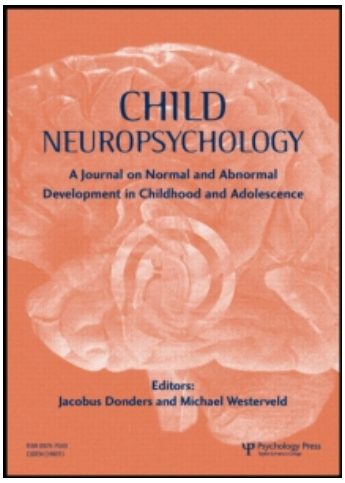

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Cerebral Laterality In Turner Syndrome: A Critical Review Of The Literature

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CEREBRAL LATERALITY IN TURNER SYNDROME: A CRITICAL REVIEW OF THE LITERATURE

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Turner syndrome (TS) is a genetic disorder in females characterized by the complete or partial absence of one X chromosome. Its most consistent physical features include short stature and ovarian dysgenesis. TS individuals demonstrate a characteristic neurocognitive profile involving weaknesses in visuospatial processing. The hypothesis of defective right hemisphere specialization has been offered to explain the visuospatial deficits in TS. In contrast, an alternative explanation proposes a more uniform dysfunction of the left and right hemispheres, based on findings of symmetrical abnormalities. This article presents an overview of the two hypotheses, along with relevant findings on hemispheric specialization with respect to TS. The impact of the genetic and hormonal mechanisms on the neurocognitive profile of TS is also discussed and directions for further empirical research are identified.

Keywords: ***Turner syndrome; neurocognitive profile; hemispheric specialization; cognitive and motor asymmetries; atypical brain development.***

Turner syndrome (TS) is a specific genetic disorder affecting exclusively females. The American Physician Henry Turner first identified the syndrome in 1938. It is also referred to in the literature as monosomy X and gonadal dysgenesis (45,X or 45,X0). In 1959, Ford and his associates identified the genetic abnormality associated with the syndrome. They linked it with an abnormality or deletion of the second X chromosome. The most common type of TS is 45,X0, indicating that an entire X chromosome is missing. It appears to be in almost 50% of cases and is often referred to as pure TS (Temple & Carney, 1993). Mosaicism occurs in 30%–40% of cases. Individuals with TS have a mosaic karyotype with some cells containing the 45,X make-up, whereas others containing the normal 46,XX make-up (Rovet & Buchanan, 1999). Among other cases of TS, some have a partial deletion of one arm of the X chromosome. In others, there is a duplication of one arm of the X chromosome with the loss of the other arm (Temple & Carney, 1993). Such karyotype is known as isochromosome of X and reported by genetics as 45 xi(xq).

The incidence of TS is 1 in 2,500 live female births and is markedly higher at conception, as only about 1% survive to birth (Hook & Warburton, 1983). There are many physical abnormalities present with TS. Characteristic physical features of Turner syndrome include short stature, ovarian failure, and any of a variety of specific somatic characteristics. Growth failure begins in utero. The final adult height of women with TS is often between 4 feet 6 inches and 4 feet 10 inches (Jones, 1988). Ovarian dysgenesis leads

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to a lack of development of secondary sexual characteristics and for the vast majority of women with TS to infertility (Jones, 1988). The somatic abnormalities include a wide variety of skeletal and facial deformities. Heart defects including coarctation of the aorta as well as kidney problems, high blood pressure, and diabetes mellitus are also common (Hall & Gilchrist, 1990).

In addition to an unusual physical phenotype, females with TS also demonstrate an atypical cognitive profile. Shaffer (1962) was the first to demonstrate a specific cognitive profile for TS. His study documented an average Performance Intelligence Quotient (PIQ) that was 19 points lower than the average Verbal IQ (VIQ). He suggested that the observed difference resulted from impaired performance in perceptual organization that was assessed by Block Design and Object Assembly of the Wechsler Intelligence Scale. The pattern of VIQ scores higher than PIQ scores has received support from studies by subsequent researchers (e.g., Cornoldi, Marconi, & Vecchi, 2001; Lewandowski, Costenbader, & Richman, 1985; Money & Alexander, 1966; Rovet, Szekely, & Hockenberry, 1994; Waber, 1979). However, the degree of difference between VIQ and PIQ varies slightly from study to study. The current literature supports the view of a Verbal IQ advantage in TS, but it suggests that overall the IQ scores for females with TS cover the full range of normal IQs (Temple & Carney, 1993).

