Empathic accuracy in adolescent girls with Turner Syndrome

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Abstract

Objective: Girls and women with Turner Syndrome (TS) demonstrate social challenges and difficulties identifying negative emotions, specifically fear. Previous studies suggest that social deficits in TS could be associated with theory of mind (TOM) difficulties or visual-spatial processing abnormalities. To further examine the potential mechanisms underlying social deficits in TS, we administered the empathic accuracy task, a naturalistic social cognition task.

Method: The performance of 14 girls with TS was compared to 12 age-matched typically developing girls (ages 12 to 17) on an empathic accuracy task and a (control) visual-motor line-tracking task. Empathic accuracy was compared across positive and negative emotionally valanced videos.

Results: We found that girls with TS differ from typically developing girls on empathic accuracy ratings for negative videos; no differences were detected for the positive videos. No between group differences were found on the control line tracking task.

Conclusion: Our findings expand upon the previously detected affect recognition problems in TS to also include impaired detection of negatively valanced empathic interactions. Such difficulties for girls with TS could contribute to their social deficits and anxiety. Results from this study provide important information about gene-body-brain interactions and their influence on emotion processing and empathic accuracy during adolescence.
Introduction

Turner syndrome (TS) is a disorder in human females in which part or all of the genetic material from one X-chromosome is absent. Girls with TS display a variety of physical, developmental and cognitive abnormalities. These include cardiovascular problems (Ho et al., 2004), short stature, ovarian failure (Ross et al., 2004) and relative deficits in visual-spatial-motor and executive functions (Mauger et al., 2018, Saenger et al., 2001). Additionally, girls with TS have documented social difficulties and struggle with social anxiety (Hong et al., 2011; McCauley et al., 2001, 1986; Ross et al., 2000). Difficulties include problems forming and maintaining social relationships, impaired social competence, and having few close friends (Lagrou et al., 2006; McCauley et al., 1995, 1987). Several recent studies suggest that girls with TS perform poorly on tasks of social cognition, which may contribute to their reported social difficulties.

Specifically, memory for faces (Hong et al., 2011), eye gaze (Elgar et al., 2002; Lawrence et al., 2003; Mazzola et al., 2006) and affect recognition (Anaki et al., 2016; Good et al., 2003; Hong et al., 2014; Lawrence et al., 2003b; Mazzola et al., 2006; Roelofs et al., 2015; Ross et al., 2004, 2002) deficits were found. For affect recognition tasks requiring participants to identify the emotions associated with static pictures of faces, girls with TS demonstrate impaired recognition for negative emotions, yet intact recognition for positive emotions (Hong et al., 2014; Lawrence et al., 2003b; Mazzola et al., 2006; McCauley et al., 1987; Skuse, 2005). Deficits were particularly pronounced for perceiving targets portraying fear (Anaki et al., 2016; Hong et al., 2014; Lawrence et al., 2003b; Francesca
Mazzola et al., 2006; McCauley et al., 1987; Skuse, 2005). Affect identification deficits were also present for targets displaying the emotions sadness and disgust (Anaki et al., 2016). Mechanisms underlying these aforementioned affect recognition and social deficits are not yet well understood.

One theory attempting to describe the nature of the social deficits seen in girls with TS suggests that theory of mind (TOM) difficulties may be present (Anaki et al., 2016; Hong et al., 2011; Lawrence et al., 2007) and could be underlying their social problems (Lepage et al., 2014). TOM describes “the ability to reflect on the contents of both one’s own and other’s minds” (p. 3; Baron-Cohen, 2001). Researchers hypothesize that TOM deficits in TS may be influenced by dysfunction in circuitry involved in mirroring (Lepage et al., 2014), affect (Burnett et al., 2010), visual spatial processing (Anaki et al., 2018, 2016) and processing of eye-gaze cues (Burnett et al., 2010; Lawrence et al., 2003a). Despite some initial evidence for the previously mentioned hypotheses, no definitive conclusions about the nature of the TOM deficits in girls with TS can be made.

