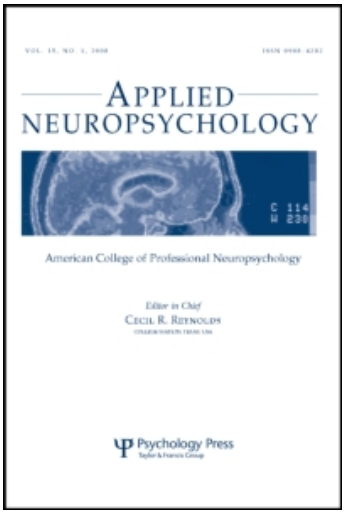

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The Concept of Anomalous Cerebral Lateralization in Klinefelter Syndrome

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The Concept of Anomalous Cerebral Lateralization in Klinefelter Syndrome

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Klinefelter syndrome (KS) is a genetic disorder in males characterized by the presence of an extra X chromosome. Its most consistent endocrinological manifestations include lower testosterone production and impaired spermatogenesis. KS individuals have a general typical appearance with taller stature, and they demonstrate a characteristic cognitive phenotype involving weaknesses in verbal processing. Anomalous cerebral lateralization involves the inverse or weak dominance of hand, language, and visuospatial abilities and has been associated with the cognitive deficits of KS individuals. This article summarizes the ongoing research in this field, discusses the main findings, and attempts to provide a thorough description of the cause of the observed functional and anatomical cerebral asymmetries associated with the syndrome. Nonetheless, efforts have been directed to incorporate evidence for and against theoretical accounts that explain the experimental findings, to discuss issues involving the implications of the chosen methodology, and present key research areas for future empirical research.

Key words: *anomalous cerebral, behavioral studies, imaging studies, Klinefelter syndrome, lateralization, sex chromosomes*

Klinefelter syndrome (KS) is a relatively common genetic disorder affecting exclusively males. The endocrinologist Klinefelter first described the syndrome as an endocrine abnormality in 1942 (Klinefelter, Reitenstein, & Albright, 1942). The observations of Jacobs and Strong in 1959 recognized KS as a chromosomal disorder. They linked it with the presence of an extra X chromosome (Jacobs & Strong, 1959). The number of chromosomes which contain genes and DNA in the typical population is 46. A pair of these chromosomes, the sex chromosomes, determines gender. In females, the sex chromosomes are called X chromosomes (XX), while males have an X and Y chromosome (XY). The majority of males with KS have one extra copy of the X chromosome (47,XXY). Occasionally, variants of KS (XXY) involve more than one extra X chromosome or extra copies of both the X and Y chromosomes in each cell. The most common variation is the XY/XXY mosaic, in which some of the cells have an additional X chromosome, and the rest have the normal XY chromosome count. The percentage of cells containing the extra chromosome varies from case to case. KS has an incidence of between 1 out of every 500–1,000 male births and is identified during late puberty or early adulthood.

KS adolescents have a general typical appearance. However, the presence of one or more extra X chromosomes is responsible for specific endocrinological manifestations such as tall stature, smaller genitals, lower testosterone production, infertility, gynecomastia, and impaired spermatogenesis (Geschwind & Dykens, 2004). KS males are generally of normal intelligence. However, they demonstrate an atypical cognitive profile. The majority of the studies (e.g., Netley, 1986; Netley & Rovet, 1984) have indicated a significant discrepancy between performance IQ (PIQ) and verbal IQ (VIQ).

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Several studies (e.g., Mandoki, Sumner, Hoffman, & Riconda, 1991; Rovet, Netley, Keenan, Bailey, & Stewart, 1996) have suggested a decrease of approximately 10 or more points of the VIQ compared with normal PIQ. However, some investigations failed to confirm this observation especially in adults who may have developed alternative strategies to compensate for their weak verbal skills (Geschwind, Boone, Miller, & Swerdloff, 2000; Porter, Gardner, DeFeudis, & Endler, 1988).

The syndrome has been reported as associated with learning disabilities (Mandoki et al., 1991; Robinson et al., 1986) and delayed language development with difficulties in articulation, word retrieval, and phonemic processing (Bender, Linden, & Robinson, 1993; Netley & Rovet, 1984). In addition, cognitive testing in KS indicated specific impairments in executive skills. However, the pattern of impairment is task specific and varies across studies (Nielsen & Sorensen, 1984; Robinson, 1986; Temple & Sanfilippo, 2003). Subsequent difficulties in other areas (arithmetic, generalized knowledge) are also observed after the age of 10 (Geschwind et al., 2000; Stewart et al., 1982). In relation to motor skills, KS was associated with persistent deficits in gross and fine motor coordination (Geschwind et al., 2000).