Although TS is typically associated with a deficit in processing visuospatial information (e.g., Money & Alexander, 1966), a wide variety of other specific deficits have been documented across studies. These include deficits in visuoconstructional skills (McCauley, Kay, Ito, & Treder, 1987; Temple & Carney, 1995), math difficulties (Buchanan, Pavlovic, & Rovet, 1998; Money & Alexander, 1966), problems with visual memory (Lewandowski, Costenbader, & Richman 1985; Money & Alexander, 1966) and deficits in working memory (Buchanan, Pavlovic, & Rovet, 1998). The cognitive deficits that have been identified in TS do appear to persist into adulthood (Downey, Elkin, Ehrhardt, Meyer-Bahlburg, Ball, Morishima 1991).

A number of studies involving neuroimaging techniques have explored the possible associated area of dysfunction within the brain that leads to the typical cognitive deficits observed in TS. Clark, Klonoff, and Hayden (1990), using positron emission tomography found that glucose uptake was reduced in the parietal occipital lobes of women with TS and suggested "the reduction of parietal glucose metabolism may reflect a lack of inervation from the occipital cortex" (p. 143). A magnetic resonance imaging (MRI) study of TS revealed that in comparison to controls, TS subjects had a significantly smaller volume of hippocampus, caudate, lentular and thalamic nuclei and of parietooccipital brain matter on both sides (Murphy et al., 1993). They suggested that their results demonstrate "X chromosome dosage effects" on morphometry of association neocortex and on verbal and visuospatial cognitive ability.

In an MRI study of a set of 10-year-old twins discordant for Turner syndrome, Reiss, Freund, et al., (1993) found reduced gray matter volume in the left parietal perisylvian and right prefrontal regions for the twin with Turner syndrome. In addition, the cerebrospinal fluid of the TS girl was increased in the right posterior parietooccipital area in comparison to her unaffected twin. Reiss, Mazzocco, et al. (1995) performed an MRI study on 30 girls with Turner syndrome and female controls. The girls with TS demonstrated the typical neurocognitive deficits (spared verbal functioning with poor visuospatial ability) combined with differences in the right parietal and temporal regions. The authors stressed the potentially important role of X chromosome genes in the development and hemispheric specialization of brain structure and functions. Those findings suggest

specific neuroanatomical irregularities associated with TS. However, more research in this field is needed to determine the cerebral regions that are responsible for the functional abnormalities that are observed in TS.

A considerable amount of research has attempted to determine whether atypical hemisphere specialization and organization explain the characteristic neurocognitive profile in TS. Based on the increased incidence of visuospatial difficulties versus intact verbal skills that are observed in individuals with TS, a number of investigators have proposed a hypothesis of altered right hemisphere functioning (Gordon & Galatzer, 1980; Rovet, 1990; Silbert, Wolff, & Lilienthal, 1977). In contrast to this explanation, other studies suggested a more diffuse cerebral alteration hypothesis based on findings of impairments in both right and left hemisphere functions (Netley & Rovet, 1982; Waber, 1979). There is however no direct support for any of these hypotheses, since the current neuroimaging studies have failed to identify a single area of dysfunction in this population, while at the same time a considerable variability is observed across individuals with TS. A comprehensive review of structural abnormalities in TS is beyond the scope of this paper and more in-depth discussions on that interesting topic can be found elsewhere (e.g., Murphy et al., 1993; Reiss, Freund, et al., 1993).