Previous TOM studies in TS have only used deconstructed and simplified social stimuli, which lack ecological validity. Social interactions, however, are complex and successful social interactions require a well-balanced synthesis of various abilities and behaviours (Zaki and Ochsner, 2012). Therefore, it is necessary to study TOM in TS with naturalistic stimuli in order to fully capture the extent of the subtle yet potentially impactful social deficits in girls with TS (Burnett et al., 2010). For this study, we implemented an empathic accuracy task (EAT) in
adolescent girls with and without TS. Empathic accuracy tasks attempt to simulate naturalistic social interactions by having study participants watch a video of a real person (i.e., not an actor) telling an emotionally laden personal story. Participants are then asked to rate or describe the internal mental states of that target. In the version used here, participants continuously rated the emotional valence felt by a target in a video. Critically, both the participant and the target person provide continuous ratings of the perceived emotional valence. These ratings are compared and provide a measure of empathic accuracy, based on the assumption that the target can report on their own affective state with high fidelity.

Because one hypothesis suggests that visual-spatial deficits in girls with TS may specifically influence their affect recognition abilities (Anaki et al., 2018, 2016) and since girls with TS also demonstrate motor deficits, we administered a vertical line tracking task as a control for the EAT. This control task was successfully used in a previous study of persons with schizophrenia (Lee et al., 2011), a condition also characterized by relative deficits in motor, attention and visual spatial processing. Here, we hypothesized that girls with TS would demonstrate relative deficits in empathic accuracy for negatively-valanced videos that would exceed any potential deficits in line tracking (visuo-motor) accuracy.

Methods

Participants

Fourteen girls with TS and 12 typically developing girls (TD), ages 11 through 17 years of age were recruited from a larger study, which examined
longitudinal brain changes associated with TS. Participants with TS were recruited nationally and TD participants were recruited from around the San Francisco Bay area. Inclusion criteria for TS included genetic confirmation of Turner syndrome. Controls with developmental delays and significant medical and/or psychiatric illness were excluded from participating in the study. Participant pubertal stage was assessed via self-report on the Tanner scale which includes ratings of breast and pubic hair development (Marshall and Tanner, 1969) and was confirmed by study physicians. Intelligence was measured using the Weschler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999)). Additional recruitment and screening details can be found here (Green et al., 2017). The Stanford University Institutional Review Board (IRB) approved the study and the study was conducted in line with the IRB’s standards. All participants assented and their parents consented prior to participating in the study.

_Empathic Accuracy Task_

We adapted a version of the empathic accuracy task (EAT) for adolescents and administered it to all study participants. For the EAT, we selected our videos from a pool of stimuli and choose videos of late-adolescent college-aged female volunteers, ages 18-21, who appeared young for their age and educational status. We only presented videos of female volunteers since we were interested in learning how empathic accuracy may influence social relationships in girls with TS. Age related preferences for friends occur in girls, such that younger teen girls primarily have same sex friendships (85% of best
friends are of the same sex in grades six through seven). With age, adolescents form more opposite sex friendships (e.g., 79% of best friends are of the same sex in eight grade for girls; Arndorfer and Stormshak, 2008). Targets appeared to be of Caucasian, Asian and Pacific Islander ethnicities, which approximated the demographics of our participants.

Procedures for creating empathic videos were similar to previous studies (See Figure 1) and stimuli were produced by Northeastern University (Zaki et al., 2009). Volunteers (not actors; also called targets) were asked to describe an emotional autobiographical event (either positive or negative) while being filmed and without knowing that their data was going to be included as stimuli within a research study. Then, each target watched and continuously rated the valence (degree of positivity vs negativity) of the emotions felt while describing the event with a dial using a nine-point rating scale (1: very negative, 5: neutral, and 9: very positive). Target volunteers provided consent for the videos to be used for future research. Participants in the present study watched and continuously rated the valence of the target’s feelings in the videos using the right and left arrow keys on a keyboard based on the same nine-point rating scale described above. We chose three positive and three negative videos that included topics applicable to adolescents. Positive video topics included telling a boyfriend or girlfriend “I love you” for the first time (Video 1), excelling at a sports competition (Video 3), and spending quality time with one’s family (Video 6). Negative video topics included death of a pet (Video 2), moving away from home for the first time (Video 4), and breaking up with a romantic partner (Video 5).
Visual-Motor Control

The visual-motor control condition mimics the visual-motor demand of the empathy condition. Participants were shown two trials of a thin vertical line that randomly moved back and forth across the monitor for 90-seconds. Participants continuously rated the line’s location throughout each 90-second trial using a nine-point visual analogue scale identical to the EAT, and displayed below the video (1: far left, 5: middle, and 9: far right) using the right and left arrow keys on a keyboard. One line trial was shown prior to the six empathy videos and a second line trial was shown after the empathy videos.