The characteristic and distinct cognitive phenotype of KS has led to speculation on a left-hemisphere dysfunction, possibly via alteration in the typical pattern of cerebral lateralization, termed ''anomalous cerebral lateralization'' (e.g., Geschwind et al., 1998; Itti et al., 2003).

Cerebral lateralization refers to the functional and anatomical asymmetries between the two cerebral hemispheres. The scientific study of cerebral lateralization dates back to Broca's discovery in 1865, according to which the left cerebral hemisphere of right-handed people is dominant for language. It is now well established in the neuropsychological literature that the two cerebral hemispheres sub-serve different functions (cf., DeRenzi, 1982; Gazzaniga & LeDoux, 1978; Hecaen & Albert, 1978; Heilman & Valenstein, 1972; Springer & Deutsch, 1981). In general, the left hemisphere is considered to be dominant for verbal/linguistic processes and planned movements (praxis), whereas the right hemisphere is dominant for nonverbal processes especially those involved in visuospatial activities (Hecaen & Albert; McFie, Piercy, & Zangwill, 1950). Such a division of function has come to be termed ''complementary specialization,'' replacing the old prevalent theory of exclusive left-hemisphere specialization.

Anomalous cerebral lateralization, or otherwise termed anomalous dominance, refers to the atypical lateralization of language areas within the brain. Anomalous cerebral lateralization involves the inverse or weak dominance of hand, language, and visuospatial abilities (Geschwind & Galaburda, 1985a, 1985b). According to Geschwind and Galaburda (1985a), this atypical pattern of cerebral lateralization is established in early postnatal life, and it has been related to testosterone levels during fetal development. Previc (1994) postulated a distinction in the term atypical laterality into anatomical atypical asymmetry and functional atypical asymmetry. The term anatomical atypical asymmetry is observed in 30% to 35% of the population and is used to describe the decreased volume of the left hemisphere particularly in the area of the temporal lobe in comparison to the right hemisphere. The term functional atypical asymmetry is used to describe the bilateral or right-hemisphere dominance for language.

During the past decades, atypical cerebral dominance has been studied in a number of neurological conditions using handedness as an index of cerebral laterality. Research on atypical cerebral dominance in individuals with neurological conditions including individuals with mental retardation (e.g., Grouios, Sakadami, Poderi, & Alevriadou, 1999), Down's syndrome (e.g., Heath & Elliott, 1999), autism (Cornish & McManus, 1996), Fragile-X (Cornish, Pigram, & Shaw, 1997), and Turner syndrome (TS) (Ganou & Grouios, 2007) was initiated more than 80 years ago. Gordon (1921) was the first researcher who explored the hand preference in a group of individuals with mental retardation of mixed etiology and age-matched controls and noticed a twofold increase in left-hand preference in the former group. It has long been debated as to whether there is a cause-and-effect relationship between atypical cerebral dominance and neurodevelopmental disorders.

In this regard, although KS is typically associated with a verbal deficit, several studies indicated that the ability in processing visuospatial information remains intact (Bender, Linden, & Robinson, 1999; Robinson et al., 1986). These findings show the opposite pattern to TS individuals, who typically perform at an average level on tests measuring verbal ability but show a marked impairment on measures of visuospatial functions (Money & Alexander, 1966). It can be observed that the development of verbal and visuospatial ability is directly or indirectly related to the presence or absence of X chromosome (Netley & Rovet, 1984). KS has been studied much less extensively than TS. However, a comparison of the cognitive pattern between KS and TS is beyond the scope of this article.

A few studies have been conducted to determine whether atypical cerebral lateralization can explicate the characteristic neurocognitive profile in KS. The purpose of the current review was to appraise the relevant evidence concerning cerebral dominance in KS individuals. Accordingly, emphasis is placed on neuroanatomical findings derived from imaging studies along with

relevant behavioral data obtained from measures of handedness, dichotic listening, and half visual field procedures. With regard to neuroanatomical findings, there is limited information referring to the neuroanatomical localization of cognitive impairments seen in KS. Few neuroimaging studies (e.g., Itti et al., 2006; Patwardhan et al., 2002) have been conducted to date producing inferential results. Additionally, research based on behavioral measures received little attention.

