Neuroscience and Biobehavioral Reviews 80 (2017) 263–275

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# Mapping the effect of the X chromosome on the human brain: Neuroimaging evidence from Turner syndrome

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ARTICLE INFO

*Keywords:*
X chromosome
Turner syndrome
Magnetic resonance imaging (MRI)
Human brain
Imaging genetics
Sex difference

ABSTRACT

In addition to determining sex, the X chromosome has long been considered to play a crucial role in brain development and intelligence. Turner syndrome (TS) is caused by the congenital absence of all or part of one of the X chromosomes in females. Thus, Turner syndrome provides a unique "knock-out model" for investigating how the X chromosome influences the human brain in vivo. Numerous cutting-edge neuroimaging techniques and analyses have been applied to investigate various brain phenotypes in women with TS, which have yielded valuable evidence toward elucidating the causal relationship between the X chromosome and human brain structure and function. In this review, we comprehensively summarize the recent progress made in TS-related neuroimaging studies and emphasize how these findings have enhanced our understanding of X chromosome function with respect to the human brain. Future investigations are encouraged to address the issues of previous TS neuroimaging studies and to further identify the biological mechanisms that underlie the function of specific X-linked genes in the human brain.

## 1. Introduction

In addition to determining physical phenotypes (e.g., skin color, body height or biological sex), genotype plays a crucial role in various cognitive/behavioral abilities (McGue and Bouchard, 1998; Plomin, 1991; Plomin et al., 1994). The brain serves as a valuable endophenotype that bridges the gap between molecular genetics and complex behaviors (Plomin and Kosslyn, 2001; Thompson et al., 2002).

In previous decades, many cutting-edge neuroimaging techniques have been applied to investigate human brain structure and function in vivo. Numerous recent studies have combined both genetic and neuroimaging analyses to identify associations between genetic variations and neuroimaging phenotypes of the human brain. This line of research is referred to as imaging genetics; it may provide valuable insight into the mechanisms of how specific genes affect brain endophenotypes and ultimately shape cognitive/behavioral functions during normal development and/or in complex brain disorders (Bigos and Weinberger, 2010).

### 1.1. X chromosome

The X chromosome is one of two sex chromosomes in humans and contains approximately 1000 genes (~4% of the human genome) (Ross et al., 2005). In typically developing (TD) women with a normal karyotype (46, XX), one of the two X chromosomes is randomly inactivated, leading to equal expression of X-linked genes with men (46, XY). However, a subset of genes escapes the X-inactivation (Carrel et al., 1999; Disteche, 1999) (Fig. 1), most of which are located on the tips of the X chromosome, namely, the pseudoautosomal regions (PARs). In contrast to the majority of the X chromosome genes, genes in these PARs remain capable of meiotic recombination with the same homological region on the Y chromosome; thus, either sex may receive two copies of genes in PARs (Heard and Disteche, 2006; Helena Mangs and Morris, 2007).

Notably, the X chromosome has long been considered to play a crucial role in the development of the human brain and intelligence (Johnson et al., 2009; Lehrke, 1972; Turner, 1996). As demonstrated by genomic data, many X-linked genes are involved in postsynaptic protein coding, which is essential for neuronal plasticity and cognitive processes (Laumonnier et al., 2007; Swingland et al., 2012). Moreover, X-linked genes have been demonstrated to have increased gross expression level in brain tissues in both humans and mammals, which further supports an essential role of the X chromosome in brain development and mental functioning (Nguyen and Disteche, 2006). Animal studies

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http://dx.doi.org/10.1016/j.neubiorev.2017.05.023
Received 23 August 2016; Received in revised form 7 April 2017; Accepted 26 May 2017
Available online 04 June 2017
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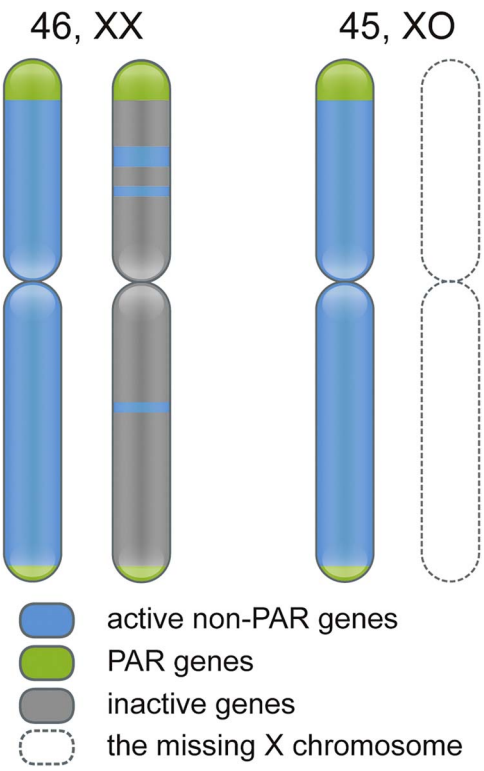


**Fig. 1.** Schematic structures of X chromosomes in typically developing (TD) and 45, XO Turner syndrome (TS) women. In TD women, one of the two X chromosomes is inactivated, which is referred to as X-inactivation. However, a number of X-linked genes escape from this process and remain active on the inactivated X chromosome. These genes were shown in color on the inactivated X chromosome in 46, XX women, with genes within pseudoautosomal regions (PAR) colored green and other genes colored blue. In contrast, there is no X-inactivation process in 45, XO TS women as a result of the congenital loss of one X chromosome. Essentially, the 45, XO TS women lack the expression or activities of the escaped genes on the inactivated X chromosome compared with TD women.

have demonstrated the involvement of X-linked genes, particularly in cognition-related molecular pathways. For example, increased fear reactivity was reported in 39, XO mice compared with normal 40, XX mice, which indicates a dosage effect of the X chromosome on emotional processing (Isles et al., 2004). At the gene level, overexpression of the X-linked gene NR2B facilitated learning and memory in transgenic mice (Tang et al., 2001).

In humans, X-linked gene defects have been disproportionately identified in various psychiatric disorders and particularly in mental retardation (Ropers and Hamel, 2005; Skuse, 2005). Empirically ascertaining the patterns in which the X chromosome influences human brain structure and function is of particular importance for understanding sex differences in the brain and cognition for elucidating sex-specific incidences and symptom presentation for many neuropsychiatric disorders (Cahill, 2006; Holden, 2005). However, empirically investigating how the X chromosome influences the human brain remains technically challenging, particularly in vivo.

### 1.2. Turner syndrome

Turner syndrome (TS) is a human disorder caused by a partial or complete absence of one X chromosome in women, which occurs in ~1 per 2500–3000 live female births (Sybert and McCauley, 2004). Approximately half of TS individuals exhibit a complete loss of one X chromosome, termed X-monosomy (45, XO karyotype) (Fig. 1), whereas approximately 10% of TS individuals exhibit structural abnormalities in one of the two X chromosomes (e.g., deletions on Xp and Xq or an isochromosome with two q arms) or more complex X chromosome abnormalities (Sybert and McCauley, 2004). The remaining TS individuals have a cryptic mosaicism and exhibit more than one cell line, such as a 45, XO cell line and either a 46, XX cell line or other cell lines (Sybert and McCauley, 2004).

The common TS physical manifestations include short stature, gonadal dysgenesis, and infertility (Hong and Reiss, 2014; Ranke and Saenger, 2001). The cognitive phenotypes of TS are characterized by severe deficits in multiple cognitive domains, including visual-spatial ability, mathematical processing, and social cognition (Hong et al., 2009; Hong and Reiss, 2014). Regarding general intelligence, numerous TS studies have demonstrated a lower performance IQ in contrast to a within-normal verbal IQ in TS individuals (Garron, 1977; Lahood and Bacon, 1985; Pennington et al., 1982; Rovet, 1993; Shaffer, 1962; Silbert et al., 1977; Temple et al., 1996). Specifically, verbal cognition, such as phonological processing, receptive vocabulary, and reading comprehension, are well preserved in TS; however, several non-verbal abilities, including attention, working memory, cognitive flexibility, visual-spatial skills, executive function, and abstract reasoning, have been demonstrated to be worse compared with TD women (Ross et al., 1996; Skuse et al., 1997; Temple and Carney, 1995). In addition, poor mathematical processing and social skills have frequently been reported in TS girls (Hong et al., 2011; McCauley et al., 2001; Mccauley et al., 1987; Rovet and Ireland, 1994; Rovet et al., 1994; Skuse et al., 1997). Difficulties in these domains may severely affect academic achievement and adaptive functioning of TS individuals.