Empathic Accuracy Behavioural Analysis

MATLAB R2017b was used to perform time series downsampling and calculations. Continuous empathy ratings obtained from participants were downsampled from 30 Hz to match the 10Hz sampling frequency of the target’s ratings. Onsets for the participant and target ratings were aligned. Statistical procedures included calculating empathic accuracy by obtaining the Pearson’s correlation between the participant and targets’ continuous ratings for each task. Fisher’s r to z conversion was then used to convert correlation coefficients to z-scores (See Figure 1). Similar procedures to previous EAT studies were followed for calculating empathic accuracy ratings in order to maintain fidelity with previously reported results in other populations (Kral et al., 2017; J. Lee et al., 2011; Mackes et al., 2018; Zaki et al., 2009). Video 1 demonstrated very poor agreement for all participants and therefore was excluded from subsequent analyses (Video 1 average $r = .01$, $SD = .14$; Video 2 average $r = .72$, $SD = .26$;
Video 3 average $r = .41$, SD = .40; Video 4 average $r = .69$, SD = .29; Video 5 average $r = .74$, SD = .12; Video 6 average $r = .70$, SD = .16). Video 3 demonstrated lower accuracy levels than videos 2, 4, 5 and 6, however, but was retained for further analysis since empathic accuracy was modest, not at floor (as in Video 1). The average emotion valence ratings and standard deviations for the target’s ratings were the following: Video 1 mean = 6.83, SD = 1.50, Video 2 mean = 4.86, SD = .91, Video 3 mean = 6.81, SD = .92, Video 4 mean = 3.77, SD = .18, Video 5 mean = 3.68, SD = .64; Video 6 mean = 7.29, SD = .80.

To assess whether developmental stage and intelligence (Full scale IQ (FIQ), Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI) should be included as a covariate within our primary analyses, separate Pearson correlations were used to examine the relationships between empathic accuracy (z-scores) with age and IQ scores. Separate Spearman’s rho correlations were used to examine the relationship between the empathic accuracy (z-scores) and the participant’s average Tanner score (the average of Tanner breast and pubic hair ratings were obtained). Significance across these correlations was determined by a Bonferroni correction, which was applied to control for multiple tests for developmental stage (age and average Tanner, $p = .005$) and intelligence (IQ, VCI and PRI, $p < .003$) separately. To examine differences in group performance on each of the videos, we conducted a one-way MANOVA that included empathic accuracy z-scores for Videos 2-6 as dependent variables.
**Visual-Motor Behavioural Analyses**

MATLAB was used to conduct line tracking analyses in a manner similar to the empathic accuracy analysis. Line tracking data was sampled at 10Hz and line tracking accuracy was calculated by conducting a Pearson’s correlation between the participant’s ratings and the values corresponding to the absolute position of the line on the screen. The Fisher’s r to z conversion was used and z-scores were compared between the TS and control groups using a mixed between-within group ANOVA; within groups included the two line trials.

**Results**

**Empathic Accuracy Behavioural Results**

The average r value for all participants on the empathic accuracy task prior to z-transformation was 0.65 (SD = .29). A one way ANOVA revealed no significant differences between the two groups in age (F(1,24) = 1.97, p = .17; TS mean = 14.41, SD = 1.98, TD mean = 13.41, SD = 1.54) and a Mann Whitney U test revealed no significant differences in groups on average Tanner stage (sum between Tanner breast and pubic hair development scores; Mann-Whitney U p = .44; See Table 1 for demographic information). Significant differences for group were found for intelligence (FSIQ: (F (1,23) = 16.86, p = .00, VCI: F (1,23) = 10.54, p= .00), PIC: F (1,23) = 11.63, p = .00); See Table 1). No significant association between age or Tanner score and empathic accuracy z-scores for individual videos was detected at a Bonferroni corrected value (p < .005).

