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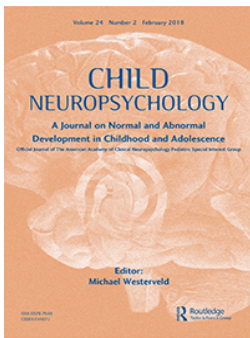
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## The effect of early life stress on the cognitive phenotype of children with an extra X chromosome (47,XXY/47,XXX)

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### ABSTRACT

Studies on gene–environment interactions suggest that some individuals may be more susceptible to life adversities than others due to their genetic profile. This study assesses whether or not children with an extra X chromosome are more vulnerable to the negative impact of early life stress on cognitive functioning than typically-developing children.

A total of 50 children with an extra X chromosome and 103 non-clinical controls aged 9 to 18 years participated in the study. Cognitive functioning in domains of language, social cognition and executive functioning were assessed. Early life stress was measured with the Questionnaire of Life Events. High levels of early life stress were found to be associated with compromised executive functioning in the areas of mental flexibility and inhibitory control, irrespective of group membership. In contrast, the children with an extra X chromosome were found to be disproportionately vulnerable to deficits in social cognition on top of executive dysfunction, as compared to typically-developing children. Within the extra X group the number of negative life events is significantly correlated with more problems in inhibition, mental flexibility and social cognition. It is concluded that children with an extra X chromosome are vulnerable to adverse life events, with social cognition being particularly impacted in addition to the negative effects on executive functioning. The findings that developmental outcome is codependent on early environmental factors in genetically vulnerable children also underscores opportunities for training and support to positively influence the course of development.

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Research over the last decades has produced a convincing body of evidence that early life experiences have a sustained impact on neurodevelopment, shaping the developing brain in a way that has long-term implications for brain function and behavior. Early life stress (ELS) is the exposure to a single event or multiple events during childhood that exceeds the child's coping resources and leads to prolonged phases of stress, thus impacting neurodevelopment (Pechtel & Pizzagalli, 2011).

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Studies on gene–environment interactions suggest that some individuals may be more susceptible to environmental factors such as ELS than others, depending on their genetic profiles (Simms, 2007). These individuals may carry specific genetic variants—typically of small effect (Simms, 2007)—that can be present in the absence of a clinical genetic “syndrome”. It may be important to also focus on individuals with clinical genetic syndromes, as the majority of such genetic syndromes are associated with compromised neurodevelopment, possibly resulting in less resilience and more vulnerability to the impacts of life adversities. The aim of this study is to evaluate vulnerability to ELS in children with an extra X chromosome as compared to children from the general population. Approximately 1 to 2 in 1000 children are born with an extra X chromosome, leading to the 47,XXY chromosomal pattern in boys (Klinefelter syndrome) and the 47,XXX chromosomal pattern in girls (Trisomy X). A range of physical, behavioral, and cognitive consequences may be present, to varying degrees, with IQ scores typically at the lower end of the normal range (i.e., 80 to 90 points; Giltay & Maiburg, 2010; Groth, Skakkebaek, Host, Gravholt, & Bojesen, 2013). However, to date there have been no studies on vulnerability for early life stress in such sex chromosome trisomies (SCTs). Therefore, in this study the association between early life stress and cognitive functioning is assessed, focusing on three domains of cognition which are important for behavioral adaptation and which are often affected in children and adults with SCT: language, executive functioning and social cognition.

## Method

In total, 50 children (29 boys and 21 girls) with an extra X chromosome and 103 non-clinical controls (44 boys and 59 girls) participated in the study. For a more detailed description of recruitment and diagnosis of this cohort, see van Rijn, Stockmann, Borghgraef, et al. (2014), van Rijn, Stockmann, van Buggenhout, van Ravenswaaij-Arts, and Swaab (2014), and van Rijn and Swaab (2015).

The group of children with an extra X chromosome included a “prenatal group” (54% of the group) comprising children from families that were actively followed-up after a prenatal diagnosis with the help of clinical genetics departments, and a “referred” group (46% of the group) comprising of children from families that were actively seeking information about the condition of their child (recruited through support groups and calls for participants) or those who were seeking help for developmental problems (recruited through pediatricians, psychologists, psychiatrists, clinical genetics departments).

A total of 9 boys with XXY were using testosterone supplements. Controls from the general population were recruited from regular schools: none of the children in this group scored in the clinical range ( $\geq 70$ ) on the Childhood Behavior Checklist (CBCL; Achenbach, 1991). A multivariate analysis of variance (MANOVA) showed no significant main effect of group for age ( $p = .21$ ) or parental education ( $p = .26$ ). Within the extra X group, parental education level ( $p = .75$ ) is similar for both the prenatal and referred subgroups. After providing a complete description of the study, which was approved by the Ethical Committee of Leiden University Medical Center, written informed consent was obtained according to the Declaration of Helsinki.

Early life stress was assessed with the Questionnaire of Life Events (Veerman, 1992), a 24-item questionnaire measuring stressful events that can occur within families, such as parental death or divorce, hospitalization, and traffic accidents (see the Appendix for all 24 items). The questionnaire was completed by the primary caretaker of the child. The questionnaire has good internal consistency, with a Cronbach's alpha of .80. The total number of negative life events is the main variable used in the statistical analyses.

Intellectual functioning was assessed using the subtests Vocabulary (V) and Block Design (BD) of the Dutch adaptation of the Wechsler Intelligence Scales for Children – Third Edition (WISC-III; Wechsler, 2003). This V-BD short form has been shown to be a valid proxy of full-scale IQ (FSIQ) in clinical and non-clinical populations (Campbell, 1998; Crawford, Allan, & Jack, 1992).