In contrast to the abundant literature on structural abnormalities in TS, the concept of hemisphere specialization in TS has rarely been investigated. The studies currently available on theme-related issues have used dichotic listening procedures (Gordon & Galatzer, 1980; Netley, 1977; Netley & Rovet, 1982; Rovet, 1990; Waber, 1979), visual T scope presentation with both verbal and nonverbal information stimuli (McGlone, 1985; Rovet, 1990), and motor skill laterality measures, such as cutting tasks and the Pin test (Elliot & Watkins, 1998; Gordon & Galatzer, 1980). The purpose of this study was to evaluate the relevant evidence concerning right hemisphere and global hemisphere dysfunction in TS. The present report explores the contradictory hypotheses by addressing the cognitive and motor deficits in TS and assessing their association to the cerebral hemispheres. A complete and definite description of the aetiology of the observed cognitive asymmetries associated with the syndrome at the level of hemispheric specialization cannot be produced from the current empirical evidence. Nonetheless, efforts have been directed at identifying key areas for future empirical research.

RIGHT HEMISPHERE DYSFUNCTION

Kolb and Heaton (1975) assessed a single patient with TS on a battery of neuropsychological tests tapping verbal, spatial, and psychomotor functions. Results demonstrated the classical profile of the syndrome: normal verbal versus impaired spatial abilities. In relation to cerebral dysfunction, the findings revealed imperceivable tactile and auditory stimuli to the left. This observed asymmetry was ascribed to right hemisphere impairment. Also, while the advantages of estrogen replacement therapy upon the physical condition of the TS individual were expected, the psychotic symptoms of the patient with TS were linked to estrogen replacement therapy. The authors concluded that it is not possible to make generalizations on the basis of the obtained results about the relationship between TS and the localization of function within the brain.

Silbert, Wolff, & Lilienthal (1977) investigated the spatial and serial processing in 13 females with TS. Participants were tested on a battery of neurocognitive measures and their performance was compared to the performance of a matched-control group. With respect to spatial abilities, individuals with TS revealed poor spatial visualization and

orientation. Furthermore, weak serial organization and sequencing skills were also reported in the TS group. However, the weak spatial ability was limited to tasks requiring the integration of details into meaningful wholes. The authors suggested that the spatial difficulties observed in their participants with TS reflect right hemisphere dysfunction. Also the weak performance of the experimental group on auditory sequencing tasks was attributed to right hemisphere dysfunction, based on findings that show that such tasks in "musically naïve listeners are preferentially processed as configurations and therefore presumably in the right hemisphere" (Silbert, Wolff, & Lilienthal, 1977, p. 20; see also Bever & Chiarello, 1974; Kimura, 1967).

Netley (1977) administered a dichotic listening test to evaluate hemispheric specialization in a group of 14 individuals with TS. The results indicated that 57% of the TS participants showed a left-ear preference while only 16% of the control group showed this phenomenon. According to Netley, these results were indicative of a tendency towards right hemisphere processing of verbal material for the experimental group. In contrast, the findings of right-ear dominance for the control group were suggestive of left hemisphere involvement during verbal processing. These findings were explained in terms of a correlation between genetic factors and indices of hemispheric specialization. It was speculated that a genetic program is responsible for the development of certain directions in the two hemispheres, concluding that "hemispheric specialization has both a phylogenetic and ontogenetic character" (Netley, 1977, p. 141).

Gordon and Galatzer (1980) similarly indicated that during verbal information processing, individuals with TS use their left hemisphere to a lesser degree while sometimes it is accompanied by increased right hemisphere involvement. In their study, they assessed hemispheric laterality in 14 females with TS, using a dichotic listening procedure and a cutting task. Their performance was compared to that of a control group matched for hand preference. The findings from the dichotic listening test revealed a left-ear advantage in reporting verbal material. These results were interpreted in terms of a right hemisphere contribution during verbal information processing. The assessment of laterality of motor skill dexterity revealed an increased variance in the TS group in comparison to controls. Thus, a great proportion of mixed-hand preference was observed in the TS group, while in controls the preferred hand was faster. Based on the obtained results, the authors stressed the influence of both the genetic and hormonal factors in the development of cerebral organization.