However, uncorrected p-values of p < .05 were observed for Video 3 for both age (r = .46, n = 24, p = .02) and Tanner score (rho = .52, n= 24, p =.01) (See Figure
No significant associations between IQ (FSIQ, VCI and PSI) and empathic accuracy z-scores were detected for any of the videos at a Bonferroni corrected level ($p > .003$).

Figure 3 demonstrates empathic accuracy z-scores for all six videos. When examining differences in empathic accuracy across all of the videos, which were specified as dependent variables, our omnibus analyses revealed significant differences for diagnostic group across all videos ($F(1,24) = 4.29, p = .008$, partial $\eta^2 = .52$). Between group effects revealed a significant difference for negative Video 5 ($F(1,24) = 4.26, p = .05$, partial $\eta^2 = .15$, TS mean = .90, SD = .21, TD mean = 1.11, SD = .30) and a trend towards significance and a medium effect size for negative Video 2 ($F(1,24) = 3.77, p = .064$, partial $\eta^2 = .14$, mean TS = .88, SD = .43, TD mean = 1.25, SD = .53). Significant between group differences were not found for positive Video 3 ($F(1,24) = 0.10, p = .75$, partial $\eta^2 = .04$, TS mean = .54, SD = .53, TD mean = .48, SD = .51), negative Video 4 ($F(1,24) = 0.23, p = .64$, partial $\eta^2 = .01$, TS mean = .95, SD = .58, TD mean = .85, SD = .46) or positive Video 6 ($F(1,24) = .31, p = .58$, TS = .91, SD = .32, TD mean = .98, SD = .25).

**Line Tracking Behavioural Results**

Data were excluded from one TS participant who refused to complete the second line-tracking task. When examining group differences in empathic accuracy across both of the line tasks, our Hotelling's Trace omnibus $F$ revealed no significant differences ($F(1, 22) = .93, p = .41$, partial $\eta^2 = .08$; Line 1 TS mean
Discussion

We found evidence supporting our hypotheses that girls with TS differ from TD girls on empathic accuracy for targets experiencing negative affect; empathic accuracy for two of the three negatively valance videos was impaired in TS yet performance was preserved for the positively valance videos (See Figure 3). These results suggest that empathic accuracy abilities in girls with TS are specific to the emotional valence of the target’s story. This is consistent with the extant literature, which demonstrates impaired affect recognition for negative emotions but intact recognition for positive emotions in TS (Anaki et al., 2016; Hong et al., 2014; Lawrence et al., 2003b; Mazzola et al., 2006; McCauley et al., 1987; Skuse, 2005). Thus, the empirically documented socio-emotional deficits in TS appear to extend beyond simple affect recognition difficulties using decontextualized stimuli and demonstrate a larger disruption of social cognition in this genetically defined population. Such a phenomenon may explain the subtle yet potentially impactful social deficits and resulting social anxiety reported by girls with TS in everyday life.

Across all participants, our findings suggest higher accuracy when rating the emotional valence of the negative videos (mean = .99, SD = .06) than the positive videos (mean = .73, SD = .06). These results differ from a recent study in which participants rated empathic accuracy according to the video’s degree of emotional intensity (rating emotional arousal level) instead of valence; our study
only examined emotional valence but not emotional intensity (Mackes et al., 2018). Our divergent findings are likely due to the different ratings schemes (rating intensity vs. valence). In particular, the Mackes et al. study implemented stimuli that depicted only one emotion for each video; videos also varied in emotional intensity. Generally, our negative videos conveyed themes pertaining to interpersonal loss and our positive videos portrayed multiple feelings including love, security, pride, and comfort. Emotional intensity was not controlled for across our administered videos and, therefore, could further influence empathy accuracy in TS.

