi et al., 2008]. However, it is unclear to what extent these psychosocial stressors are due simply to burden of physical stigmata of disease or whether independent deficits in social cognition may better explain previous reports of psychosocial dysfunction. Replacement of growth hormone and estrogen in Turner syndrome has become a standard of care in clinical practice and has shown efficacy in addressing some physiological sequelae. However, studies examining psychosocial function in women who have received hormone replacement indicate that improvement on psychosocial measures are often not well correlated to hormone treatment alone [McCauley et al., 1986; van Pareren et al., 2005; Carel et al., 2006], suggesting that psychosocial effects are not exclusively due to putative differences in physical appearance but also include core deficits in social processing.

Numerous studies have described atypical social cognition in Turner syndrome. Facial recognition has been repeatedly shown to be an area of vulnerability as determined by tasks such as the Benton Facial Recognition Test [Reiss et al., 1993; Ross et al., 1997; Romans et al., 1998] and delayed face matching tests [Murphy et al., 1994; Buchanan et al., 1998]. Everhart et al. [2004] also reports differential ERP activation in face recognition while using an auditory probe in prepubertal girls with TS when compared with control males and females. Lawrence et al. [2003] note poor facial recognition based on a number of tasks examining faces manipulated by several visual–spatial constructs, such as less accurate performance in recognizing halftone images of faces. In other syndromes where face recognition is impaired, such as autism or Williams syndrome, deficits are attributed to problems with global or configural processing [Joseph and Tanaka, 2003; Annaz et al., 2009]. In these instances, there is evidence of piecemeal processing styles being used preferentially to holistic face recognition, which has been interpreted as a decreased sensitivity to typical social cues. Mazzola et al. found that eye-tracking patterns in girls with TS showed preferential fixation to mouth regions when looking at faces, when compared with peers whose gaze was more equally distributed between mouth and eye regions. This difference was found to be particularly significant in faces with a fearful expression; however, analyses did not account specifically for performance IQ and deficits were noted to be widely heterogeneous in the TS group [Mazzola et al., 2006a,b]. In contrast, Lawrence et al. [2003] notes that women with TS do not significantly differ from controls in configural facial processing. The authors report that on tasks thought to be representative of configural processing, such as matching inverted and upright faces and matching parts of a face to its whole, differences in accuracy in women with TS failed to reach significance when compared with controls. Importantly, the insignificant differences found were largely accounted for by differences in performance IQ, suggesting an underlying association with problems with visual–spatial processing. This observation led the authors to posit that difficulty with facial recognition is not a result of more typical configural processing deficits, but instead involves a different pathway of dysfunction in the circuitry for encoding and memorizing faces.

Additional evidence demonstrates that facial recognition deficits extend to selective impairments in recognition of facial expressions of emotional affect as well. Facial emotion processing is a complex process that integrates a number of social cognitive functions, including interpretation of gaze and configural face processing. Women with TS have repeatedly been found to perform poorly on tasks of categorization of affect using well-established images based on Ekman and Friesman's Pictures of Facial Affect [McCauley et al., 1987; Ross et al., 2002; Good et al., 2003; Lawrence et al., 2003]. Interestingly, women with TS had selectively poor performance in recognizing expressions of anger and fear when compared with controls [Good et al., 2003; Lawrence et al., 2003; Mazzola et al., 2006a,b]. The discrimination between specific deficits in anger and fear when compared with other universal expressions such as happiness, sadness, surprise, or disgust suggest that these deficits are not exclusively attributable to underlying problems with visual–spatial processing or facial recognition as a whole. This is further supported by the findings that these group effects continue to be consistent even when accounting for differences in performance IQ between karyotypes [Lawrence et al., 2003]. The distinct characteristic profiles, when compared with karyotypically normal females and people with autism, implicate an independent pathway for facial recognition in women with TS.