The present article summarizes the ongoing research in this field, discusses the main findings, and attempts to provide a thorough description of the cause of the observed functional and anatomical cerebral asymmetries associated with the syndrome. Nonetheless, efforts have been directed to incorporate evidence for and against theoretical accounts that explain the experimental findings, to discuss issues involving the implications of the chosen methodology, and to present key research areas for future empirical research.

BEHAVIORAL STUDIES

The methodology of behavioral research to the evaluation and treatment of developmental disorders is in its primal and formative stage. There are several issues that are important. The first deals with acquiring adequate sample size within realistic time frames. Another issue related to the behavioral studies of individuals with developmental disorders is in the area of behavioral evaluation. More specifically, it is necessary to use a variety of tasks to evaluate performance across a wide range of cognitive abilities. This is a very critical method, especially because it is an effort of researching complicated relationships between structure and function in the brain of such an exceptional and infrequent population. The variations among tasks and the degree of variability among individuals with developmental disorders provide the ability to determine the location of dysfunction in the brain that may be associated with the observed behavioral decadent.

Given the limited natural resources and the complexity of problems in individuals with developmental disorders, it seems crucial that research has been directed to identify the functional outcomes. However, a limited number of behavioral researchers have focused on the study of KS. Taking into consideration the functional asymmetry of intact spatial versus impaired verbal ability, a circumscribed amount of studies focused on the examination of the pattern of cerebral dominance in KS individuals. Netley and Rovet (1982) measured handedness in 33 individuals with KS and compared them to a control group. Results showed an increased incidence of non-right handedness (24%) compared with control participants (10%). Increased non-right handedness was reported when measured with tasks assessing hand skill and not hand preference. Taking into account the dissociation between hand skill and hand performance that Geschwind et al. (1998) observed in individuals with KS, it was concluded that atypical cerebral dominance is more pronounced in tasks measuring hand skill than hand preference.

Ratcliffe and Tierney (1982) reported different findings from those of Netley and Rovet (1982). They examined handedness and hand performance in a group of 32 KS boys with a 47, XXY karyotype. Non-right handedness was not found to be statistically significant in the KS group. The authors stressed the importance of familial basis, instead of the developmental karyotype-based etiology that was proposed by Netley and Rovet (1982), as an explanation for the increased percentage of non-right handedness that was observed in their sample of males with KS. They further argued that to clarify the role of the abnormal karyotype is important to establish the consistency of the relationship between handedness and verbal deficit and measure handedness in three groups of KS participants: (a) a right-handed group; (b) a familial left-handed group; and (c) a non-familial left-handed group.

Bender, Pennington, Puck, Salbenblatt, and Robinson (1983) compared handedness and ear advantage between 14 boys with KS and a normally developing control group. Findings showed an increased incidence of right handedness in both groups. Similarly, a dichotic listening task revealed a consistent right-ear advantage in both groups. The authors suggested that the right-ear advantage that was evident in both groups possibly reflects a normal pattern of contralateral left-hemisphere prevalence for language.

Netley and Rovet (1984) assessed laterality in 32 individuals with KS on three primarily verbal and three nonverbal tasks, employing dichotic listening and half visual field measures for both types of tasks. The performance of individuals with KS was compared with that of a control group matched for age. The results showed that individuals with KS demonstrated reduced asymmetries on a left-hemisphere task and increased asymmetries on two right-hemisphere tasks compared with controls. Significant differences were not reported for the residual tasks, but the mean performance of the KS group was in the same direction. With respect to the reported findings, the authors stressed the primary role of the right-hemisphere involvement in both verbal and nonverbal processing, while they commented on the left-hemisphere involvement to a lesser extent. Atypical cerebral dominance was explained in terms of the inhibitory processes involved in the differentiation of function of each hemisphere and the divergent development of the two hemispheres (Corballis & Morgan, 1978).