Dellantonio, Lis, Saviolo, Rigon, and Tenconi (1984) examined the hypothesis of right hemisphere specialization by testing 11 patients with TS in a variety of verbal and spatial tasks including hand preference measures. The analysis of the results revealed a significantly low score for the nonpreferred left hand (controlled by the right hemisphere) in the group of girls with TS. These findings were interpreted in terms of a defective right hemisphere specialization in TS individuals. The genetic hypothesis of a recessive sex-linked gene being responsible for the observed deficits in TS was not supported from the preceding data. The poor performance of TS subjects was rather explained by indicating an association between the functional differentiation of hemispheres with the quality and quantity of hormones secreted in the earlier and in the later phases of the developmental course (Dellantonio et al., 1984).

Lewandowski, Costenbader, and Richman, (1985) employed a series of performance procedures and a three-condition dichotic listening task to compare the neuropsychological competence of a TS group to that of a matched-control group. The findings indicated similar scores in mean VIQ for both groups. Nevertheless, the TS group showed impaired performance on tests tapping visual-perceptual, visual-memory, and motor

processes. With respect to the dichotic listening results, no significant group differences were reported. However, TS participants showed a slightly greater than normal tendency to use their right hemisphere while processing verbal material across tasks.

Rovet (1990) reported the results on four laterality tasks, measuring right and left hemisphere capacities, in 15 participants with TS. Their performance was compared to that of a control group consisted of 118 normal women. Left hemisphere laterality was measured with the dichotic presentation of stop consonants and a tachitoscopically presented letter recognition task. On the other hand, right hemisphere laterality was assessed with a musical dichotic listening task and a tachitoscopically presented dot enumeration task. Results demonstrated that individuals with TS showed an advanced left hemisphere involvement for spatial-information processing in relation to controls, while they showed a weak left hemisphere contribution during verbal information processing. On the basis of these findings, Rovet (1990) suggested that individuals with TS are characterized by a lack of development of normal hemispheric lateralization and he concluded that some verbal processes might be subserved by the right hemisphere.

Ross, Kushner, and Roeltgen (1996) examined the developmental changes in motor performance in 78 girls with TS. Participants were administered a series of cognitive and motor tasks tapping both spatial and nonspatial functions. The findings demonstrated inadequate performance in the older TS group of girls for motor tasks that required the greatest spatial demands. In addition, the older control group exhibited increased speed on tasks tapping motor performance, suggesting a developmental deficiency in motor skills associated with TS. With respect to handedness, both the experimental and the control group showed an advanced performance of the dominant versus the nondominant hand. This pattern of results was attributed to a dysfunction of the right posterior systems.

These results were further supported by a second study, in which Ross, Roeltgen, Feuillan, Kushner, and Cutler (1998) investigated the contribution of estrogen replacement therapy in selected deficits in motor performance that were evident in females with TS as well as in the time that these girls required to perform certain nonverbal tasks (i.e., nonverbal processing speed). A total of 47 girls with TS were administered a battery of cognitive tasks. Thus, a smaller number of participants were examined at several motor tasks such as finger tapping, pegboard, and pursuit rotor. An additional goal of the study included the investigation of the effects of estrogen treatment on the lateralized asymmetry in right-handed girls with TS for motor tasks. The findings supported the contention that the motor difficulties and the deficient nonverbal processing speed of girls with TS can be attributed to estrogen insufficiency. Further the results revealed a similar performance for both the TS girls and the control group in the dominant relative to the nondominant hand for nonverbal tasks. To this end, the authors suggested a right posterior dysfunction in TS participants that generates slower spatial motor function performance for both hands and can be improved by estrogen replacement therapy.

Molko et al. (2003) have attempted to link arithmetic performance with the cerebral structures in the TS group. Using fMRI and structural imaging, they examined the functional correlates of arithmetic performance in 14 TS participants. In line with previous behavioral studies (Temple & Marriot, 1998), they observed arithmetic difficulties characterized by slower reaction times. Further an abnormal development of numerical representations was observed in individuals with TS. fMRI and morphological analysis revealed "an insufficient recruitment of the right intraparietal sulcus with an abnormal length, depth, and sulcal geometry" (Molko et al., 2003, p. 9). The authors stressed the important role of the right parietal lobe in the development of numerical abilities.