Both physical and psychological features highly vary across women with TS as a result of the varied structural defects on the X chromosome or mosaicism (Bharath et al., 2010). In general, small deletions on the X chromosome or mosaicism likely manifest fewer and subtler TS features, whereas large deletions, critical region deletions, or non-mosaicism karyotypes may result in the full spectrum of TS features. Accordingly, most typical TS phenotypes are expected to occur in women with TS who express a 45, XO karyotype, i.e., X-monosomy.

Interestingly, TS individuals can be regarded as a natural human "knock-out model" of the X chromosome and, therefore, represent a valuable opportunity to investigate the function of the X chromosome in humans. Many neuroimaging techniques have been applied to TS individuals, which have provided valuable insight into the role of the X chromosome in human neural systems (Hong and Reiss, 2014; Printzlau et al., 2017). For example, structural and diffusion magnetic resonance imaging (MRI) studies have demonstrated specific abnormalities in the cortical gray matter (GM), subcortical nuclei, and the white matter (WM) in TS individuals. In addition, specific alterations in human brain activity/function have been identified using various functional neuroimaging techniques, such as positron emission tomography (PET) and functional MRI (fMRI). A list of previously published neuroimaging studies of TS is provided in Supplementary Table 1.

This review aims to summarize the recent progress in TS-related neuroimaging studies and to emphasize how these findings have enhanced our understanding of the influences of the X chromosome in the human brain. In addition, current issues and future considerations in this field are elaborated. The neuroimaging findings of TS are herein organized into five categories: 1) GM morphometry; 2) WM integrity; 3) functional activity/connectivity; 4) brain-behavior relationships; and 5) confounding factors. Issues and future considerations cover four topics: 1) neuroimaging brain phenotypes; 2) relating brain abnormalities to cognitive deficits; 3) differentiating between genetic and hormonal effects; and 4) investigating beyond the TS model.

## 2. Neuroimaging findings in TS

### 2.1. GM morphometry

Structural MRI (sMRI) is the most frequently used neuroimaging modality for studying TS individuals. This particular type of MRI can provide an image contrast between brain tissues (i.e., GM, WM, and

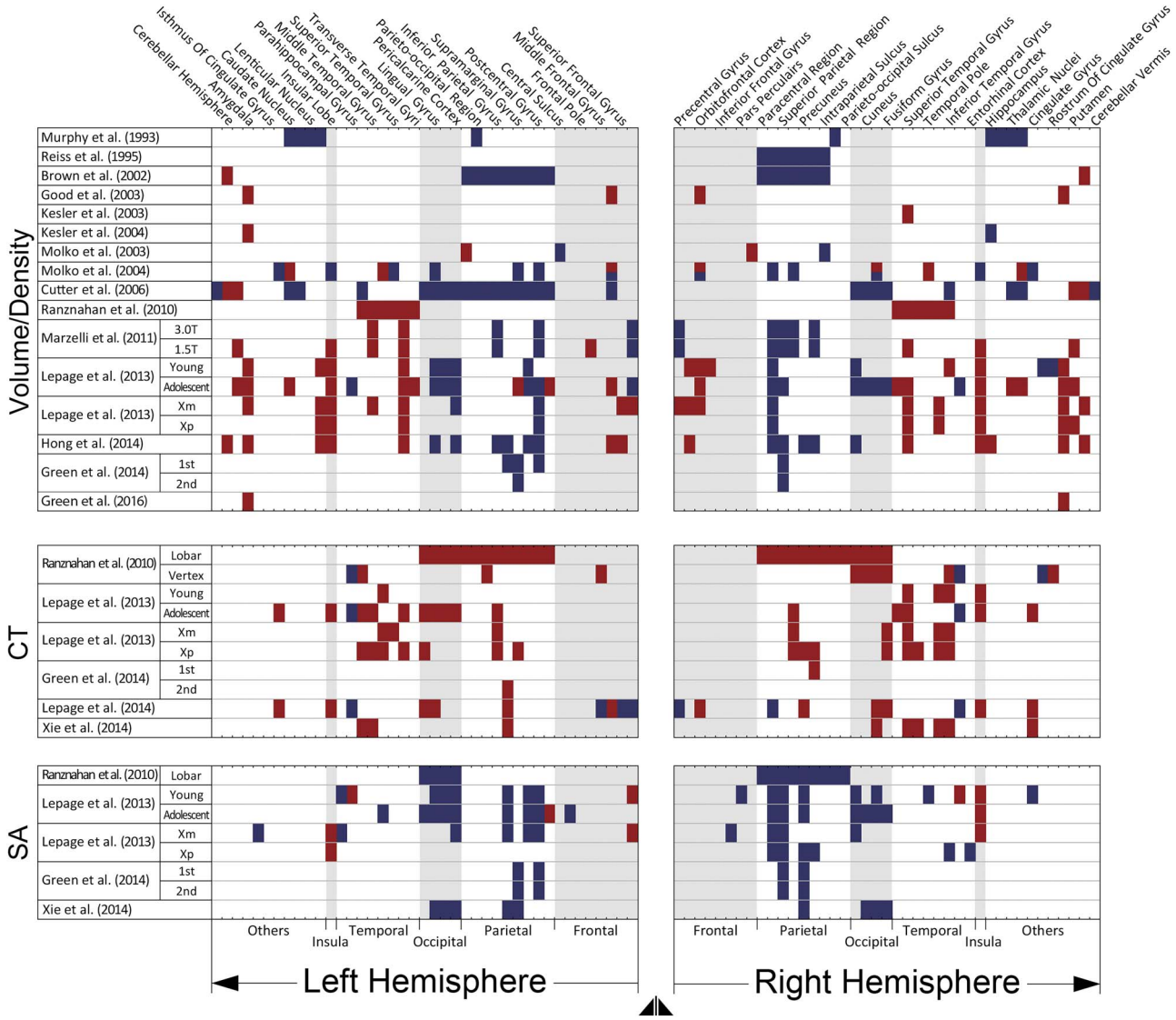


**Fig. 2.** Block chart summary of published gray matter (GM) morphometric findings in TS. The GM morphometric measures derived from structural MRI included GM volume/density, cortical thickness (CT) and surface area (SA). The studies are listed in chronological order. The block chart is divided according to left and right brain hemispheres, with the location arrangement mirrored along the central vertical line. The color of the blocks indicates the direction of the difference between TD controls and TS individuals. Blue: the value of the brain measure is significantly decreased in TS; red: the value of the brain measure is significantly increased in TS. All region of interests (ROIs) are labeled at the top of the block chart, with one-half in the left hemisphere and the other half in the right. Notably, the ROI set was post-selected/post-defined according to a set of text phrases for all reported brain regions in prior studies. To determine the selected ROIs, four qualitative criteria were applied: 1) the least amount of overlap among ROIs as possible; 2) covering all reported significant regions in the TS studies; 3) including a frequently reported name as generally well-known in the literature; 4) reporting a spatial resolution lower than the entire cortical gyrus/sulcus and subcortical nuclei. Each reported significant brain region was then carefully assigned to one of the post-selected/post-defined ROI sets.

CSF) and, therefore, enable accurate quantification of the size/volume, position, and shape of brain tissues or anatomical structures (Symms et al., 2004). Using sMRI, numerous studies have demonstrated GM morphometric abnormalities in TS individuals, as summarized in Fig. 2. The reported morphometric measures include GM/WM volume or density, cortical thickness (CT)/surface area (SA), and deep subcortical structure volume/shape.

As shown in Fig. 2, Murphy and colleagues conducted the first neuroimaging study of TS using sMRI, which revealed bilateral volume reductions in both parietal-occipital regions and subcortical structures in TS adults compared with controls (Murphy et al., 1993). Reiss and colleagues further identified reduced volume in the right parietal region in TS children (Reiss et al., 1995). In these early pioneering studies, prior regions of interest (ROIs) or anatomical structures were manually outlined on sMRI. Later, automated computational methods were predominately applied, e.g., the well-known voxel-based morphometry (VBM) and surface-based morphometry (SBM). The VBM approach can locate group differences in the GM/WM density or volume (GMD/GMV) by searching the entire brain. Similarly, SBM analysis implements the same search strategy on the cortical surface and focuses on two lower-order spatial properties of cortical volume: CT and SA. Notably, CT and SA are genetically and phenotypically independent (Winkler et al., 2010); therefore, it is highly recommended to analyze these two measures separately in genetic diseases, such as TS.