Another well-studied component of social cognition includes directional eye gaze as a representation of social cueing and joint attention [Adolphs, 2009; Itier and Batty, 2009]. Elgar et al. observed that direct eye gaze ("egocentric gaze") as well as line-of-sight gaze toward objects ("allocentric gaze") were comparable with controls in conditions where eye gaze and head position were congruent. However, they note that in both egocentric and allocentric gaze conditions, women with TS performed more poorly than controls when the head remains in a fixed position and only eye gaze is varied, a more sophisticated visual–spatial task [Elgar et al., 2002]. The authors argue that poorer performance on eye-head incongruent conditions represent possible social gaze deficits, given that covarying for performance IQ neither change statistical significance of the effects nor do subjects with TS perform more poorly on a task assessing small spatial variance in the position of objects (not involving facial stimuli). In contrast, Lawrence found that women with TS were acutely sensitive to directional gaze and facial cues in an attentional task assessing reflexive responsiveness to social gaze. In fact, they found that eye gaze was actually a more powerful social cue than head position for women with TS. However, differences in response time or accuracy were correlated to performance IQ, suggesting a possible influence of underlying executive visual–spatial processes on this task. In summary, there is some indication that eye gaze processing may be atypical in women with TS; however, the degree to which it is affected by associated deficits in visual–spatial processing is less clear. In contrast to social deficits seen in other syndromes, however, eye gaze does appear to be a relevant social stimulus in this population.

Higher social cognitive processes have also been studied extensively, particularly the concept of mentalization or "theory of mind," the ability to attribute mental states to the behavior and intentions of others. Much of this work has been done in studies of individuals with autism, including interpretation of intentional emotion states based solely on a limited view of the eye region of a face, a study which was replicated in the TS population. Compared with peers, women with TS were significantly less accurate in assigning intentional emotional labels (such as "shy," "hostile," "flirtatious") to visual cues limited to the upper half of the face [Lawrence et al., 2003]. Similarly, mental state attribution was found to be impaired in women in TS in a task using inanimate objects, where triangles were animated to move either in a corresponding or reactive pattern. Lawrence et al. [2007] posited that descriptions of animations involving reactive or nonreciprocal patterns require greater sophistication in terms of attribution of intentional states and found that reactive

patterns elicit significantly less intentional language descriptors in women with TS when compared with controls.

Atypical social cognition processes occur in women with TS, which cannot be ascribed solely to associated deficits in visual–spatial and executive function. However, these deficits also differ markedly from social cognitive profiles as seen in autism, Williams syndrome, or nonverbal learning disorder (NVLD). Although several features between these groups may overlap, including difficulties with facial and affect recognition, gaze processing, and mentalizing, it appears that these deficits are more selective in women with TS in a distinctive profile. Furthermore, there is increasing evidence for neuroanatomical differences in TS that correlate to these cognitive-behavioral phenomena and argue for the characterization of a TS-specific social cognitive profile rather than a more generalized approach to conceptualizing social cognitive deficits in TS.

ECOLOGICAL RELEVANCE OF DEFICITS

Visual–spatial, social cognition and executive skills are essential for perception of and adaptive responses to the changing demands of the environment. These skills involve a significant degree of overlap and interdependence. Deficits in these areas can result in significant impairment of everyday functioning. For example, fluid or perceptual reasoning skills including mental flexibility are critical for generating alternative solutions to problems, recognizing that there is more than one answer or approach to a certain task, which responses might be more or less effective, and when mistakes have been made. Individuals with deficits in these areas may struggle to recognize connections between different concepts or how different parts of a problem, task, or idea are fit together. This weakness may result in failure to understand increasingly complex information involving concepts that build upon each other, (e.g., science, math). Individuals with working memory deficits struggle with multitasking and often forget or lose track of what they were doing or thinking. They may have trouble with reading as decoding words requires the storage of sounds that have been decoding in short-term memory while subsequent sounds are decoded. Math is also highly dependent on executive skills including working memory, attention, and mental flexibility.