GLOBAL HEMISPHERE DYSFUNCTION

Waber (1979) assessed 11 individuals with Turner syndrome on a test battery and compared their performance with that of a matched-control group. Results failed to identify a specific deficit in spatial ability. In addition, the TS group showed deficits in word fluency, right-left discrimination, visual memory, and motor coordination. The researcher argued for a more general nonlateralized impairment, for which a hypothesis of developmental delay cannot account for all the observed differences. The only exception was the finding of a left-ear advantage that was demonstrated by the experimental group on the dichotic listening test. This finding was consistent with the earlier results reported by Netley (1977) and was interpreted accordingly by pointing out the significant role of sex hormones for the laterality of language to the left hemisphere. Since females with Turner syndrome lack such hormones, the authors hypothesized that language can similarly lateralize to both hemispheres.

Netley and Rovet (1982) evaluated the performance of 38 females with Turner syndrome on tasks of dichotic listening and hand preference, assessing hemispheric lateralization. The findings from the dichotic listening task indicated that TS participants were less likely than controls to show the right-ear advantage. In addition a relationship was demonstrated between dichotic ear asymmetries and Verbal IQ. These findings were interpreted in the framework of hypothesized weak left hemisphere contribution for verbal material and were further associated with the representation of verbal processes bilaterally. In relation to hand preference, results revealed no difference between the two groups. However, the results may have been limited by the scoring criterion that was used in this study, according to which the person was considered right handed if the right hand was chosen at least seven times at each of ten unimanual items (Elliot & Watkins, 1998).

Bender, Puck, Salbenblatt, and Robinson (1984) examined the cognitive development of 25 girls (aged 8 to 17) with TS, grouped according to their karyotype (45,X, 45,X variant karyotypes, 45,X mosaics). The participants were administered two developmental tests, the Wechsler Intelligence Scale for Children, three tests measuring perceptual-motor skills, and one test measuring spatial skills. The findings showed an impaired performance in perceptual organization, fine motor skills, auditory processing and memory in the group of nonmosaic TS participants with X or partial X monosomy. On the basis of their results they proposed that TS females suffer from a more generalized cognitive impairment that is not restricted to right hemisphere functioning. The authors have suggested the possibility of a relationship between hormone variations and cognitive variations in TS individuals.

Pennington, Heaton, Karzmark, Pendleton, Lehman, and Shucard (1985) tested 10 females with TS on the Halstead-Reitan battery (Reitan & Wolfson, 1985). Their performance was compared to that of 12 individuals with right hemisphere damage, 10 individuals with left hemisphere damage, 10 with diffuse brain damage, and 20 normal control participants. Overall, results demonstrated that the TS group was more impaired than the normal participants. In comparison to the rest of the groups, the performance of individuals with TS was similar to that of the patients with diffuse brain damage. More specifically the TS group revealed abnormal performance in tasks tapping memory functions, auditory processing, verbal fluency, and attention.

McGlone (1985) investigated the spatial abilities of 11 females with TS and 22 controls by administering a series of tasks tapping perceptual, constructional, and nonverbal memory functions. Also, she examined central nervous system (CNS) function and speech lateralization. The different measures of spatial ability showed that the spatial impairments in

the TS group were more pronounced on tasks tapping visual perception than on purely constructional tasks. Moreover the findings revealed a 27% incidence of non-right-hand dominance in the TS group. However, this result may be highly attributable to the inclusion of one non-right- handed participant with a neurological condition (global brain atrophy and hydpochephalus) that is highly atypical of TS. A more pronounced finding of the present study was the slower speed right-hand tapping that was demonstrated by the experimental group, suggesting impaired laterality for motor functions in individuals with TS. In relation to CNS focal dysfunction and speech lateralization, the findings showed slightly increased somatosensory threshold of the left palm, attenuated manual asymmetry and diminished right-visual field superiority on letter identification. McGlone (1985, p. 375) concluded that "a unitary explanation in terms of focal CNS dysfunction or atypical speech representation can not account for the pattern of neuropsychological deficits seen in Turner's syndrome."