Consistent with the findings of the early studies that manually outlined ROIs (Murphy et al., 1993; Reiss et al., 1995), VBM studies of TS have consistently demonstrated reductions in GM density or volume around the parietal and occipital lobes (Brown et al., 2002; Cutter et al., 2006; Green et al., 2014; Holzapfel et al., 2006; Hong et al., 2014b; Lepage et al., 2013a; Lepage et al., 2013b; Marzelli et al., 2011), whereas only one VBM study identified an enlarged GM cluster around the right superior lingual gyrus in TS (Molko et al., 2004). These parietal-occipital volume abnormalities are likely associated with impairments in visuospatial, attention, and executive functions in TS (Brown

et al., 2002; Cutter et al., 2006; Green et al., 2014; Holzapfel et al., 2006; Hong et al., 2014b; Lepage et al., 2013a,b; Marzelli et al., 2011; Murphy et al., 1993; Reiss et al., 1995). In the vast majority of SBM studies, increased CT and reduced SA in the parieto-occipital region were found in TS subjects (Green et al., 2014; Lepage et al., 2014; Lepage et al., 2013ab; Raznahan et al., 2010; Xie et al., 2015), indicating that the identified volumetric reductions in these regions were mainly driven by atrophy of cortical SA rather than CT. Another consistent finding across TS morphometric studies is enlarged superior temporal gyri (STG) and increased CT around the temporal lobe (Kesler et al., 2003; Lepage et al., 2013ab; Marzelli et al., 2011; Raznahan et al., 2010; Xie et al., 2015). These findings may be related to the relatively preserved verbal skills in TS (Hong et al., 2009; Marzelli et al., 2011).

However, reported findings of cortical morphometry, e.g., in the prefrontal cortex, have been inconsistent. For example, some previous VBM studies reported increased GM density or volume of the orbitofrontal cortex in TS (Good et al., 2003; Hong et al., 2014b; Lepage et al., 2013a), whereas others reported decreased GM density or volume (Cutter et al., 2006; Molko et al., 2004). Based on SBM analyses, the middle frontal gyrus of TS subjects was reported to be thicker in Raznahan et al. (2010) but thinner in Lepage et al. (2014). These contradictory findings might be related to differences in sMRI computational methodologies, the age range of subjects, and TS subject inclusion criteria among studies. However, it should be noted that cortical morphometric findings of the parietal, occipital, and temporal lobes in TS are relatively consistent across studies relative to the prefrontal cortex. This contrast could imply tenuous or unstable effects, or a smaller effect size of X chromosome loss on the cortical morphometry of the prefrontal cortex.

In addition to the cortical morphometric aberrations, the size of deep subcortical structures has also been repeatedly investigated in TS. Multiple sMRI studies have consistently demonstrated volumetric changes of the amygdala and hippocampus in TS, which may underlie abnormal affective processing (e.g., facial affective recognition and social functions) (Good et al., 2003; Green et al., 2016; Hong et al., 2014b; Kesler et al., 2004; Lepage et al., 2013a,b; Murphy et al., 1993). Particularly, complex shape analyses have been applied to the amygdala in TS, which may facilitate the identification of specific local shape changes in the amygdala. Specifically, increased radial distances in TS children have been reported in areas of the basomedial and basal nuclei, expanding to the lateral nucleus in the left amygdala (Green et al., 2016). Consistently, another study demonstrated surface shrinkage around the laterobasal subregion of the left amygdala in TS adolescents (Li et al., 2016). Abnormalities of specific amygdala sub-nuclei, reflected in local shape changes, may play critical roles in face emotion processing and anxiety in TS.

### 2.2. WM integrity

WM tissue is primarily composed of neural fibers that connect various GM structures. sMRI has been applied to estimate morphometric measures for WM, including the manually outlined or VBM-based WM density/volume (WMD/WMV). These sMRI-derived measures putatively reflect WM integrity (Walhovd et al., 2014). As summarized in Table 1, WMD/WMV of TS individuals has been repeatedly demonstrated to be decreased in WM regions adjacent to the parietal and occipital cortices but increased around the temporal cortex (Cutter et al., 2006; Green et al., 2014; Holzapfel et al., 2006; Kesler et al., 2003; Lepage et al., 2013a; Molko et al., 2004; Reiss et al., 1995; Yamagata et al., 2012). These WM abnormalities indicate a disruption of brain connectivity, which may also contribute to the specific cognitive deficits in TS.

In addition to these WM morphometric changes, several TS studies have demonstrated abnormalities in the WM integrity using diffusion MRI (dMRI), a technique that has been widely applied to investigate the WM microstructure by measuring random motions of water molecules (Basser and Jones, 2002). The two most commonly used imaging indices derived from dMRI are fractional anisotropy (FA) and mean diffusivity (MD), which are effective indicators of axonal density, axonal diameter, and the degree of myelination of neural fiber microstructures (Beaulieu, 2002). In TS, both MD and FA have been demonstrated to be abnormal in widespread WM regions, with TS individuals predominately exhibiting decreased FA and increased MD (Table 1). However, the WM regions/tracts that have been identified as abnormal vary across studies, which may be a result of methodological differences among studies, e.g., voxel-based, tract-based, or atlas region-based analyses.

Xie and colleagues reported decreased FA in a very diffusive pattern across the entire brain, with the strongest decrease around WM adjacent to the bilateral temporal and occipital cortices (Xie et al., 2015). In contrast, other studies have demonstrated FA decreases in a more spatially specific pattern. For example, FA decreases have consistently been demonstrated in the parieto-occipital, fronto-parietal, and sensorimotor pathways (Holzapfel et al., 2006; Molko et al., 2004; Xie et al., 2015; Yamagata et al., 2012). Notably, increased FA in language-related WM regions has also been reported in TS (Holzapfel et al., 2006). This result is compatible, in part, with the previously reported enlarged WM around the temporal cortex and may also be related to the preserved verbal ability in TS individuals.

### 2.3. Functional activity/connectivity

fMRI techniques have been used to investigate anomalies of neural/functional activity or inter-regional coupling/connectivity in TS. The fMRI technique is based on blood oxygen level-dependent (BOLD) signals (Ogawa et al., 1990) and provides excellent spatial resolution while preserving acceptable temporal resolution when recording human brain activities during cognitive tasks or resting-state. Therefore, it has been extensively applied in cognitive neuroscience and to evaluate brain disorders or diseases (Faro and Mohamed, 2006).

In TS, fMRI has been used to identify anomalies in functional activation during cognitive tasks, including executive function (Tamm et al., 2003), arithmetic processing (Kesler et al., 2006; Molko et al., 2003), working memory (Bray et al., 2011; Haberecht et al., 2001; Hart et al., 2006), visuospatial function (Bray et al., 2013; Kesler, 2004), spatiotemporal attention (Beaton et al., 2010), and social cognition (Hong et al., 2014a; Skuse et al., 2005). As indicated in Table 2, both increased and decreased functional activation have been identified across the brain, depending on the specific tasks and spatial location. TS individuals also exhibit changes in functional connectivity during working memory and visuospatial tasks (Bray et al., 2011; Bray et al., 2013). Specifically, the parieto-occipital regions consistently exhibit aberrant functional activation or functional connectivity during visuospatial tasks (Bray et al., 2013; Kesler, 2004), whereas a reduction in glucose metabolism has also been demonstrated (Clark et al., 1990). In contrast, the prefrontal, fronto-parietal, and limbic regions exhibit functional activation abnormalities primarily during arithmetic processing, executive function, spatiotemporal attention, emotion recognition, and working memory tasks (Beaton et al., 2010; Bray et al., 2011; Haberecht et al., 2001; Hart et al., 2006; Hong et al., 2014a; Kesler et al., 2006; Molko et al., 2003; Tamm et al., 2003). Finally, increased functional activation of the amygdala has been identified during social cognition tasks in TS (Skuse et al., 2005). These abnormalities in functional activation or connectivity provide important insight into the physiological basis that underlies cognitive deficits in TS.