Visual–spatial skills are critical for perception of one’s environment as well as physical coordination and other visuomotor activities such as driving and sports participation. For example, individuals with deficits in skills such as mental rotation and spatial orientation may have difficulty with the sense of direction and navigation. The spatial relationships inherent in math processing may be deficient resulting in difficulties with arithmetic concepts and operations. Visual–spatial skills also play an inherent role in executive function tasks. For example, visualization is a common strategy used during planning and organization as well as memory and learning. Individuals with visual–spatial deficits may struggle with reading and constructing graphs, charts, diagrams, maps, and tables. They may have reduced ability to judge heights and distances and may seem clumsy and uncoordinated. These individuals may struggle with activities such as models or puzzles, playing sports, and certain art projects. They may have difficulties in following a route between two places, and therefore get lost more frequently than their peers.

Social cognitive deficits can result in social isolation, peer neglect and/or rejection, reduced number of meaningful relationships, difficulties understanding the emotions of others as well as one’s own emotions, and deficits in recognizing another’s point of view, among others. Visual–spatial impairments may, in part, contribute to social cognitive difficulties. For example, deficits in visual perception may reduce one’s ability to accurately interpret nonverbal social cues such as body language and facial expression. Executive deficits also

influence social cognition. For example, attention to rather than actual interpretation of social cues may be disrupted. Individuals with impairments in switching or mental flexibility may also perseverate on certain topics and/or respond rigidly to social stimuli, failing to adapt to changing social situations and cues. Difficulties in realizing another's viewpoint (e.g., theory of mind deficits) may stem partially from mental flexibility impairments as well. Specifically, one may not recognize that other viewpoints besides one's own are possible. Deficits in serial reasoning and pattern recognition may interfere with identification of causal connections between behaviors and certain social consequences (i.e., failure to recognize/monitor one's impact on others). Decreased response inhibition may contribute to impulsiveness in social conversations, situations, and relationships.

Few studies have examined the relationships among cognitive features in the TS profile. Because of the high level of interdependence between cognitive domains commonly impaired in TS, these relationships may significantly advance our understanding of the TS cognitive profile. For example, the use of composite scores that capture function across domains may provide more specific and sensitive measures of cognitive function in TS. Additionally, these relationships between cognitive domains may inform and direct syndrome-specific interventions, critical for improving quality of life in individuals with TS. For example, math intervention programs for individuals with TS might include visual–spatial, working memory, and mental flexibility strategies and practice in addition to calculation strategies and training.

SUMMARY

Individuals with TS may demonstrate impairments on visual–spatial, executive, and/or social cognitive tasks, perhaps particularly on integrative tasks that require multiple cognitive domains functioning together. Significant individual variation exists among females with TS in terms of particular cognitive strengths and weaknesses. Although it generally held that females with TS typically demonstrate normal to above-average verbal skills, these may be negatively impacted in some individuals due to executive deficits. Additionally, TS has often been compared with autism and/or nonverbal learning disorder. However, research points to a TS-specific social cognitive profile. Because of the high degree of overlap between visual–spatial, executive, and social cognitive deficits, research regarding the interactions between these domains of impairment in individuals with TS may lead to syndrome-specific intervention options. Such interventions will be essential for improving the quality of life in TS given the significant impact that these deficits can have on independent, adaptive function.

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Table 1

Tests Demonstrating Significantly Lower and/or Impaired Neuropsychological Performance in Females with TS