Salbenblatt, Meyers, Bender, Linden, & Robinson, (1989) examined the developmental status of 21 girls with TS, grouped according to their sex chromosome types (45,X, 45,X variants, sex chromosome mosaics and 47,XXX). The Bruininks-Oseretsky (Bruininks, 1978) test of motor proficiency (BOTMP) as well as the clinical assessment revealed both gross and fine motor dysfunction in the 45,X group. Further evaluations indicated hypotonia and poor joint stability. In addition, the findings showed that the performance of the control group was more similar to that of the TS girls with mosaic karyotypes. On the basis of these findings, Salbenblatt et al. (1989) suggested that TS individuals may suffer from a general neurologic dysfunction.

Bender, Linden, and Robinson (1993) evaluated the abilities of 42 adolescents with sex chromosome abnormalities. A variety of neuropsychological tests measuring cognitive and academic skills were used along with tests assessing brain functions localized to the right-left hemisphere and frontal lobes. The performance of the experimental groups was compared to that of 25 control participants. With respect to 45,X girls, the results showed weak performance in attention, concept formation, verbal fluency, and spatial thinking. What is more, an abnormal pattern of hand dominance was reported, with TS girls demonstrating deficient dominant hand superiority in comparison to controls. According to the authors these results were suggestive of an atypical hemispheric specialization, providing support to Rovet and Netley's suggestion (1982) of a bilateral distribution of verbal functioning in this population, indicative of a more diffuse cerebral abnormality.

Elliot and Watkins (1998) examined hand preference, motor skill functioning, and their relationship to spatial and verbal abilities in 45 individuals with TS, through the administration of the Pin Test. Findings demonstrated a 75% incidence of right-hand preference in the TS sample. What is more, no significant relationship between hand preference and cognitive functioning was reported, since neither Verbal nor Performance IQ was significantly different in any of the three hand preference groups (right-handers, left-handers, ambidextrous group). Motor skill laterality testing revealed a significant curvilinear relationship with Performance IQ scores, demonstrating that either extreme of laterality (weak or strong) produced more damage to visuospatial skills than moderate laterality. In addition, lower verbal skills were reported by the more strongly lateralized participants. The authors argued that their findings were in agreement with those reported by Netley and Rovet (1982) who related bilateral representation of language with high Verbal IQ. They further suggested that extremely weak laterality seen in individuals with TS may reflect bilateral impairment; strong laterality may reflect unilateral impairment, while moderate laterality may reflect unimpaired cognitive functioning.

With respect to motor performance in TS, Nijhuis-van der Sanden and colleagues conducted a number of studies. Using the Movement Assessment Battery for Children (MABC), Nijhuis-van der Sanden, Smits-Engelsman, and Eling (2000) reported an overall impaired motor performance in 15 girls with TS. In more recent studies Nijhuis-van der Sanden and colleagues have attempted to determine the specific motor difficulties associated with the syndrome and to provide a deeper insight into the nature of the differences in motor performance between TS girls and controls. Using graphical aiming tasks (Nijhuis-van der Sanden, Smits-Engelsman, Eling, 2000; Nijhuis-van der Sanden, Smits-Engelsman, Eling, Nijhuis, & Van Galen, 2002; Nijhuis-van der Sanden, Eling, Van Asseldonk, & Van Galen 2004), kinematic data from dynamic task conditions (Smits-Engelsman, Nijhuis-van der Sanden & Duysens, 2003), and isometric aiming tasks (Nijhuis-van der Sanden, Van Asseldonk, Eling, & Van Galen, 2003), they showed that although both the experimental and the control group moved with the same accuracy, the movement speed was lower in the TS group in both the discrete and the serial order condition independent of the task variations in visuospatial demands. Also, velocity and variability remained intact in both groups in isometric conditions. The authors concluded that the main difficulty in girls with TS is in motor execution rather than in the visuospatial domain.