In addition to task-associated functional activity and connectivity, resting-state functional activity and connectivity have emerged as effective tools for investigating human brain function and organization (Biswal et al., 1995; Buckner, 2013). However, to date, there has only been one resting-state fMRI study of TS, in which TS girls exhibited

**Table 1**
Published white matter (WM) findings in TS females.

| Author (year) | Neuroimaging Measure | Main findings |
|---|---|---|
| Reiss et al. (1995) | WMV | TD > TS: right parietal WM |
| Brown et al. (2002) | WMV | TD > TS: bilateral occipital WM |
| Kesler et al. (2003) | WMD | TD < TS: bilateral STG WM |
| Kesler et al. (2004) | WMV | TD > TS: right hippocampal WM |
| Molko et al. (2004) | WMV | TD > TS: WM adjacent to bilateral caudate, left superior STG, left LING, left occipito-parietal junction, right PoCS and right SMG<br>TD < TS: bilateral BCC and WM adjacent to bilateral ACC, left STG, right IPS and right ENT |
| Cutter et al. (2006) | WMV | TD > TS: bilateral cerebellar WM, left IFOF, WM adjacent to right ENT, right SCC, and right parieto-occipital region<br>TD < TS: brainstem WM, bilateral GCC, bilateral temporal and bilateral orbitofrontal WM, right CSO and right PreCG WM |
| Holzapfel et al. (2006) | WMD | TD > TS: bilateral IC, left CSO and WM adjacent to left SFG and left PreCG<br>TD < TS: left IPG and left temporal WM |
| Yamagata et al. (2012) | WMV | TD > TS: right SLF, CST and WM adjacent to right PreCG and right PoCG, right SPL and right PCUN<br>TD < TS: left SLF, ILF, IFOF, PLIC, right ALIC and WM adjacent to right fusiform gyrus |
| Lepage et al. (2013a) | | |
| Xm | WMV | TD > TS: bilateral PoCG and bilateral PCAL WM, WM adjacent to left ENT, right PCUN, right POPE, right frontal pole, and right rACC |
| Xp | | TD > TS: bilateral PoCG and bilateral ENT WM, WM of right POPE, right PCUN, right frontal pole, and right rACC |
| Lepage et al. (2013b) | | |
| Young | WMV | TD > TS: WM adjacent to bilateral parietal region, left ENT and right rACC<br>TD < TS: left STG and left PreCG WM and right SFG WM |
| Adolescent | | TD > TS: bilateral parietal, bilateral occipital WM and left temporal WM<br>TD < TS: bilateral frontal WM |
| Green et al. (2014) | | |
| 1st | WMV | TD > TS: bilateral PCUN, left PoCG, and right superior parietal WM |
| 2nd | | TD > TS: bilateral superior parietal WM, left PoCG and left PCUN WM |
| Molko et al. (2004) | FA | TD > TS: deep WM of bilateral STS, right CSO and right EC |
| | MD | TD < TS: bilateral occipito-temporal WM and bilateral cerebellar WM, WM of left LING and right fusiform gyrus |
| Holzapfel et al. (2006) | FA | TD > TS: bilateral IC, left SLF, deep WM of left parietal-occipital region, left frontal lobe, left globus pallidus, and right prefrontal region<br>TD < TS: left IPG and left temporal WM |
| Yamagata et al. (2012) | FA | TD > TS: bilateral SLF, ALIC, GCC, tapetum, and PTR, left ILF, IFOF, PLIC and left fusiform gyrus WM, right SCC and right STG WM |
| | AD | TD < TS: bilateral SLF, ILF, PCR, and EC, left PTR, right tapetum and right STG WM |
| | RD | TD < TS: bilateral SLF, ALIC, tapetum, PTR, GCC, left ILF, IFOF, PLIC and left fusiform gyrus WM, right SCC and right STG WM |
| Xie et al. (2015) | FA | TD > TS: widespread WM regions across the entire brain, with the strongest decrease around WM adjacent to bilateral temporal and occipital cortex |

TS, Turner syndrome; TD, typically developing; TD > TS indicates a decreased value in TS individuals compared with TD controls, whereas TD < TS indicates an increased value in TS individuals. AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; WMD, white matter density; WMV, white matter volume; ACC, anterior cingulate cortex; ALIC, anterior limb of the internal capsule; BCC, body of corpus callosum; CSO, centrum semiovale; CST, corticospinal tract; EC, external capsule; ENT, entorhinal cortex; GCC, genu of corpus callosum; IC, internal capsule; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; IPG, inferior parietal gyrus; IPS, intraparietal sulcus; LING, lingual gyrus; PCAL, pericalcarine cortex; PCR, posterior corona radiation; PCUN, precuneus; PLIC, posterior limb of the internal capsule; PoCG, postcentral gyrus; PoCS, postcentral sulcus; POPE, pars opercularis; PreCG, precentral gyrus; PTR, posterior thalamic radiation; rACC, rostral anterior cingulate cortex; SCC, splenium of corpus callosum; SFG, superior frontal gyrus; SLF, superior longitudinal fasciculus; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus.

significantly reduced whole-brain functional connectivity strength (wFCS) within the bilateral postcentral gyrus/intraparietal sulcus, angular gyrus, cuneus and right cerebellum (Xie et al., 2017). Furthermore, a specific functional subnetwork was identified in which the resting-state functional connectivity between nodes was predominately reduced in TS girls. This subnetwork is composed of three functional modules, and the disruption of resting-state functional connectivity within one of these modules was associated with deficits in arithmetic-related cognition in TS girls.

### 2.4. Brain-behavior relationships

As previously discussed, various brain and behavioral/cognitive phenotypes have been demonstrated to be abnormal in TS. Notably, relationships between specific brain phenotypes and behavioral/cognitive abilities may also be altered, that is, X chromosome loss may moderate brain-behavior relationships.

In many TS neuroimaging studies, this possibility has been implicitly investigated by independently evaluating the correlations between neuroimaging measures and specific behavioral data within TS and/or TD groups. In most of these studies, IQ-related scores were selected as behavioral data (Brown et al., 2002; Fryer et al., 2003; Kesler et al., 2003; Lepage et al., 2014 2013a; Reiss et al., 1995; Xie et al., 2015; Yamagata et al., 2012). Several studies have also used other behavioral measures, such as Child Behavior Checklist (CBCL) scores and Emotional Quotient Inventory (EQ-I) scores (Kesler et al., 2004; Lepage et al., 2014; Reiss et al., 1995). A few studies found significant brain-behavior correlations for TS or TD groups or both. For example, IQ-related scores were negatively correlated with the tissue volume of the bilateral STG in the TS group but not in the TD group (Kesler et al., 2003). Furthermore, Lepage and colleagues reported significantly positive correlations between CT of the right middle temporal gyrus/inferior parietal gyrus and IQ-related scores for both TS and TD groups, and the correlation of the TD group was significantly lower than that of the TS group (Lepage et al., 2013a). Regarding WM integrity, a significant correlation between FA of the left SLF and IQ-related scores was reported for TS subjects, although results for TD subjects were not reported (Yamagata et al., 2012). Additionally, total anxiety and social anxiety scores were significantly negatively correlated with radial distance in the left amygdala of the TS group; however, the between-group differences in these correlations did not reach significance (Green et al., 2016). Finally, Green and colleagues revealed a similar age-related change in the gap in parietal morphometry and in visuospatial abilities between TS and TD girls, supporting a developmental link between parietal structures and visuospatial functions (Green et al., 2014).

Two recent studies investigated the moderating effect of X chromosome loss on the brain-behavior relationship by statistically evaluating the “brain × group” interaction on behavioral scores. Using this approach, Lepage and colleagues identified a significant group effect on the correlation between EQ-I scores and CT of the bilateral insula,

**Table 2**
Published functional MRI findings in TS females.

| Task domain | Author (year) | Neuroimaging measure | Main findings |
|---|---|---|---|
| Executive function | Tamm et al. (2003) | Functional activation | *Go/NoGo task*<br>TD < TS: bilateral SFG and MFG |
| Arithmetic processing | Molko et al. (2003) | Functional activation | *Number processing task*<br>TD > TS: bilateral ACC |
| | Kesler et al. (2006) | Functional activation | *Two-operand task*<br>TD > TS: bilateral SFG, MFG, IFG, caudate, cuneus, left ACG, IPS, SPL, SMG, ANG, fusiform, and posterior MTG<br>*Three-operand task*<br>TD < TS: bilateral ACG, left MFG, IFG, PreCG, PoCG, SMG, MTG, STG |
| Social cognition | Skuse et al. (2005) | Functional activation | *Fearful-neutral faces task*<br>TD < TS: right amygdala<br>TD has a rapid but transient activation in left amygdala, whereas TS has a persisting pattern of activation with a less marked peak |
| | Hong et al. (2014a) | Functional activation | *Emotion recognition: Happy vs. scrambled*<br>TD < TS: right ITG, extending to the anterior fusiform region<br>*Emotion recognition: Fearful vs. scrambled*<br>TD > TS: right dorsolateral prefrontal cortex, ACC and posterior cingulate cortex<br>*Emotion recognition: Neutral vs. scrambled*<br>No significant differences between TS and TD |
| Working memory | Haberecht et al. (2001) | Functional activation | *2-back task*<br>TD > TS: bilateral IFG, MFG, caudate<br>*1-back task*<br>TD < TS: bilateral anterior SMG, precuneus<br>*2-back minus 1-back*<br>TD > TS: left IFG, bilateral MFG, posterior SMG, IPS and right premotor cortex |
| | Hart et al. (2006) | Signal change percentage | *Verbal and spatial delayed-response tasks*<br>Effects of group and task on bilateral MFG, IFG, IPS, ITG |
| | Bray et al. (2011) | Functional activation | *Working memory task*<br>TD > TS: left MFG, IPL, right SFG, SMG |
| | | Functional connectivity | TD > TS: seed: right IPS targets: bilateral IPL, left MFG<br>TD < TS: seed: right IPS targets: bilateral ACC, caudate, thalamus |
| Spatiotemporal Attention | Beaton et al. (2010) | Functional activation | *One-target tracking task*<br>TD > TS: bilateral occipital fusiform, LING, culmen of anterior cerebellum, left declive of posterior cerebellum<br>TD < TS: bilateral frontal precentral gyrus, left lentiform nucleus, left IFG, thalamus, cingulate gyrus, PoCG, STG, MTG |
| Visuospatial function | Kesler (2004) | Functional activation | *Hard JLO task*<br>TD > TS: bilateral IFG, SFG, medial frontal lobe, MOG, SOG, motor and sensory cortices, IPL, SPL, right cingulate gyrus<br>TD < TS: bilateral MFG, SFG, caudate, putamen, left precuneus, left cingulate gyrus, left STG, left MTG<br>*Easy JLO task*<br>TD > TS: right motor and sensory cortices, right IPL, right SPL |
| | Bray et al. (2013) | Functional activation | *JLO task*<br>TD > TS: bilateral IPL |
| | | Functional connectivity | TD > TS: seed1: right posterior SPL targets: bilateral calcarine sulcus, STG, left LING<br>seed2: right SMG/IPL targets: bilateral LING, LOPC<br>seed3: left SMG/IPL targets: bilateral LING, LOPC<br>TD < TS: seed1: left posterior SPL targets: bilateral MFG, SMA, PCL, right posterior SPG |
| | | Connectivity-clustering | Group differences in clustering of PPC: bilateral IPL, right SPL |
| Resting state | Xie et al. (2015) | Functional connectivity (wFCS) | TD > TS: cuneus, right cerebellum, right PoCG/IPS, left PoCG/IPS, left and right ANG |