Neuroimaging studies in adults elucidate how empathic accuracy is associated with a balanced dynamic between two neural systems (Zaki et al., 2009). Cognitive empathy, is the ability to “explicitly consider (and perhaps understand) one’s state and their sources.” It recruits the temporal pole, temporal parietal junction, medial prefrontal cortex, and the precuneus, thus largely mapping onto the default mode network (Zaki and Ochsner, 2012). Emotional empathy, however, is the ability to “vicariously share one’s internal state” (p.675), recruits the anterior insula, premotor cortex, inferior parietal lobule and the anterior cingulate cortex, and thus involves key regions for interoception and largely maps onto the salience network (Zaki and Ochsner, 2012). Regions involved in cognitive empathy, such as the medial prefrontal cortex develop rapidly during adolescence (Cachia et al., 2016; Raznahan et al., 2011; Shaw et al., 2008), making it a critical time for empathic development. In fact, in typically developing teens, increased BOLD activation in regions associated with cognitive
empathy, rather than emotional empathy, are associated with higher empathic accuracy (Kral et al., 2017). Thus, the development of brain regions underlying metacognitive abilities during adolescence may improve empathic accuracy and enhance a person’s ability for “putting one’s self into another persons’ shoes” (Zaki and Ochsner, 2012). Conversely, high levels of BOLD activation in regions associated with emotional empathy are associated with decreased empathic accuracy (Kral et al., 2017). Girls with TS demonstrate functional and structural deficits in regions associated with both cognitive and emotional empathy (Bray et al., 2011; Green et al., 2017; Hong et al., 2014; Marzelli et al., 2011) and, therefore, deficits in empathic accuracy may be related to cortical dysfunction associated with both systems.

In addition to struggling to recognize emotional faces, girls with TS also demonstrate alexithymia, the inability to name and describe emotions (Roelofs et al., 2015). Poor emotion processing negatively impacts empathic accuracy, given the considerable overlap in self and other processing in this domain (Ochsner et al., 2008; Zaki et al., 2012; Zaki and Ochsner, 2012). Thus, for disorders characterized by disturbed emotion processing, such as TS (Hong et al., 2014; Lawrence et al., 2003b; Skuse, 2005), the ability to share in the affective states of others is likely impaired as well (Aan Het Rot and Hogenelst, 2014). Since empathic accuracy differs in emotional valence and does not impact all empathetic responses in TS, disturbances in emotional empathy may particularly drive empathic accuracy deficits in TS. Reasons underlying emotion processing deficits in TS remain unknown and could be driven by a number of factors.
Explanations for such difficulties include poor emotional differentiation, visual spatial deficits and internal body cue processing deficits.

Because alexithymia may be present in TS, it is possible that impaired social cognition in affected individuals may be due to poor emotion differentiation, a limited lexicon for precisely labelling emotions (Kashdan et al., 2015). Girls and women with TS, however, demonstrate verbal strengths relative to visual spatial performance (Ross et al., 2002), thus, making it less likely that affect processing deficits in TS are driven by an impaired emotional lexicon. Additionally, girls with TS demonstrate intact empathy during auditory-verbal empathy tasks (Anaki et al., 2018). None-the-less, future studies should further assess this hypothesis.

Regarding the theory that emotion processing deficits in TS are influenced by visual-spatial deficits (Lawrence et al., 2003b; Skuse et al., 2005), we found intact visual-spatial tracking abilities in TS on a moving line-position rating task. Thus, empathic accuracy deficits are unlikely due to tracking abilities, attention problems or difficulties with rating abilities in our participants. This control task, however, may not have tapped into the primary visual-spatial deficits impacting TS. Previous studies suggest that girls with TS particularly struggle to perceive and process visual details within a larger global-visual context (Mazzocco et al., 2006), which is also called figure-ground processing. Girls with TS also tend to process facial features in a piecemeal fashion (Anaki et al., 2016). This tendency, however, may be affectively driven for the processing of faces rather than being primarily driven by visual factors. In fact, emotional reactivity within the amygdala impacts fear processing and reduces one’s tendency to examine the eyes for
emotional context. This may contribute to problems with affect recognition since the eyes are the primary feature for examining negative emotions such as fear (Adolphs et al., 2005; Benuzzi et al., 2007). Abnormal emotional reactivity is present in girls with TS (Hong et al., 2014), thus fear processing deficits in TS may be affectively driven and could explain why girls with TS may spend more time examining non-eye facial features than controls according to eye tracking studies (Lawrence et al., 2003; Mazzola et al., 2006). This could influence emotional empathy more so than visual spatial deficits in TS and thus, should be further examined.