Everhart, Shucard, Quatrin, & Shucard, (2004) examined event-related potential (ERP) differences in a group of 12 girls with TS and 40 normal controls (20 girls, 20 boys) during a face recognition memory task. More specifically both auditory and visual stimuli elicit ERPs while participants performed cognitive tasks that are localized differently in the brain. The authors hypothesized that ERPs would reveal differences in cortical organization between the TS girls and the control group. Their findings showed no asymmetry between the hemispheres in the TS group. In contrast control boys revealed overall a greater right than left hemisphere amplitude, while control girls showed the opposite pattern. On the basis of their findings, the authors suggested that the observed symmetry in the TS group reflected a more general involvement of both hemispheres during face recognition. They further proposed a possible association between the development of hemispheric specialization and the resulting failure of individuals with TS to produce estrogen.

DISCUSSION AND CONCLUSIONS

In line with previous research, two alternative interpretations were proposed to explain the cognitive and motor difficulties in TS: "the right hemisphere dysfunction hypotheses" and the "global hemisphere dysfunction hypotheses." It is apparent the aforementioned studies have attempted to define the specific cognitive functions that are impaired in TS and to further locate the relevant area of the brain that is involved. Although available evidence firmly establishes that intrahemispheric processing is atypical in TS in comparison to the normal population, it does not explicitly address whether the observed cerebral dysfunction is restricted to the right hemisphere or is the product of a more diffuse cerebral impairment. Across studies no single problem has been identified and considerable variability exists among individuals with TS.

Despite this variability, the patterns of impairment that are evident in TS are thought to reflect both hormonal and genetic factors. Turning to the hormonal influences, the preceding data stresses the important role of estrogen production for development (i.e., Everhart, Shucard, Quatrin, & Shucard, 2004; Ross, Roeltgen, et al., 1998). Although the precise contribution of estrogen production upon the characteristic neurocognitive profile of girls with TS is not yet entirely clear, estrogen imbalance at different stages of development has been associated with certain aspects of cognitive dysfunction. Girls with TS have

gonadal dysgenesis and, therefore, lack the ability to produce estrogen. According to many theorists (e.g., Bender, Linden, & Robinson, 1993; Everhart, Shucard, Quatrin, & Shucard, 2004; Rovet, 2004), absent estrogen levels is the most likely aetiology for the observed differences in hemispheric specialization in this particular population. Also a potential link between lack of estrogen exposure and impaired motor function has been reported (Ross et al., 1996). Another hormone issue that these studies raise and further complicates the interpretation of TS impairments concerns the effects of growth hormone replacement therapy on cognitive functions (Bruadent, Molko, Cohen, & Dehaene, 2004; Nijhuis-van der Sanden, Eling, & Otten, 2003; Rovet, 2004). However, no specific influences on the neuropsychological profile of individuals with TS have been reported, even when the therapy started in early developmental stages (Ross, Feuillan, et al., 1997).

Given the absence of estrogen among TS girls, particularly early in childhood, it is reasonable for researchers in this field to assume that sex hormones affect at some level the development of specific neurocognitive functions (i.e., Ross, Zinn, & McCauley, 2000). However, the exact influence of hormones upon certain neurocognitive processes remains debatable. Studies focusing on the effects of estrogen replacement therapy starting in adolescence have noted persistent discrepancy between Verbal and Performance IQ as well as impaired visuospatial abilities in individuals with TS (Downey et al., 1991; Ross, Zinn, & McCauley, 2000), while motor function, executive ability, and memory seem to improve (Romans Stefanatos, Roeltgen, Kushner, & Ross, 1998). Clearly, more studies of young children with TS are needed to explore these issues further. Particularly, long-term developmental studies are needed to identify the mechanisms of these estrogen effects on neurocognitive functioning of individuals with TS.