TS, Turner syndrome; TD, typically developing; TD > TS indicates a decreased value in TS individuals compared with TD controls, whereas TD < TS indicates an increased value in TS individuals. JLO, judgment of line orientation; wFCS, whole-brain functional connectivity strength; ACC, Anterior cingulate cortex; ANG, Angular gyrus; IFG, Inferior frontal gyrus; IPL, Inferior parietal lobule; IPS, Intraparietal sulcus; ITG, Inferior temporal gyrus; LING, Lingual gyrus; LOPC, Lateral occipitotemporal cortex; MFG, Middle frontal gyrus; MOG, Middle occipital gyrus; MTG, Middle temporal gyrus; PCL, Paracentral lobule; PoCG, Postcentral gyrus; PPC, Posterior parietal cortex; PreCG, Precentral gyrus; SFG, Superior frontal gyrus; SMA, Supplementary motor area; SMG, Supramarginal gyrus; SOG, Superior occipital gyrus; SPG, Superior parietal gyrus; SPL, Superior parietal lobule; STG, Superior temporal gyrus.

anterior cingulate, orbitofrontal cortex, temporal pole, and left inferior frontal gyrus (Lepage et al., 2014). In another study, Xie and colleagues demonstrated that CT and SA in multiple cortical regions are positively correlated with working memory performance in TD girls but negatively correlated in TS girls (Xie et al., 2015). These group differences indicated an X chromosome effect on brain-behavior relationships, which has been overlooked in many previous TS studies.

Notably, there has been remarkable variability of significant brain-behavior correlations among reports, implying a relatively tenuous relationship between brain and behavioral phenotypes in TS. However, identifying a robust brain-behavior correlation is difficult due to the relatively small sample sizes included in previous TS neuroimaging studies (Supplementary Table 1). In addition, many other factors such as the choice of brain neuroimaging technique and behavioral analysis, the inclusion criteria for TS individuals, and the age range of subjects can substantially influence brain-behavior correlations and, therefore, increase the complexity of robust identification.

### 2.5. Confounding factors

Multiple TS-related confounding factors, such as karyotype, hormonal treatment, and genetic imprinting, may influence the brain abnormalities of TS individuals. Using neuroimaging phenotypes, a few studies have preliminarily assessed these factors.

#### 2.5.1. Karyotype

TS individuals exhibit wide variations in karyotype, e.g., differential structural defects of the X chromosome or mosaicism (Bharath et al., 2010). Given limited sample sizes, several studies simply ignored the karyotype differences within the TS group and combined X-monosomy individuals with other TS individuals (e.g., mosaic) as a single group (Bray et al., 2011; Molko et al., 2003; Molko et al., 2004; Reiss et al., 1995). In contrast, most studies have included only X-monosomy TS individuals, which may effectively avoid the confounding effect of karyotype while maximizing the effect of X chromosome loss.

Nonetheless, karyotype differences across TS individuals provide an opportunity to evaluate the "dosage effect" of X chromosome loss on brain phenotypes. X chromosome loss may fundamentally influence specific brain phenotypes in similar manners across TS individuals. Alternatively, the degree of brain phenotype change may be a function of the type of X chromosome loss, i.e., karyotype. Two studies have investigated this effect by comparing X-monosomy with mosaic TS individuals, in which mosaic TS was characterized by X-monosomy and another cell line presenting the second X chromosome, that is, the loss of the entire second X chromosome in only a proportion of their cells (Murphy et al., 1993; Xie et al., 2015). In their pioneering study, Murphy and colleagues reported significant volumetric differences in the left caudate nucleus and thalamus between mosaic and X-monosomy TS individuals (Murphy et al., 1993). More recently, Xie and colleagues identified a significant "dosage effect" (mosaic vs. X-monosomy) on cortical SA of the right angular gyrus and WM integrity of the left tapetum of the corpus callosum (Xie et al., 2015). These two studies provide evidence supporting a "dosage effect" of X chromosome loss on neuroanatomy. In the future, it is important to further validate these results and assess this "dosage effect" on other brain phenotypes of TS.

Finally, it must be noted that the karyotype of TS individuals is largely confirmed using peripheral blood samples, but it remains unknown if the karyotype detected in the blood indicates the karyotype in brain tissue (Xie et al., 2015). It has been hypothesized that all viable TS individuals are actually cryptic mosaics with a "rescue cell line" (Hook and Warburton, 2014). Therefore, the karyotype of TS individuals should be cautiously considered.

#### 2.5.2. Hormonal treatment

Short stature and gonadal dysgenesis are very common in TS individuals. To increase height in adulthood, most TS girls are clinically treated with exogenous growth hormone (GH) during childhood, although no significant physiological deficiency in GH secretion has been observed in TS (Sybert and McCauley, 2004). GH therapy exposes treated TS individuals to more GH than non-treated individuals, providing an opportunity to investigate the effect of GH on the human brain. In addition, due to gonadal dysgenesis, the vast majority of TS individuals have an estrogen deficiency compared with TD controls (Bondy, 2007). TS girls who do not go through spontaneous puberty will typically receive estrogen replacement (ER) to artificially induce puberty (Sybert and McCauley, 2004), and TS individuals who are not treated with ER remain deficient in estrogen compared to ER-treated individuals. Given the well-documented role of growth hormone and estrogen in neurodevelopment (Noguchi, 1996; Peper et al., 2011; Yates and Juraska, 2008), these two hormonal treatments likely have an impact on cognitive deficits and brain abnormalities in TS individuals.

Behaviorally, multiple studies have demonstrated significantly better visual perceptual abilities and motor planning skills in estrogen-treated TS females than in non-treated TS females (Rovet, 2004). Regarding brain phenotypes, only one neuroimaging study included two separate TS groups stratified by estrogen treatment: estrogen-naïve and estrogen-treated (Lepage et al., 2013b) groups. Interestingly, compared with the estrogen-naïve group, the estrogen-treated TS girls exhibited significantly larger mean CT and total SA compared with TD controls. However, the estrogen-treatment effect was complicated by developmental differences between the two groups: the estrogen-naïve TS group included only young children (4 − 11 yrs) before puberty, and the estrogen-treated TS group included adolescents (14–21 yrs) after puberty (Lepage et al., 2013b). Prior studies have demonstrated that brain morphometric changes in TD populations during puberty are at least, in part, driven by estrogen (Bramen et al., 2011; Peper et al., 2009). Therefore, to delineate the relative contributions of estrogen and age effects, longitudinal studies of both TS and TD cohorts are needed. Along this line, Green and colleagues revealed an aberrant trajectory of brain development in TS by conducting a longitudinal investigation of TS girls at two time-points (Green et al., 2014). This study, however, included only pre-pubertal TS girls who did not receive ER therapy, except for one who started only three weeks before the second time-point. In the future, longitudinal data from post-pubertal TS girls with or without ER therapy should be evaluated.

