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Review

Social cognition in Turner's Syndrome

Alice C. Burnett [a], David C. Reutens [a,b,*], Amanda G. Wood [a,c]

[a] Department of Medicine, Southern Clinical School, Monash University, Melbourne, Victoria, Australia
[b] Centre for Advanced Imaging, QBI Building 79, Upland Road, University of Queensland, St Lucia, Brisbane, Queensland 4072, Australia
[c] Critical Care and Neurosciences, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia

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ABSTRACT

Turner's Syndrome (TS), or X-monosomy, is a common chromosomal disorder in women, and provides a valuable paradigm to investigate genotypic contributions to social cognition. We review evidence suggesting that some facets of social cognition, particularly emotion recognition and gaze perception, are impaired in women with TS, despite the absence of a global social-processing impairment. Further, these deficits co-exist with neuroanatomical abnormalities of the amygdala and other regions implicated in social processing. A parallel is drawn between the non-verbal profile of sociocognitive dysfunction in TS and autism spectrum disorders, possibly underpinned by genomic imprinting effects. TS provides a unique opportunity to identify genetic, and particularly sex chromosome, influences on social cognition and behaviour.

1. Introduction

Impaired social cognition is sometimes a prominent feature of neurological disorders affecting the frontal lobes and limbic system, such as frontotemporal dementia. Studies of the effects of brain lesions have contributed substantially to our understanding of the neurobiology of social cognition. The study of genetic disorders is an important extension of this paradigm, potentially providing insights into genotypic influences on social behaviour.

Turner's Syndrome (TS) is one of the most common chromosomal disorders in women, affecting around 1 in every 2,500 live births. It occurs when one X-chromosome in a phenotypic female is missing, and it therefore produces, in the classic case, a karyotype of 45,X rather than the usual female karyotype of 46,XX. Physically, TS commonly results in ovarian failure with consequent oestrogen deficiency. Substantial inter-individual variability exists; however, the physical characteristics of TS usually include short stature, webbing of the neck, micrognathia, and low-set ears and hairline.[1] TS is also associated with a consistent neurocognitive profile.[2,3] The cognitive phenotype of TS includes relatively strong verbal IQ but deficits in visuospatial perception and memory, motor abilities, and attentional processes.[4]

Although social competence is not grossly impaired in TS, specific deficits in aspects of social processing have been identified. In contrast to some cognitive deficits associated with TS, which have been widely researched, the social and emotional difficulties these women face have received relatively little attention.

2. Psychosocial skills are commonly impaired in Turner's Syndrome

TS is not characterised by increased risk of psychiatric illness relative to women attending gynaecological clinics or healthy controls. Nonetheless, TS is associated with increased risk of psychosocial difficulties and below-average social competence.[3,5,6] Girls with TS tend to have fewer friends, to engage in fewer social activities, to have greater attentional and social difficulties, and to withdraw from social interactions more often than do controls.[7,8] Studies of adolescent girls with TS have revealed the potential for social difficulties, although these difficulties are not ubiquitous, and, in the main, do not substantially interfere with day-to-day functioning of affected adolescents.[5] Past research has identified adjustment problems including immaturity, poor concentration and poor peer relationships in adolescents with TS,[3] despite normal conversational language abilities.[6]

Comparison of girls with TS and their normal-karyotype sisters indicates that greater social and attentional problems in the girls with TS cannot be ascribed purely to familial environment.[9] Further, parents of girls with TS rate their daughters as less socially competent compared to those of short-statured and typical-height controls, indicating that elements of the syndrome beyond short stature influence social relationships.[2,3,5] Peer teasing about body appearance, however, has been shown to be the most significant predictor of depression and self-image in adolescents with TS,

* Corresponding author. Tel.: +61 7 3346 6374; fax: +61 7 3346 6301.
E-mail address: d.reutens@uq.edu.au (D.C. Reutens).

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exceeding the influence of body shape and height dissatisfaction, although this evidence was derived from girls with heterogeneous karyotypes.[10]

Social difficulties in women with TS do not appear to end after the tumultuous adolescence. Women with TS seem more likely to be delayed in achieving adult sexual and social developmental milestones compared with norms.[11] Research with young adults with TS has shown a self-perception of poor social competence among women with mixed TS karyotypes when compared with controls, and of greater withdrawal from peer-interactions among women with 45,X karyotypes compared with other karyotypes.[12] Women with TS, along with karyotypically normal women with premature ovarian failure, have also reported heightened levels of shyness, social anxiety, depression, and decreased self-esteem in comparison with healthy women.[13] This finding contrasts with evidence from adolescents with TS showing typical levels of social anxiety.[5] These findings in adults, however, are not universal. In a Swedish study, women with TS, regardless of karyotype, rated themselves as more sensation-seeking and less socially withdrawn than norms, indicating divergence between the subjective and objective assessments of social difficulties reported elsewhere.[14] As Ross and colleagues noted, most women with TS are well-educated and find gainful employment, but nevertheless experience enduring self-esteem problems.[4] Women with TS are also less likely to have intimate partners than are other women, and leave the parental home and have their sexual debuts later in life.[4,11]