Reference	Test/Index Name	Test Domain(s)
Shaffer, 1962	Verbal IQ (VIQ)[a] > Performance IQ (PIQ)[a], Freedom from Distractibility (FFD)[a], Perceptual Organization Index (POI)[a], Benton Visual Retention Test	Perceptual reasoning (+ processing speed, motor skills), attention, working memory, processing speed, visual–spatial processing, visual memory
Alexander et al., 1966	Benton Visual Retention Test, Benton Visual Motor Gestalt Test, Draw a Person Test	Visual memory, space-form perception and orientation, visuoconstructive recognition, and performance
Silbert et al., 1977	VIQ > PIQ, Object Assembly[a], Picture Completion[a], Digit Span[a], Beery Visuomotor Integration (VMI), Graham-Kendall Memory for Designs, Embedded Figures, Tactual Performance Test, Seashore Rhythm Test, Auditory Figure-Ground Test	Perceptual reasoning, fine motor skills, spatial relationships, visuomotor, working memory, serial reasoning, tactile-motor, visual–spatial processing, figure-ground perception, auditory processing
Waber, 1979	FSIQ[a] and VIQ[a], Digit Span (backward)[a], FFD[a], Stroop, Word Fluency, Wisconsin Card Sorting Test (WCST), Rey Osterrieth Complex Figure (ROCF), Faces Upright, Consonant Tri-gram Visual, Roadmap Test, R-L Orientation, Finger Tapping	General cognitive ability, verbal comprehension, working memory, response inhibition, processing speed, attention, verbal fluency, mental flexibility/switching, visual–spatial/construction/organization, L/R perception, fine motor coordination and speed
Rovet and Netley, 1980	PIQ, Mental Rotation Test	Perceptual reasoning (with some processing speed, motor skills), spatial processing
Reske-Nielsen et al., 1982	VIQ > PIQ[a], Arithmetic[a], Digit Span[a], Luria Battery	Perceptual reasoning, working memory, mental math skills, sensory function, spatial relationships, memory, sequential order
Rovet and Netley, 1982	VIQ > PIQ[a], Mental Rotation Task, Sentence Verification Task (reaction time)	Perceptual reasoning, processing speed, spatial processing, verbal fluency
Bender et al., 1984	Full Scale IQ (FSIQ)[a], PIQ[a], Spatial Relations Test, VMI, Bender Gestalt, Human Figure Drawing, Token Test	General cognitive ability, perceptual reasoning, spatial orientation, visuomotor skills, visual perception, construction, receptive language
LaHood and Bacon, 1985	VIQ > PIQ[a], Coding[a], Benton Visual Retention Test	Perceptual reasoning, processing speed, visual memory
Pennington et al., 1985	PIQ[a], POI[a], FFD[a], Halstead Reitan Battery (Tactile Performance Test, Location, Spatial Relations, Story Memory Test)	Perceptual reasoning, processing speed, attention, working memory, visuospatial skills, tactile motor, visuomotor, long-term auditory memory
McCauley et al., 1987	PIQ[a], Arithmetic[a], Digit Span[a], Object Assembly[a], Picture Completion[a], VMI	Perceptual reasoning, processing speed, working memory, motor skills, serial/sequential order, visuomotor skills
Downey et al., 1991	FSIQ[a], PIQ[a], Digit Span[a], Arithmetic[a], Block Design[a], Object Assembly[a], Benton Visual Retention Test	General cognitive ability, perceptual reasoning, processing speed, motor skills, working memory, mental math, visual–spatial processing, attention, visual memory, visuoconstructive ability
Bender et al., 1993	FSIQ[a], Woodcock-Johnson (Math, Reading), Spatial Relations Test, Trails B, Boston Naming Test, WCST	General cognitive ability, math, reading, attention, switching, spatial reasoning, mental flexibility, verbal fluency
Rovet, 1993a,b	FSIQ[a], PIQ[a], VIQ > PIQ[a], Digit Span[a], Block Design[a], Coding[a], Wide Range Achievement Test (WRAT) Revised (Reading, Arithmetic)	General cognitive ability, perceptual reasoning, sequential ordering, short-term memory, visual–spatial reasoning/processing, working memory
Swillen et al., 1993	PIQ[a], Object Assembly[a], Block Design[a]	Perceptual reasoning, visuospatial reasoning/processing