Slightly better performances in psychological function, internalizing emotional behaviors, and arithmetic abilities have been identified in GH-treated TS individuals compared with non-treated TS individuals (Rovet, 2004). Following these behavioral studies, Cutter and colleagues conducted the only neuroimaging investigation to ascertain the effect of GH treatment on the neuroanatomy of TS individuals. Intriguingly, a significantly decreased GM volume was found in the bilateral parieto-occipital region, posterior temporal lobes and basal ganglia in TS individuals who had never received GH treatment compared with treated TS individuals (Cutter et al., 2006). In addition, this study also investigated the effect of androgen (oxandrolone) treatment on the neuroanatomy of TS individuals; a significant enlargement of the left caudate was identified in androgen-treated TS individuals compared with non-treated TS individuals. These findings, although limited, highlight the possibility of an influence of hormonal treatment on brain phenotypes of TS individuals, which warrants further scientific research and clinical attention.

#### 2.5.3. Genetic imprinting

Genomic imprinting is defined as an epigenetic phenomenon by which one allele in imprinted genes is selectively silenced depending on its parent-of-origin (Isles and Wilkinson, 2000). Both animal and human studies have demonstrated significant imprinting effects of the X chromosome on specific brain and behavioral traits (Davies, 2010). In TS females with a 45, XO karyotype, the remaining X chromosome may be exclusively paternal (Xp) or maternal (Xm); therefore, X chromosome imprinting differs among TS individuals.

Several TS studies have investigated X chromosome imprinting effects on cognitive abilities, and mixed findings have been reported (Bishop et al., 2000; Donnelly et al., 2000; Good et al., 2003; Kesler et al., 2003, 2004; Lepage et al., 2013a; Loesch et al., 2005; Skuse et al., 1997). For instance, Skuse and colleagues demonstrated that TS females with Xm had more impaired social-cognitive skills, verbal skills, and executive function compared with TS females with Xp (Skuse et al., 1997). However, other studies reported no significant differences in verbal IQ or social cognitions between Xm and Xp (Ergur et al., 2008; Good et al., 2003; Kesler et al., 2003, 2004; Lepage et al., 2013a).

A few TS neuroimaging studies have explored the effect of X chromosome imprinting on specific brain phenotypes, but only in their additional analyses. Two of them reported the existence of a genomic imprinting effect on brain structure in the temporal lobe (Cutter et al., 2006; Kesler et al., 2003) and the caudate nucleus (Cutter et al., 2006), but the others did not identify significant results (Brown et al., 2002; Good et al., 2003; Kesler et al., 2004). More recently, Lepage and colleagues summarized these neuroimaging findings and conducted an exclusive assessment of an imprinting effect by applying a surface-based morphometric analysis to estrogen-naïve young TS girls with X-monosomy (Lepage et al., 2013a). The analyses indicated significantly increased temporal and parietal CT and smaller superior frontal and superior temporal GMV in TS girls with Xp than in TS girls with Xm (Lepage et al., 2013a).

### 2.6. Summary

There exist widespread changes in structural and functional neuroimaging phenotypes in TS individuals, and various confounding factors can alter specific changes. Despite the diversity and inconsistency, neuroimaging findings have generally revealed prominent TS-induced brain anomalies in two functional systems/networks: the visuospatial system mainly consisting of multiple parieto-occipital regions (Kravitz et al., 2011; Whittingstall et al., 2014), and the social cognition system mainly involving the amygdala, prefrontal cortex, temporal regions and anterior cingulate cortex (referred to as the "social brain", Adolphs, 2009). For each of the systems, a variety of related neuroimaging phenotypes (e.g., brain morphometry, structural or functional connectivity, and functional activity during tasks) are abnormal in TS individuals. These findings highlight a fundamental role of the X chromosome in visuospatial function and social cognition of humans and provide important clues for studying the genetic underpinnings of these two cognitive domains.

## 3. Issues and future considerations

Thus far, neuroimaging studies of TS have provided accumulating evidence that has contributed to our understanding of how the X chromosome influences the human brain. While many findings are consistent across studies, discrepancies exist among some results. These discrepancies may be related to the differences in MRI acquisition, analysis methods, and age ranges of the TS participants among studies (Supplementary Table 1).

Given the rarity of TS populations, TS neuroimaging studies have typically included a relatively small number of TS subjects (Supplementary Table 1). Therefore, TS brain abnormalities with a small effect size may be missed because of the limited statistical power. Including larger sample sizes is highly desired in future single-site TS studies. Alternatively, given the ongoing data sharing wave in the scientific community (Poldrack and Gorgolewski, 2014), neuroimaging data sharing may be applied across TS investigating groups, which may help effectively address the issue of sample size.

In addition to these general issues, several other specific aspects deserve particular consideration, which will be elaborated in the following sections.

### 3.1. Neuroimaging brain phenotypes

Various brain phenotypes/measures derived from sMRI, dMRI, or fMRI have been utilized in TS studies. The investigated neuroimaging phenotypes have included GM/WM volume, CT, SA, diffusion parameters (e.g., FA and MD), functional activation, and functional connectivity; however, some widely applied neuroimaging phenotypes/measures remain largely uninvestigated in TS studies, even though these phenotypes/measures appear closely related to the X chromosome.

One intriguing brain phenotype of TS is the asymmetry of various neuroimaging measures. Multiple theories have implicated a potential association between the X chromosome and brain asymmetry. For example, the influential Geschwind-Galaburda hypothesis proposed that brain asymmetries are predominately determined by circulating sex hormones in the intrauterine environment (Geschwind and Galaburda, 1985). Given the role of the X chromosome in the development of gonads, an X chromosome effect in brain asymmetry is highly plausible. Moreover, genetic theories for brain asymmetry pose a strong link between brain asymmetry and the X chromosome (Corballis, 2009). For example, Crow argued that the asymmetry gene is located in the Xq21.3/Yp11.2 region of homology on X/Y chromosomes (Crow, 2002). According to these theories/hypotheses, human brain asymmetries may be dramatically altered in TS individuals. To date, few neuroimaging studies on brain asymmetries have only slightly touched on the asymmetry of brain phenotypes of TS individuals in the trivial section of their study, showing that TS individuals do exhibit changes in brain asymmetries (Leroy et al., 2015; Rezaie et al., 2009). Taken together, future studies are highly encouraged to exclusively investigate brain asymmetries of various neuroimaging phenotypes in TS.

Another important and overlooked brain phenotype in TS is the whole-brain network topology. In the previous decade, human brain network topological properties have been intensively investigated in both normal and abnormal conditions (Sporns, 2013). Whole-brain networks, which are composed of network nodes (i.e., brain regions) and edges between nodes (e.g., brain connections), are initially constructed using multi-modal neuroimaging techniques. Graph theoretical approaches are subsequently applied to extract various topological parameters that characterize the organizational properties of the constructed human brain networks. This line of research has opened novel avenues for investigating the structure and function of the human brain, and many non-trivial topological properties of the human brain have been identified, such as small-worldness (Gong et al., 2009; Iturria-Medina et al., 2007), central communication hubs and highway connections (Gong et al., 2009; Hagmann et al., 2008; Li et al., 2013), modular structure (Hagmann et al., 2008; Yap et al., 2011), and rich-club architecture (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013). Importantly, human brain network topologies have revealed genetic associations (Fornito et al., 2011) and asymmetric patterns (Zhong et al., 2017), which imply a potential X chromosome effect on the network topologies of the human brain. To date, only Xie and colleagues have investigated the brain network structure in TS individuals by indicating network modular changes in TS; however, this was confined to a particular functional sub-network rather than the whole-brain network (Xie et al., 2017). To determine how the X chromosome influences the organizational patterns of functional or anatomical connectivity at the whole-brain scale, brain network analyses of TS are highly recommended in the future, which may provide a novel conceptual understanding of the X chromosome effects on human brain structure and function.

Finally, numerous neuroimaging studies have demonstrated how the functional activities of the human brain relate to its structure at a large-scale systems level (Honey et al., 2010; Skudlarski et al., 2008; van den Heuvel et al., 2009). For example, intrinsic brain activities (derived from resting-state fMRI) have been linearly correlated with brain size (derived from sMRI), with larger brains exhibiting stronger fluctuations in intrinsic brain activities (Qing and Gong, 2016). Moreover, tight coupling between functional and structural connectivity has been well established not only regarding connectivity strength but also in network topological organization (Wang et al., 2015). Intriguingly, the coupling of structural-functional connectivity undergoes significant changes during normal development and in neuropsychiatric disorders, such as schizophrenia and epilepsy, which suggests that these brain structural-functional relationships may be influenced by genetic and environmental factors. To date, it remains unknown whether the X chromosome has an impact on these relatively complex brain phenotypes, i.e., brain structural-functional relationships. In the future, it would be interesting to determine whether and how specific brain structural-functional relationships are altered in TS individuals by simultaneously employing both structural and functional neuroimaging techniques.