Expanding upon the theory that empathy deficits in TS are affectively driven provides the basis for another testable hypothesis: poor social-emotional processing in TS may be influenced by interoceptive deficits – deficits in the sense of one’s internal condition of the body (Craig, 2002). Emotion processing is considerably dependent upon changes within the body. When detected, changes (whether expected or unexpected) are assigned labels pertaining to their perceived emotional valence (Dunn et al., 2010). In TS, girls have high rates of heart deficits (Ho et al., 2004). Cardiac deficits in TS may impact one’s internal physiological senses, thus potentially impacting interoception, emotion processing and empathy in TS. Thus, future studies should replicate studies of empathy accuracy with a version of the EAT that rates emotional intensity instead of valence but also assesses the potential influence of interoceptive processing on emotion processing and social cognition in TS.
The results of our study are important since studying empathic accuracy in girls with TS may not only improve our understanding of the mechanisms underlying their social deficits, but studying TS also provides a model for better understanding gene-body-brain interactions. Thus, the continued study of TS allows us to ascertain how aberrant gene expression of the X-chromosome influences the physical body, brain development and social cognition. Future studies of TS may provide important clues into the links between specific phenotypic characteristics (i.e. physiological deficits) and their impact on specific brain functions, such as emotion processing and empathy.

Limitations

Our study has several limitations. First, our sample size was small and we implemented a cross sectional design. Future studies should examine the impact of development by examining empathic accuracy longitudinally with larger samples. Moreover, another study weakness includes our limited range and number of stimuli, which should be increased for future replications of this study.

Conclusions

This is the first known study to examine empathic accuracy in girls with Turner Syndrome as compared to age-matched controls. As hypothesized, we found between-group differences in empathic accuracy for some of the videos characterized by negative emotions. Between group differences were not due to visual-spatial deficits involved in rating the task, as demonstrated by intact accuracy for both groups on a visual moving line tracking task. Our results suggest that the previously detected deficits for negative emotions may influence
empathic accuracy abilities in TS during negatively valance empathic interactions. These deficits may help explain the self-reported social cognition deficits and social anxiety in TS.
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EMPATHY TURNER SYNDROME


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Figure 1. Empathic task and analysis procedures

**Task:** Participant watches and continuously rates the emotional valence of the target

**Individual Subject Analyses:**
Determine empathic accuracy by comparing participant (orange) and target’s (blue) continuous ratings over time (s) by calculating a Pearson’s correlation and then converting this to a T-Score.

**Group Level Analyses:**
Compare Z Scores obtained for each participant across diagnostic groups (TS= red, control= black) across each video to assess differences in empathetic accuracy (target’s rating = blue).
Figure 2. Associations between empathic accuracy and age or average Tanner score

Empathic accuracy across both groups were correlated with the participant’s age and average Tanner scores (average of Tanner breast and public hair ratings) for videos 2-6 (displayed left to right). Top rows are correlations with age and the bottom rows display correlations with Tanner Scale.
Figure 3. Mean Empathic Accuracy Z-Scores for Each Video
Figure 4. Continuous ratings of the target’s perceived emotional valance

Blue Line = Continuous rating of emotional valence by the target. Black line = Mean continuous ratings by control girls. Red line = Mean continuous ratings by the girls with Turner syndrome. Ratings were within a 1 to 9-point scale. Time was measured in seconds.
Table 1. Demographic data for each participant

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<td>3.5</td>
</tr>
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<td>13.59</td>
<td>Turner</td>
<td>100</td>
<td>91</td>
<td>111</td>
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<tr>
<td>13.33</td>
<td>Turner</td>
<td>136</td>
<td>100</td>
<td>114</td>
<td>3.5</td>
</tr>
</tbody>
</table>

VCI = Verbal Comprehension Index on the WISC-IV, PRI = Perceptual Reasoning Index on the WISC-IV, and FSIQ = Full Scale IQ as measured by the WISC-IV, Average Tanner Stage = average of breast and pubic hair ratings