Netley and Rovet (1987), based on the theory proposed by Geschwind and Behan (1982), examined whether atypical cerebral dominance is related to hormonal function. They employed the same behavioral procedure (three primarily verbal and three nonverbal tasks) on the same sample of KS individuals as in their previous study (Netley & Rovet, 1984). Hormonal concentrations of testosterone, estradiol, follicle-stimulating hormone and luteinizing hormone were measured using radioimmunoassay techniques. Pre-pubertal boys with KS showed no differences in the levels of hormonal functioning when compared to the control group. Moreover, following the theory of immature prenatal hemispheric development proposed by Corballis and Morgan (1978), Netley and Rovet (1987) measured total finger ridge count (TFRC), which is assumed to provide an index of prenatal rates of mitotic cell division (Barlow, 1973). The TFRC was found to be lower in individuals with KS in comparison to the control group, reflecting slow prenatal growth rates. The authors concluded that prenatal growth processes affect the development of hemispheric organization resulting in the specific cognitive profile observed in KS.

IMAGING-BASED STUDIES OF BRAIN STRUCTURE AND FUNCTION

The last few years have seen an explosion in the scope and scale of brain imaging studies. Imaging technology has rapidly advanced and so have the computational methods to analyze images. Patterns of brain structure and function associated with the major diseases of the brain can be visualized and analyzed (e.g., Altshuler, Bookheimer, Townsend, Proenza et al., 2008). Brain changes with time can be tracked with unprecedented sensitivity, shedding light on development and disease (e.g., Kessler, 2003). Dynamic effects of drug treatment on the brain can also be mapped (e.g., Lingford-Hughes, 2005). Brain imaging techniques have offered a broad range of investigative tools to basic and clinical research that fulfill the popular fantasy of being able to ''read the mind,'' albeit in the form of ''seeing the brain'' both structurally and functionally (Kerr & Denk, 2008).

Despite the large and growing literature describing patterns of brain structure and function in the diseased and healthy human brain, research on neurodevelopmental disorders has not been well integrated into the mainstream of human brain research. Nevertheless, a few investigators have demonstrated success in applying digital imaging technology in individuals with KS. For example, Warwick et al. (1999), using high-resolution magnetic resonance imaging (MRI), reported reduced whole brain volumes and enlarged right and left lateral ventricles in a group of 32 KS individuals compared with a control group. Moreover, IQ measures demonstrated a weak correlation with brain volumes. This finding is indicative of an opposite extra chromosome effect on brain development of KS individuals. However, the significance of these findings remains unclear.

In another MRI study, Patwardhan, Eliez, Bender, Linden, and Reiss (2000) investigated the neuroanatomical basis of the cognitive profile in KS. The authors were interested in examining the neuroanatomical effect of the extra X chromosome on the brain in the presence and absence of testosterone supplementation. Brain volumes of 10 individuals with KS, 5 of whom had received testosterone supplementation, were compared to an equally sized, matched for age, control group. The findings showed that whole brain and lateral ventricular volumes were not significantly different between KS participants and the control group. However, the group of five KS individuals who had not received testosterone supplementation demonstrated reduced left temporal lobe gray matter compared with the control group. KS was associated with left temporal gray matter reduction, a brain site which is responsible for the verbal deficits observed in KS. The comparison between the two groups (received testosterone supplementation/did not receive testosterone supplementation) was indicative of an androgen effect on KS morphology and cognition. Testosterone supplementation was associated with the preservation of left temporal gray volume in KS men. However, given the observed impairments that individuals with KS exhibit even before puberty when testosterone levels are normal, the effect of testosterone upon cognitive functioning is equivocal.

Patwardhan et al. (2002), considering the increased number of KS among individuals with schizophrenia, focused on the measurement of the hippocampus and the amygdale, the brain structures most frequently altered in individuals with schizophrenia. Medial temporal lobe structures were measured in 10 individuals with 47, XXX and 10 individuals with 47, XXY karyotypes. Their findings were compared to those of a control group of 20 individuals. No significant decrease was reported in whole brain and hippocampus volumes. However, reduced amygdale volumes were observed in men with 47, XXY karyotypes while the decrease in amygdale volumes was not clearly indicated for the group of women with 47, XXX. The findings were discussed in relation to the interactive role of hormonal and genetic influences that take action in early development.

Warwick, Lawrie, Beveridge and Johnstone (2003), considering the high incidence of KS among individuals with schizophrenia, examined an individual with KS who developed schizophrenia, using structural MRI. The authors suggested that a genetic site for schizophrenia may be located on the X chromosome. Furthermore, they hypothesized that the associated genetic site is

involved in the development of normal cerebral asymmetries. Their findings did not support the expected pattern of cerebral asymmetry, according to which in right-handers, prefrontal and temporal brain sites are enlarged on the right side compared with the left, while left occipital lobe sites are greater than right. On the contrary, MRI scans showed reversal of both prefrontal and temporal lobe asymmetries on the KS participant. The authors supported Crow's (1990) argument of an abnormal cerebral lateralization in schizophrenia possibly implicating a genetic site that can be found on the X chromosome.