### 3.2. Relating brain abnormalities to cognitive deficits

Most TS neuroimaging studies have included specific cognitive/behavioral data such that the potential links between brain abnormalities and cognitive deficits in TS can be evaluated. While specific brain-behavior correlational analyses have been applied in these studies, the two underlying theories for these analyses, i.e., the mediation and moderation hypotheses, should be more explicitly specified.

In imaging genetics, it has been widely hypothesized that the

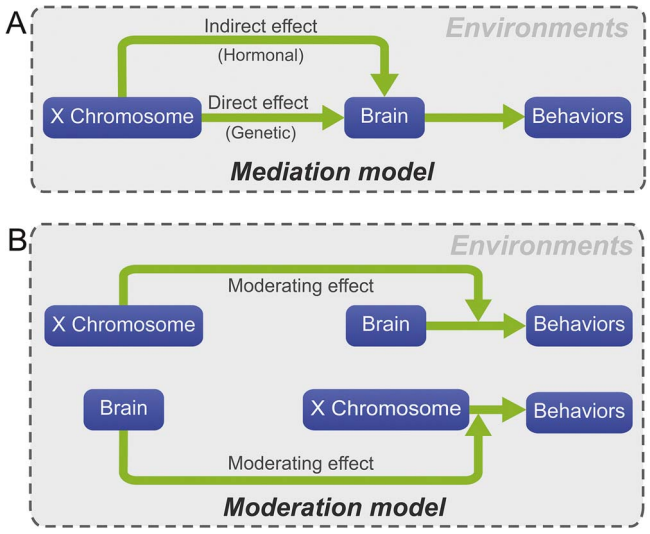


**Fig. 3.** Schematic causal models for the X chromosome, brain, and behavior. There are two casual models: (A) the mediation model and (B) the moderation model. In the mediation model, the X chromosome directly or indirectly acts on the brain, inducing behavioral traits. Thus, the brain serves as a mediating factor for the effects of the X chromosome on behavior. In contrast, in the moderation model, either the brain or the X chromosome may be considered a moderating factor for the relationship between the other factor and behavior. Notably, environmental factors may play a non-trivial role in or interact with these two models.

genetic effects on specific behavioral phenotypes are mediated by specific neural functions, which is referred to as the mediation model (Fig. 3A). To test this model, specific statistical approaches, such as a mediation analysis, may be applied (Hayes, 2013), and a number of gene-to-brain-to-behavior pathways have been established (Buckholtz et al., 2008; Green et al., 2013; Stevens et al., 2014; Sun et al., 2017). By conceptually articulating gene-to-brain-to-behavior pathways, mediation models provide useful frameworks for directional/causal hypotheses (Green et al., 2013). Consistent with this approach, specific brain abnormalities present in TS should comprise mediating factors that underlie specific cognitive deficits caused by X chromosome loss. Most previous TS studies have frequently interpreted brain abnormalities in TS as potential underlying sources of specific cognitive deficits, which essentially assumes mediation pathways in an implicit manner. To date, the complete X chromosome-brain-behavior pathways based on the mediation analysis remain unreported; however, pairwise relationships among the X chromosome, brain, and behavior (i.e., X chromosome-behavior, X chromosome-brain, and brain-behavior relationships) in humans have been thoroughly investigated in TS individuals. One potential reason is that mediation models are statistically more rigorous than individual pairwise correlations because these models require three concurrent relationships between three variables rather than one relationship between two variables. Such hypotheses become more difficult to statistically prove given the typical small sample sizes of TS neuroimaging studies. In the future, explicit investigations of these mediation pathways are highly encouraged with the inclusion of a large number of TS subjects.

In contrast, brain phenotypes may act as moderators for genetic effects on cognition (Fig. 3B). According to this model, cognition is jointly affected by both genes and the brain, which may be considered two independent variables. Statistically, there should be a significant "gene × brain" interaction on specific cognitive phenotypes, which suggests 1) that the relationship between brain and cognitive phenotypes is influenced by genetic factors or 2) that the relationship between gene and cognitive phenotypes is influenced by brain phenotypes. Accordingly, genetic factors or brain phenotypes may be regarded as moderators for brain-behavior or gene-behavior relationships, although they are statistically equivalent. In TS neuroimaging studies, this moderation model has been occasionally tested via direct assessment of the "group × brain" interaction effect on cognition or via independent assessment of the brain-behavior correlation within a TS or TD group followed by the subsequent assessment of group differences. As reviewed in Section 2.4, there are significant differences in specific brain-behavior correlations between TD and TS groups, which supports a moderating role of X chromosome loss in brain-behavior relationships.

As illustrated in Fig. 3, both the mediation and moderation models are applicable for a casual path of X chromosome loss, brain abnormalities, and cognitive deficits in TS. These two models are not mutually exclusive, and their applicability should depend on specific brain and behavioral/cognitive phenotypes. Finally, environmental factors may confound the effects of X chromosome loss on brain and behavioral/cognitive phenotypes in TS. Thus, it would be interesting to include specific environmental variables in these models when investigating TS individuals in the future.

### 3.3. Differentiating between genetic and hormonal effects

X-linked genes affect the brain in at least two ways: by directly acting on the brain and by indirectly acting on the gonads to induce differences in specific gonadal secretions (i.e., hormones) that have specific effects on brain development (Arnold, 2004). Regarding the effects of the X chromosome on the human brain in TS individuals, it is difficult to differentiate between direct genetic effects and indirect hormonal effects on the brain. The changes in brain and behavioral/cognitive phenotypes in TS individuals may be the result of a direct genetic factor, an indirect hormonal factor, or a combination of the two factors.

To best isolate a direct genetic effect from an indirect hormonal effect, identical hormonal levels should be ensured between control and TS individuals. However, this is difficult to achieve in practice because hormonal deficits as a result of gonadal dysgenesis are extremely common in TS. A suboptimal alternative is to match the pubertal stage of individuals as an approximation of equal sex hormone levels between groups. Several studies have matched TS and controls by confining both groups within the prepuberty stage; thus, the identified TS-related brain abnormalities are more likely to be driven by direct genetic effects (Green et al., 2014, 2016; Hong et al., 2014b; Lepage et al., 2013a,b; Marzelli et al., 2011; Yamagata et al., 2012). However, although sex hormone levels may be approximately matched between pre-puberty TS and control girls at the time of assessment, TS girls do not experience the boost in ovarian estrogen concentration during their first year of life in contrast to control girls (Bidlingmaier et al., 1987). This early life estrogen deficiency likely has a non-trivial influence on brain development in TS girls, which therefore complicates the previous conclusion that supported a direct genetic effect.

To extract the pure hormonal effect, individuals must be matched in karyotype but exhibit different hormonal levels. Thus, one potential scheme is to investigate the neuroimaging contrasts between TD controls and endocrine patients who have normal karyotypes but exhibit specific hormonal deficits. As an alternative approach, correlating hormone levels with neuroimaging phenotypes across a TD population may be applied, given the inter-subject variation in both hormonal levels and neuroimaging phenotypes. In TS individuals, hormone treatments may yield a hormonal contrast between treated and non-treated TS individuals, and any neuroimaging differences between these subgroups would suggest a hormonal effect. As discussed in section 2.5.2, studies have demonstrated significant brain differences between TS individuals treated by ER and non-treated TS individuals (Cutter et al., 2006; Lepage et al., 2013b); relevant neuroimaging results should therefore point to a hormonal effect. To better quantify the hormonal effect in TS, longitudinal studies that compare the neuroimaging phenotypes of TS individuals before and after specific hormonal treatments could be conducted in the future.

Despite the difficulties in differentiating between these two effects

among TS-related findings, some MRI studies in humans have provided important clues on this issue. Cortical thinning of the temporal cortex was identified in Klinefelter syndrome individuals (i.e., 47, XXY men) compared with 46, XX women and 46, XY men (Savic and Arver, 2014). This finding is reciprocal to the thickening temporal cortex that has been widely identified in TS girls (Lepage et al., 2014; Lepage et al., 2013a,b; Raznahan et al., 2010; Xie et al., 2015). Given that the sex steroids are low in both 47, XXY males and 45, XO females, a direct genetic effect on the thickness of the temporal cortex is likely (Savic and Arver, 2014). In particular, Hong and colleagues included both TS and KS individuals in the same study and demonstrated that the increase in X chromosome copy number was associated with a relative decrease in parieto-occipital GMV and a relative increase in temporo-insular GMV, which strongly supports a direct genetic effect on these brain phenotypes (Hong et al., 2014b). In addition, the neuroanatomical differences between non-mosaic and mosaic TS individuals (i.e., the "X chromosome dosage effect") also imply a direct genetic effect: both TS groups exhibit gonadal dysgenesis but have different amounts of the X chromosome (Murphy et al., 1993; Xie et al., 2015).