A variant explanation that accounts for atypical brain development in TS individuals recognizes that restricted chromosomal regions contribute to different phenotypic characteristics (Rovet, 2004). In other words, the influence of genetic factors on the neuropsychological profile of TS has been documented across studies. Netley (1977) suggested that a genetic program to development predisposes the two cerebral hemispheres in specific directions. The genetic factors include the individual's particular karyotype and genomic imprinting (Rovet, 2004). Research indicated that TS women with mosaic karyotype are generally less impaired than classic 45,X patients (Salbenblatt et al., 1989; Temple & Carney, 1995). However, this dichotomy has been challenged by the X-chromosome dosage effect. Recent studies have attributed the different neuropsychological profiles of women with TS to genetic imprinting, depending on whether the remaining X chromosome originates from the father or the mother (Bishop et al., 2000). The genetic etiology theory serves as a plausible explanation for hemispheric specialization. However, additional research is required to discover the specific genes that influence the particular cognitive deficits that are evident in TS. Detailed neuroimaging studies linking structural, functional, and genetic data might provide a deeper insight in to the genetic predisposition in this population.

With respect to motor function, the available evidence indicates an overall weak motor performance in individuals with TS. Two lines of interpretations have been offered to explain weak motor function in TS. The first suggests that motor difficulties in TS may lie in the decreased visuospatial abilities of this population. The second proposes that while visuospatial difficulties may play a role in motor achievement, other components such as motor execution may be involved. The relevant literature in the area of genetic disorders cannot determine the exact nature of motor deficits that are observed in TS. It remains, however, unclear if the observed motor impairments reflect deficits in visuospatial abilities and/or in the motor initiation level and whether these deficits are lateralized or not.

It has become evident from the preceding data that the neurocognitive phenotype of TS is heterogeneous. While some TS individuals demonstrate difficulties in some areas others show no deficits. This degree of variability among women with TS is increasing by the methodological differences in all domains (varying karyotypes, inadequacies in the reported karyotypes, sample selection, age range, physical attributes, social functioning, lack of detailed data, and group size) that are observed across studies. In general caution must be taken when comparing results between different studies. Methodological differences prevent the ability to draw clear conclusions from the TS literature with respect to hemispheric specialization. Empirical research has used a wide range of test procedures to discover the impaired localized area in TS individuals, including dichotic listening techniques, tachistoscopic presentation of visual and verbal stimuli, and motor skill laterality measures. Although these instruments provide a description of the observed impairment, they fail to detect the specific associated area of dysfunction. The different theoretical perspectives, sometimes conflicting, may reflect methodological variations across the studies rather than a valid evaluation of the results.

DIRECTIONS FOR FUTURE RESEARCH

The evidence outlined above has demonstrated an atypical cognitive laterality profile in TS. One area of research argues for poor right hemisphere functions in TS, whereas both right and left hemispheric dysfunction is consistently reported by subsequent researchers. The two theories seem to be mutually exclusive. Hormonal and genetic factors seem to serve as plausible explanations for atypical hemispheric specialization. However, while emphasis is given in hormonal and genetic mechanisms that underlie the neurocognitive development in TS, no clear theoretical framework integrating these factors is yet available. In order to distinguish the outcomes caused solely by genetic mechanisms from those caused merely by hormonal and other biological factors, future research may require the investigation of both genetic and hormonal influences in the same participants. Further research warranted in this field, linking genes-karyotypes-brain and cognition.

Nonetheless more studies — probably longitudinal — examining larger groups of individuals with TS would be critical to determine the differential impact of genetic and hormonal mechanisms at different stages of development. The longitudinal evaluation of individual developmental profiles probably is the key to the solution of the relative roles of genetic and hormonal influences in the determination of the observed variability in TS as to the degree and the severity of the deficit. Longitudinal studies would be necessary in identifying the risk and protective factors that contribute to the observable heterogeneity in the particular population, as well as in determining certain phenotypic traits that may be predictive of poorer outcome.

Future advances in the field of neuropsychological evaluation using measures specialized in discovering the possible associated brain areas of dysfunction coupled with electrophysiological measures, such as MRI and PET scans, might prove promising in clarifying the atypical pattern of performance in TS, as well as in determining a causal relationship between anatomical and functional abnormalities in certain brain sites and behavioral dysfunction. A concerted effort should be made to better identify the specific underlying neurocognitive and biological factors in TS populations.

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