Itti et al. (2003) focused on the examination of variation in brain perfusion and its possible association with the characteristic neurocognitive phenotype of KS. Single-photon emission computed tomography was performed on nine, right-handed KS participants. To assess their cognitive abilities, an extensive neuropsychological battery was administered to KS individuals. Their performance was compared to that of an equally matched control group of right-handed males. It has been suggested that in normally developing right-handed individuals, verbal skills are located in the left hemisphere, occurring mostly in the temporal lobe. However, the results showed evidence of the opposite pattern in KS participants, revealing a lack of a left-side cerebral perfusion asymmetry. Furthermore, in comparison with the control group, KS males had increased overall regional cerebral blood flow in many cortical regions located on the right side of the cerebellum. The authors suggested that individuals with KS exhibit an atypical pattern of cerebral laterality, with the right hemisphere being more involved in verbal processing. Consistent with earlier studies (Patwardhan et al. 2000), the atypical cognitive profile observed in KS cannot be considered an outcome of low testosterone stimulation, because KS individuals show cognitive deficits even before puberty where testosterone levels are normal.

Shen et al. (2004) investigated brain variation in 34 individuals with KS and compared them to a control group of 62 individuals, using a volumetric analysis of brain tissues from MRI images. Group differences in brain structures between individuals with KS and the control group were obtained. More specifically, individuals with KS had significantly reduced volumes in the regions of insula, temporal gyri, amygdale, hippocampus, cingulate, occipital gyri, and parietal lobe when compared with the control group. The observable altered structures are potentially associated with the dysfunctional abilities (e.g., verbal) seen in KS individuals.

DeLisi et al. (2005) examined whether the impact of the X chromosome on brain structural variation in individuals with KS is corresponding to the psychiatric and cognitive abnormalities that often characterize the specific population. They evaluated 11 adults with KS using diffusion tensor imaging, a structured psychiatric interview and a cognitive battery. Their performance was compared to that of 11 age-matched male controls. MRI scans revealed reductions (particularly superior temporal gyrus; STG) in temporal lobe and gray matter volumes with corresponding white matter tract abnormalities in the KS group. The majority of individuals with KS showed some form of psychiatric disturbance and deficits particularly in language processing and executive functions that were attributed to abnormalities in temporal and frontal lobe structures. The authors suggested that the presence of an extra X chromosome in KS is influencing the abnormal development of both gray and white matter in the frontal and temporal lobes which in turn may contribute to the specific cognitive deficits observed in KS males.

In a second MRI study, Itti et al. (2006) investigated brain morphometry in KS focusing on the examination of the possible relationship between brain structures and performance on neuropsychological tests. In the study, 18 individuals with KS were compared to an age-matched control group on brain MRI and neuropsychological testing of verbal and nonverbal skills. Inconsistent with the earlier study of Itti et al. (2003), decreased relative volumes were evident primarily in the region of the left temporal lobe in right-handed KS participants. In terms of neuropsychological testing, results showed suppressed verbal processing speed, whereas nonverbal skills were found impaired to a lesser extent. The authors supported the hypothesis of an altered gene contribution from the pseudoautomosomal locus (Geschwind et al., 1998) as the most plausible explanation for the neurocognitive profile of KS.

Giedd et al. (2007) used MRI to investigate the effects of the extra X chromosome in 42 males with KS aged from 5 years to 26 years old. The results of the 42 males in the sample were compared to those obtained from 87 males matched for age who were selected as controls. In terms of regional brain volumes and cortical thickness, the results showed specific effects of the extra X chromosome on brain development. Total cerebral and lobar volumes, except parietal white matter, were shown to be significantly smaller in the 42 males with KS, whereas lateral-ventricle volume was larger. In terms of cortical thickness, results showed widespread differences in the group of males with KS. More specifically, the cortex was found significantly thinner in the temporal lobes bilaterally and the left inferior parietal, frontal lobe and superior motor regions. The authors concluded that the current brain-imaging findings are consistent with the reported cognitive and behavioral strengths and weaknesses (i.e., executive dysfunction, impaired planning, and integration of motor movements, language dyspraxia) that characterize the syndrome.