3. Haploinsufficiency and genomic imprinting in TS

In normal women (46,XX), one of the two X-chromosomes is randomly inactivated, although some genes on that chromosome escape inactivation. Two copies of the latter genes are assumed to be required for normal female development. Haploinsufficiency of these genes in women with TS (45,X) is presumed to play a role in determining the TS phenotype.[15] Females with mosaic TS (karyotypes other than the "pure" 45,X) typically demonstrate a more variable phenotype than 45,X women.[16–18] A "dosage-effect" hypothesis was proposed to account for this observation, reflecting the varying "dosage" of X chromosome material.[17,19–21]

The parent of origin of the intact X chromosome may also affect the phenotype of classical TS, providing support for imprinted loci on the X chromosome.[22–24] A much-cited study demonstrated that women with TS whose maternal X chromosome is active (45,X_m) tend to perform more poorly on measures of social cognition and adjustment than do women whose paternal X chromosome is active (45,X_p).[23] Controversy remains, however, over the degree and direction of parent of origin effects on cognition. Skuse and colleagues found that verbal IQ was significantly lower in 45,X_m women than in 45,X_p women. Across the sample as a whole, verbal IQ correlated negatively with a measure of social dysfunction in the 45,XO ($r = -0.41$), where high scores reflected worse social abilities; better verbal skills appear associated with intact social abilities. Conversely, Loesch et al.'s study suggests that inheritance of the paternal X-chromosome was associated with lowered verbal cognition relative to the maternal X-chromosome.[25] As Ross et al. noted, Skuse and coworkers' findings are yet to be independently replicated[26] and it is premature to draw robust conclusions from the literature.

4. Core emotion and face processing deficits may underlie the difficulties women with TS experience in social settings

Sociocognitive processes such as emotion recognition and gaze have been reported as aberrant in the TS population. Lawrence et al.'s study of 45,X_m women revealed statistically (but not clinically) significant impairment in face recognition, irrespective of depressed performance intelligence quotient (PIQ) score.[27] This finding supports earlier work identifying facial recognition and "fear" and "surprise" recognition deficits in adolescents and young women of mixed TS karyotype.[28] Lawrence et al.'s (2003) results indicate that alterations in processes other than visuospatial processing impair memory for faces in women with TS, as PIQ did not covary significantly with recognition and processing style appeared not to differ from the TS participants to controls. These researchers proposed that the neural circuitry underlying learning and memory for faces was anomalous, and suggested that abnormalities in the amygdala and hippocampal region were contributory. Women with TS in this study also performed significantly more poorly than controls in recognition of "fearful" and "angry" faces, strongly reminiscent of the cognitive profile after amygdalar damage.[29] Skuse et al. and Mazzola et al. observed that women with 45,X_m TS showed an impairment in cognitive appraisal of fearful faces, recognising "fear" in facial expressions significantly more poorly than controls irrespective of PIQ.[30,31] Recently, women with 45,X_m TS were shown to have deficits in attributing mental states to inorganic animations, suggesting an impairment in mentalising that extends beyond facial processing and which may represent a more global "theory of mind" disruption.[32]

The mechanism underlying alterations in emotion recognition in TS is not well understood. Lawrence et al. point to prior evidence that men are poorer than women at recognition of facial affect,[32] and that fear recognition and face recognition do not correlate in men but do so positively in healthy women.[33] A parallel may be drawn here between Lawrence and colleagues' TS data and that of healthy men; both groups inherited the maternal X-chromosome and do not possess any X_p-linked genes that escape inactivation in healthy women, and both demonstrate decrements in face and affect recognition compared to healthy women.[34] Genotypic analysis has indicated a potential genetic locus for fear recognition, without evident parent-of-origin effects.[35]

Another critical aspect of social interaction is the identification of gaze direction.[36,37] In TS, this is not globally impaired, and women are largely able to detect the direction of allocentric gaze, or non-engaged gaze without a direct social component.[38] Accuracy in allocentric gaze identification deteriorates, however, when only the gazer's eyes, rather than eyes and face, provide directional cues. In Elgar et al.'s task, women with both 45,X_m and 45,X_p TS were impaired in identifying whether or not a pictured female was engaging gaze with them or with a horizontally displaced location. The results of this study suggest that women with TS have difficulty discriminating similar angles of view from a face with engaged and averted gaze.

5. The neuroanatomical substrate of emotion processing may be abnormal in Turner's Syndrome

The amygdala has a crucial role in social cognition and, particularly, the processing of emotionally salient visual information.[37] Kluver and Bucy's seminal studies of primates after bilateral temporal lobectomy showed strikingly inappropriate behaviour in social contexts and a greatly diminished fear response to the extent that the term "psychic blindness" was applied to the behaviour.[39] More recent primate and human studies, with lesions more confined to the amygdala, were able to dissociate performance of social behaviours from social cognitive processes.[40–42] In humans, the amygdala has been implicated in the recognition of emotions from facial expressions, with consistent evidence for a particular role in processing negatively-valenced facial expressions, in the detection of gaze direction and eye contact, and in the mediation of arousal engendered by affective stimuli.[29,30,43–45] But the amyg-