Reference	Test/Index Name	Test Domain(s)
Murphy et al., 1994	FSIQ[a], PIQ[a], VIQ > PIQ[a], POI[a], Stroop, Trails B, Wechsler Memory Scale, Category Naming, Ravens Progressive Matrices, Hiskey Nebraska Blocks, Extended Range Drawing, Block Tapping	General cognitive ability, perceptual reasoning, short- and long-term verbal and visual memory, attention, visual–spatial reasoning/processing, response inhibition, visual tracking, switching, processing speed
Rovet et al., 1994	FSIQ[a], PIQ[a], VIQ > PIQ[a], Arithmetic[a], Block Design[a], Coding[a], FFD[a], WRAT-Revised (Arithmetic), Keymath Diagnostic Arithmetic Test (arithmetic, subtraction, multiplication)	General cognitive ability, perceptual reasoning, visual–spatial processing, working memory, attention, processing speed, arithmetic skills
Temple and Carney, 1995	Street Task, Object Assembly, Draw-a-Man, Draw-a-Bicycle	Visual perceptive, visual constructive, visuomotor
Romans et al., 1996	Digit Span[a], FFD[a], ROCF, Tower of Hanoi	Attention, working memory, visual– spatial processing/organization, planning
Ross et al., 1996a,b	FSIQ[a], PIQ[a], Coding[a], Physical and Neurological Examination for Soft Signs, Pegs, Rotor, Money Errors	General cognitive ability, perceptual reasoning, processing speed, motor function, visual–spatial motor skills, arithmetic skills
Ross et al., 1997	FFD[a], Picture Completion[a], Test of Facial Recognition, ROCF, Motor-Free Visual Perception Test, VMI, WRAT	Attention, working memory, processing speed, object discrimination, visual memory, visual motor, academic achievement, face processing, academic achievement, visual–spatial processing/ organization
Buchanan et al., 1998	WRAT (Arithmetic), MNFAC	Visual–spatial working memory, facial emotion/identity processing, arithmetic
Mazzocco, 1998	Judgment of Line Orientation (JLO), WISC-R 3rd factor[a], Woodcock-Johnson (Math calculation and applied problems)	Spatial orientation, working memory, attention, math achievement
Romans et al., 1998	FSIQ[a], PIQ[a], Arithmetic[a], Digit Span[a], Picture Completion[a], Picture Arrangement[a], Block Design[a], Coding[a], POI[a], WRAT (reading, arithmetic), Word List, Token Test, Controlled Oral Word Association Test, Semantic fluency, ROCF, Facial Recognition, JLO, Road Map, Motor-Free Visual Perception Test, Click/Clack, VMI, Test of Variables of Attention, Matching Familiar Figures Test, Tower of Hanoi, Pegs, Finger Tapping	General cognitive ability, perceptual reasoning, attention, working memory, processing speed, receptive language, fluency, construction, organization, spatial orientation, visual perceptive ability, visuomotor, fine motor skills, planning, visual–spatial processing/organization
Temple and Marriott, 1998	Arithmetical Problems (multiplication, division)	Calculation skills
Bishop et al., 2000	ROCF, Beardsworth and Bishop's Story Recall Test (delayed when compared with immediate)	Visual–spatial processing/organization visual–spatial memory, delayed verbal recall
Nijhuis-van der Sanden et al., 2000	Movement Assessment Battery for Children	Motor skills (manual dexterity, ball skills)
Cornoldi et al., 2001	VIQ > PIQ[a], Test of Memory and Learning (# 6, 8, 10), Image generation, puzzle, Image updating, Corsi, Spatial Description, Visual Pattern Span Test, Zoo's Test, Matrices, Mental Scanning	Perceptual reasoning, visual–spatial working memory (active, passive visual–spatial tasks, sequential spatial tasks), planning, mental flexibility, serial reasoning/pattern recognition
Collaer et al., 2002	Differential Abilities Test (Numerical Ability), Digit Span[a], Coding[a], Purdue Pegboard, Finding As, Number Comparison, Addition, Alpha Symbol, Verbal Fluency, Object Memory, Location Memory, Plumb-Line, JLO, Arithmetic Aptitude	Fine motor speed, verbal fluency, visual memory, arithmetic ability, working memory, processing speed, attention, visual perceptive ability, spatial orientation
Elgar et al., 2002	PIQ[a], Head orientation/displacement	Perceptual reasoning, inefficient gaze monitoring/detection
Ross et al., 2002	FSIQ[a], PIQ[a], Arithmetic[a], Digit Span (backward)[a], Picture Completion[a], Picture Arrangement[a], Block Design[a], Object Assembly[a], Coding[a], WRAT (Arithmetic), Wechsler Memory Scale (delayed recall), Token Test, Controlled Oral Word Association Test, Semantic Fluency	General cognitive ability, perceptual reasoning, attention, visual–spatial perception, visuoconstructive ability, visual memory, receptive language, working memory, processing speed, arithmetic, serial reasoning, verbal fluency