DISCUSSION

The aforementioned studies, based on behavioral measures and imaging techniques, have attempted to define and locate the relevant brain area of dysfunction that is involved in the atypical cognitive performance of KS individuals. In regard to behavioral measures, collectively, the studies to date examining cerebral lateralization in KS individuals are focused on measures of handedness, visual field techniques, and dichotic listening procedures. Research conducted by Netley and Rovet (1982, 1984, 1987) supports an anomalous pattern of cerebral lateralization in KS individuals that is characterized by a greater-than-normal right-hemisphere implication in processes involving verbal and sometimes nonverbal stimuli. Low scores on tests measuring verbal skills in KS individuals led to the assumption of a left-hemisphere dysfunction. Overall, findings showed minor asymmetries on tasks measuring left-hemisphere processing (e.g., dichotic stop consonants) and larger asymmetries on tasks measuring right-hemisphere processing (dichotic melodies). In contrast to these data, a couple of follow-up studies have questioned the validity of these findings arguing that the cerebral lateralization of KS individuals is not different from that of the normally developing group (Bender et al., 1983; Ratcliffe & Tierney, 1982).

Despite the observed discrepancy between studies, the finding of reduced left-hemisphere involvement for verbal tasks and increased right-hemisphere involvement for nonverbal tasks suggests an anomalous cerebral lateralization in KS males. This pattern of atypical cognitive phenotype was thought to reflect developmental slowing both fetally and in early childhood for the KS population (Netley & Rovet, 1984). Slow maturation rates were further illustrated by reduced TFRC that was inversely related to verbal skills in KS syndrome (Netley & Rovet, 1987).

An alternative approach to the traditional assumption that holds that the left hemisphere is the verbal and the right hemisphere is the nonverbal, to conceptualizing hemispheric specialization has been suggested by Goldberg Vaughan, and Gerstman (1978) and Goldberg and Costa (1981) that is considered a more fundamental explanation of the functional differences between the two hemispheres. These researchers proposed that the left hemisphere is decisive for processing based on preexisting representations and routinized cognitive strategies. The right hemisphere is critical for the exploratory processing of novel cognitive situations to which none of the preexisting codes or strategies in the individual's cognitive repertoire readily applies. The traditional verbal/nonverbal dichotomy then becomes a special case of this more fundamental principle. This principle of hemispheric specialization is intriguing and addresses many shortfalls of the more traditional verbal/nonverbal distinction, because it meaningfully applies to any species capable of learning, emphasizes individual differences, argues against the fixed assignment of particular materials and tasks to one or the other hemisphere, and offers a dynamic rather than a static view of hemispheric specialization (Podell, Lovell, & Goldberg, 2005).

Turning to the developmental delay etiology, the patterns of atypical dominance that are evident in KS are thought to reflect abnormal hormonal influences that take place at puberty. According to Geschwind and Galaburda (1985a, 1985b) the cause of the atypical dominance has been related to the secretion of testosterone during fetal development which has consequences to the immune system. More specifically, the main correlate of laterality is proposed to be related to the hormonal environment of the embryo which induces the larger proportion of the population to be right-handed, left-hemisphere language dominant, and right-hemisphere visuospatial dominant. Any departure from this typical hormonal environment may trigger anomalous dominance. Low testosterone stimulation in KS boys (Boone et al., 2000; Ratcliffe & Tierney, 1982), in combination with normal or high levels of estradiol, may disrupt the function of the right hemisphere. It is possible that the verbal deficits observed in the KS population arise from anomalous cerebral lateralization, which is in turn caused by androgen deficiency. However, it should be noted that androgen deficiency in KS does not appear until puberty. Therefore, it is reasonable for researchers in this field to assume that sex hormones affect at some level the development of hemispheric organization; it remains controversial whether low testosterone concentration has a direct and predictable impact upon hemispheric organization and cognition in KS.

As already mentioned, most evidence for cerebral lateralization has been based on behavioral measures, the validity of which has been questioned. According to Bishop (1980), in specific cases, left handedness should be examined separately with a familial, developmental, and environmental basis. However, although the validity of handedness is debatable, it is distinctly reliable, because within non-right-handed populations, the percentage of individuals with left-hemisphere specialization for language is higher.