Regarding the hormonal effect, several studies have demonstrated significant correlations between hormone levels and brain phenotypes, such as the GMV of the amygdala and parahippocampus (Lentini et al., 2013). Particularly, in summarizing the MRI findings of the human brain, a recent review indicated consistent changes in the medial temporal lobe structures among different endocrine disorders with sex steroid excess or deficiency (Mueller, 2013), which indicates a hormonal effect on these structures. These findings imply that the previously described TS-related changes in medial temporal lobe structures (e.g., the amygdala and hippocampus) are likely attributed to hormonal effects.

### 3.4. Investigating beyond the TS model

Unquestionably, TS serves as a valuable human "knock-out model" for investigating how the X chromosome influences human neural systems and cognitive functions. It is worth noting that other useful models exist at the chromosome level (Fig. 4). For example, there are well-established animal X-monosomy models that are ideal for dissociating genetic and hormonal effects of the X chromosome on the neural system. In fact, a variety of mammals, including mice, dogs, cats, and monkeys, can exhibit X-monosomy. Given its high genetic tractability and short generation time, the mouse X-monosomy model, i.e., 39, XO mice, have become the most popular model (Arnold, 2009). Unlike human TS individuals, 39, XO mice are free of cryptic mosaicism and allow the X chromosome parent-of-origin to be pre-specified (Davies, 2010; Lynn and Davies, 2007). Importantly, 39, XO mice are fertile, as they possess grossly intact ovarian function (Lynn and Davies, 2007; Probst et al., 2008), thus allowing the direct X chromosome effects to be dissociated from those of circulating hormones. Using this mouse X-monosomy model, a dosage effect of the X chromosome on emotional processing has been observed by showing increased fear reactivity in 39, XO mice (Isles et al., 2004). In addition, 39, XO mice with Xm were found to be more sensitive to deficits in behavioral inhibition (Davies et al., 2005). More recently, a high-resolution whole-brain ex-vivo MRI investigation was conducted using 39, XO mice and their XX and XY littermates. Morphometric anomalies of the parietal cortex and striatum in 39, XO mice were observed compared with their XX littermates (Raznahan et al., 2013). This result is highly compatible with human TS findings and strongly supports a direct X chromosome gene effect on morphometric phenotypes in these brain areas. To our knowledge, this MRI study remains the only neuroimaging investigation of 39, XO mice. Additional future explorations in this area will provide valuable information for elucidating the biological substrates of TS-related neuroimaging findings.

In addition to the "knock-out model", naturally occurring human "knock-in models" of the X chromosome, including 47, XXX triple X syndrome, 47, XXY Klinefelter syndrome, and other X chromosome aneuploidies, can also be used to study X chromosome effects on the human brain. Although less frequently than TS, these X chromosome aneuploidies have also been investigated using neuroimaging techniques (Hong and Reiss, 2014; Lenroot et al., 2009; Lin et al., 2015; Mankiw et al., 2017; Printzlau et al., 2017; Reardon et al., 2016). Intriguing findings have been reported, such as that supernumerary X chromosome can lead to pallidal atrophy and deformation of striato-pallidal shape (Reardon et al., 2016). Combining these human "knock-in" and "knock-out" models in the same study will provide novel insight into X chromosome effects on the human brain (Hong et al., 2014b).

The identified associations between the X chromosome and the human brain in TS do not indicate which specific X chromosome genes contribute to these findings. To address this issue, TS individuals with partial X chromosome deletions or other X-linked brain diseases could be assessed to identify the candidate X chromosome genes that are

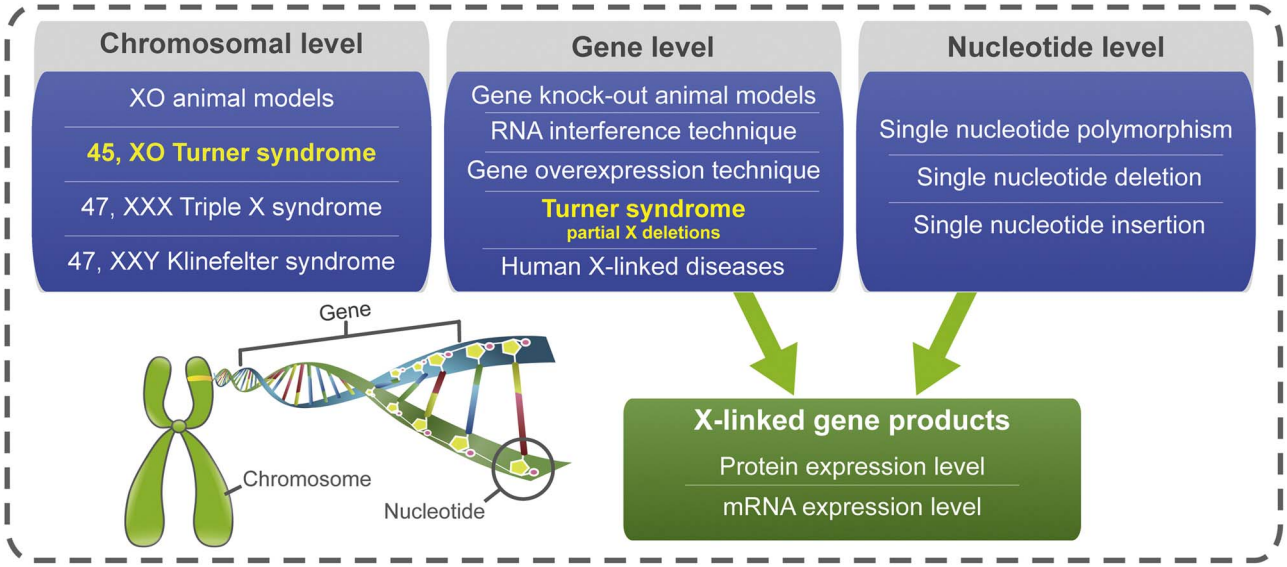


**Fig. 4.** The TS-beyond framework for investigating the effects of X chromosome/genes on neural systems. Three analysis levels should be considered: the chromosomal level, gene level, and nucleotide level. Complementary and heuristic research paradigms will facilitate the identification of candidate X-linked genes to identify the underlying biological mechanisms and ultimately elucidate how the X chromosome/genes function in the human brain.

responsible for the neural and cognitive anomalies induced by X chromosome loss. For example, by applying the deletion-mapping technique in TS individuals with partial X deletions, Good and colleague demonstrated that a 4.96-Mb interval at Xp11.3 is associated with amygdala development, and the MAOB was proposed as a gene contributing to this association (Good et al., 2003).

Once candidate X chromosome genes are identified, the biological mechanisms that underlie their functions in neural systems may be further investigated using gene knock-out animal models or by regulating gene expression with RNA interference or gene overexpression techniques (Agrawal et al., 2003; Prelich, 2012). Furthermore, publicly available gene expression data in whole-brain tissue for both mice and humans, e.g., the Allen Brain Atlas (http://www.brain-map.org) (Lein et al., 2007; Shen et al., 2012) can be used. These valuable datasets make it possible to locate brain regions where candidate X chromosome genes are over- or under-expressed, thereby yielding specific ROIs for future studies. Moreover, the identified brain regions in TS neuroimaging studies could be applied to search for candidate X chromosome genes, i.e., highly expressed X chromosome genes in these regions. Successful identification of these X-linked genes will provide strong support for a direct genetic effect that underlies previous TS-based neuroimaging findings. Finally, mutations at the nucleotide level within identified candidate X chromosome genes (e.g., single nucleotide polymorphisms/deletions/insertions) may also influence neural systems but require more specific investigations in the future.

## 4. Conclusion

This review thoroughly surveyed existing TS neuroimaging studies that have employed multi-modal MRI techniques. Widespread structural and functional neuroimaging phenotypes were found to be altered in TS, and two brain functional systems, i.e., the visuospatial system and the social cognition system, exhibited the most prominent neuroimaging anomalies in TS, highlighting a fundamental role of the X chromosome in visuospatial function and social cognition in humans. Future investigations that focus on new neuroimaging measures or phenotypes are encouraged. The mediating or moderating role of the X chromosome in the brain-behavior pathway should be more specifically investigated, and differentiating between direct genetic effects and indirect hormonal effects requires specific attention. In addition to TS neuroimaging findings, it is important to investigate non-TS models at the chromosome level and further at the gene level or even finer levels in the future.

## Acknowledgements

This work was supported by the 973 program (grant number 2013CB837300), the National Science Foundation of China (grant numbers 81271649, 81322021), the 863 program (grant number 2015AA020912), the Beijing Municipal Science & Technology Commission (grant numbers Z151100003915117, Z151100003915122), and the Fundamental Research Funds for the Central Universities. The authors have no conflicts of interest to declare.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.05.023.

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