Reference	Test/Index Name	Test Domain(s)
Temple, 2002	Verbal Fluency, Boston Aphasia Battery (Cookie Theft)	Verbal fluency (higher # low freq. words), language retrieval processes, episodic memory
Good et al., 2003	PIQ[a], Ekman Pictures of Facial Affect	Perceptual reasoning, impaired facial fear recognition
Ross et al., 2003	POI[a], ROCF, Digit Span (backward)[a], Missouri Auditory Verbal Learning Test (immediate recall)	Perceptual processing, working memory, visual–spatial processing/organization, auditory memory
Bruandet et al., 2004	Computerized tests of cognitive estimation, subitizing, and calculation	Cognitive estimation, subitizing, and calculation
Kesler et al., 2004	Peabody Picture Vocabulary Test, Boston Naming Test, Category Fluency, Non-word Reading, Mental Rotation Test, Benton Faces, Object Assembly[a]	Receptive language, naming, semantic fluency, spatial orientation, face recognition, visuoconstruction ability, reading decoding, visuomotor
Rae et al., 2004	FSIQ[a], PIQ[a], Arithmetic[a], Digit Span[a], Picture Completion[a], Picture Arrangement[a], Block Design[a], Object Assembly[a], Coding[a], ROCF, Wechsler Memory Scale (visual), Warrington Faces, Facial Recognition, Pursuit Rotor, Arithmetic Achievement, WRAT (arithmetic), Controlled Oral Word Association Test, Semantic Fluency	General cognitive ability, perceptual reasoning, short-term memory/attention, visuoconstructive ability, arithmetic ability, fluency, executive function, visual memory, visual motor, verbal semantic processing
Ross et al., 2004	Continuous Naming Test	Working memory, processing speed, mental flexibility, response inhibition
Kirk et al., 2005	FSIQ[a], VIQ[a], PIQ[a], POI[a], Verbal Comprehension Index[a], Behavioral Dyscontrol Scale, ROCF, WCST	General cognitive ability, perceptual processing, visuoconstructive ability, attention, working memory/flexibility, visual memory
Loesch et al., 2005	VIQ[a], JLO, Woodcock-Johnson (Numbers Reversed), Wechsler Memory Scale (Spatial span reversed)	Verbal ability, spatial orientation, working memory
Hart et al., 2006	FSIQ[a], Test of Early Mathematics Ability-2, Woodcock-Johnson (Calculations), Developmental Test of Visual Perception-2	General cognitive ability, math performance, visual perceptive ability, spatial orientation, form detection, shape constancy
Kesler et al., 2006	FSIQ[a], VIQ > PIQ[a]	General cognitive ability, perceptual processing
Mazzocco et al., 2006a,b	Turner Syndrome Composite Score (TSCS)	Visual–spatial and executive skills
Messina et al., 2007	FSIQ[a], POI[a], Perceptual Reasoning Index (PRI)[a], Enumeration Task	General cognitive ability, short-term memory/attention, visual–spatial attention/ processing
Zinn et al., 2007	Test/Index Name	Test Domain(s)
Simon et al., 2008	VIQ > PIQ, FFD, POI, BVRT	Fluid reasoning, processing speed, motor skills, attention, visual memory

[a]Wechsler intelligence scale measure.