Although, people with sex chromosome abnormalities exhibit a variable neurocognitive profile, the verbal disability observed in XXY, XXX, and XYY individuals suggests that a gene common to the X and Y might be responsible for the verbal deficiency shared among the patients with sex chromosome aneuploidies (Geschwind et al., 1998). In relation to this argument, it is notable that TS individuals demonstrated the

opposite pattern of deficits from that evident in KS (Netley, 1986). In terms of lateral preference, in individuals with XO, it is hypothesized that left-hemisphere specification for language would benefit at the expense of right-hemisphere functioning, while in individuals with XXY, left-hemisphere specification for language would suffer and right-hemisphere functioning would remain unimpaired (Geschwind et al., 1998; Netley & Rovet, 1987).

In regard to imaging-based studies of brain structure and function, it is apparent that despite the usefulness of imaging research for providing evidence for cerebral lateralization in KS, only a limited number of imaging studies have been conducted to date. The evidence obtained from the aforementioned data has been conflicting and inferential. While some researchers (i.e., Warwick et al., 1999) point out reductions of whole brain volumes in KS population, others (i.e., Patwardhan et al., 2000) demonstrate reductions of left temporal lobe gray matter in KS individuals who did not receive testosterone therapy. Depletion of androgen detected in puberty may lead to a feminization of the brain, disrupting the typical process of right-hemisphere functioning. Although testosterone supplementation may prove useful in reversing the neurocognitive characteristics, its impact still remains a controversial issue because various factors (concentrations of metabolizing enzymes and different effects of testosterone mediated by androgen and estrogen receptors in dissimilar organs) seem to play a crucial role.

The available evidence to date does not establish whether inter-hemispheric processing is atypical in KS in comparison to the normal population. This is partially due to the fact that despite the high incidence of KS syndrome, a very limited number of studies was conducted, producing rather inferential results. These contrasting findings may have been the result of the assessment of a different type of skills in the experimental population, of different study designs, instrumentation, sample composition, and size, or of the methods used for data collection and analysis. It should be noted that different laterality measures have been used to assess hand preference in KS individuals, and also various age groups have been selected for each study. In general, caution must be taken when comparing results between different studies. Methodological issues are at least as important as etiological factors for the comprehension of cerebral dominance in KS.

The development of reliable and valid behavioral measures such as dichotic listening and handedness to assess cerebral laterality in individuals with KS is of vast importance. Behavioral measures are easy and safe to administer to such populations and provide significant information. Research focusing on the use of behavioral measures provides insight into the functioning of the brain and its lateralization by accumulating evidence for the representation of cognitive systems within the brain.

On the other hand, studies using structural imaging techniques such as MRI scans obtain an extra set of measurements in addition to behavioral measurements. Structural imaging methods allow for more detailed theory testing and inference on perceptual and cognitive processes by detecting correlations between brain activation and the task the participant performs during the scans. Structural imaging experiments attempt to explain human cognition and behavior in terms of physical (anatomical) mechanisms and allow relating these to specific brain structures. Ultimately, structural imaging techniques in combination with behavioral measures could result in the presentation of certain brain areas that are predominately involved in specific processes and in the determination of other areas that are unable to execute their intended function.

DIRECTIONS FOR FUTURE RESEARCH

The present review of the relevant literature shows a substantial amount of inconsistency. On a conceptual level, there is recognition among these studies that the prediction and understanding of cerebral dominance in KS population requires a multivariate, bio-psychosocial perspective. Results from these studies indicate that mild–to-moderate alterations in brain structures along with difficulties in performing certain behavioral measures assessing laterality are a frequent finding in KS males. Although the different substantive cognitive areas represented by the collection of studies seem to have acted to different degrees, there is general agreement that hormonal and genetic factors may be plausible explanations for the atypical hemispheric organization observed in KS. Along these lines, the understanding of hormonal and genetic factors requires the consideration of any one factor in the context of others. Future structural and functional measures should focus on the investigation of the interaction of these two factors in the same group of individuals.

Further studies using a larger sample size in combination with task-specific activation procedures are needed to determine the functional consequences of the altered volumes seen in KS males. In addition, to determine the effects of exogenous testosterone supplementation on cognition in KS individuals, a longitudinal study of never-treated adolescents administered either standardized hormone replacement or placebo is essential. In summary, there is a need to continue and expand the research in this field particularly in the light of X-linked effects in areas of cognitive strengths and weaknesses to improve our knowledge of the cognitive phenotype of KS.

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