The Formulated Sentences subtest of the Clinical Evaluation of Language Fundamentals – Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003) was used to assess expressive language skills. Receptive language skills were measured using the Comprehension of Implicit Sentences subtest of the Dutch Language Tests for Children (van Bon, 1982).

The Social Cognitive Skills Test (SCST) was used to assess Theory of Mind (van Manen, Prins, & Emmelkamp, 2009). Facial affect labeling was examined using a computerized test based on the Karolinska Directed Emotional Faces (KDEF) set, a full description of which is provided in van Rijn, Stockmann, van Buggenhout, et al. (2014).

The Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville, 1999) was used to evaluate executive functioning (see also van Rijn, & Swaab, 2015). The Shifting Set Visual subtest (number of errors) was used to measure inhibition and mental flexibility, the Sustained Attention – Dots was used to measure sustained attention regulation (tempo fluctuation), and the Spatial Temporal Sequencing subtest (number of identified targets in correct order, backwards) was used to measure working memory.

Correlational analyses show that within the extra X group, IQ is significantly correlated with language, both receptive ( $r = .64, p < .001$ ) and expressive ( $r = .59, p < .001$ ), as well as measures of executive functioning, including inhibition ( $r = -.27, p = .04$ ) and working memory ( $r = .47, p < .001$ ). Therefore, in the analyses of these parameters, IQ was used as a covariate. MANOVAs and multivariate analyses of covariance (MANCOVAs) were used with the cognitive scores as independent factors and group (control, extra X) and ELS (high, low) as the fixed factors. Because of the multivariate nature of the methodology there was some data loss (ranging from 2 to 12 participants in total) due to incomplete series of test variables for some children who were not able to complete the full range of tests.

## Results

### *Early Life Stress (ELS)*

The mean number of negative life events for the extra X group ( $M = 2.8, SD = 2.2$ ) is not significantly different from that of the control group ( $M = 2.7, SD = 2.0, p = .72$ ). Table 1 shows the distributions of the number of negative life events across groups, which is not significantly different ( $p = .96$ ). Furthermore, there are

**Table 1.** Percentage of Children Exposed to Various Degrees of Early Life Stress (ELS).

Number of negative life events group	Control group	Extra X
0	12.6%	10.0%
1	19.4%	16.0%
2	20.4%	32.0%
3	20.4%	16.0%
> 3	27.2%	26.0%

no significant group differences in the distribution of the type of life events across the control group and the extra X group ( $p = .71$ ). The top five negative life events are very similar across the groups: 1) Death of a pet, 2) One of the grandparents died, 3) A close friend moved away, 4) One of the parents was admitted to hospital, and 5) Parental divorce (control group) or The child was admitted to a hospital (extra X group).

Subgroups were formed from the control group and the extra X group. The full range of the number of negative life events was split up to include about 50% of the children across two subgroups: a subgroup of children with 0, 1 or 2 negative life events (low ELS group) and a subgroup of children with 3 or more negative life events (high ELS group). There is a difference of borderline significance in the sex distributions between the subgroups ( $p = .07$ ). As can be seen from Table 2, there are no significant group (control, extra X) by ELS (low, high) interactions for IQ ( $p = .69$ ), age ( $p = .40$ ), or parental education ( $p = .62$ ). Within the extra X group and the control group there is no significant correlation between parental education and ELS ( $r = -.06$ ,  $p = .69$  and  $r = .06$ ,  $p = .56$ , respectively). Furthermore, within the SCT group, the mean number of life events is similar for the prenatal recruited and referred subgroups ( $p = .38$ ). The distribution of prenatal and referred cases is similar for the low and high ELS groups ( $p = .65$ ). In the low ELS group, 54% are prenatal cases and 46% are referred cases; in the high ELS group, 61% are prenatal cases and 39% are referred cases.

### Intellectual Functioning

There is a main effect of group for IQ,  $F(1, 149) = 90.3$ ,  $p < .001$ , with lower scores in the extra X group (Table 2). The average norm score for Block Design is 10.5 (3.2) in the control group and 7.5 (3.3) in the extra X group, which is significantly different

**Table 2.** Group Characteristics Stratified According to Low and High Early Life Stress (ELS).

Group	<i>n</i> (boys/girls)	Age (years), <i>M</i> ( <i>SD</i> )	IQ, <i>M</i> ( <i>SD</i> )	Parental education, <i>M</i> ( <i>SD</i> )
Control	103 (44/59)	11.9 (2.9)	103.6 (12.5)	2.1 (0.6)
Low ELS	54 (23/31)	11.6 (2.8)	103.6 (12.9)	2.1 (0.6)
High ELS	49 (21/28)	12.3 (3.0)	103.6 (12.1)	2.2 (0.6)
Extra X	50 (29/21)	12.7 (3.1)	82.8 (14.8)	2.2 (0.6)
Low ELS	29 (17/12)	12.8 (3.0)	81.7 (16.7)	2.3 (0.5)
High ELS	21 (12/9)	12.5 (3.5)	84.4 (12.1)	2.3 (0.6)

( $p = .002$ ). The average norm score for Vocabulary is 9.9 (2.4) in the control group and 5.7 (3.8) in the extra X group, which is significantly different ( $p < .001$ ).

### **Cognitive Performance in Boys versus Girls with an Extra X Chromosome**

To assess if boys with XXY and girls with XXX have different cognitive scores, which would call for the inclusion of the factor “sex” in the analysis of ELS, all cognitive scores were compared. None of the cognitive domains show significant group differences (Table 3). Based on this, boys and girls with an extra X were grouped together in all further analyses.

### **Language**

A MANCOVA with the group (control, extra X) and ELS (low, high) as the fixed factors, IQ as a covariate and total scores for receptive language and expressive language as the independent factors showed no significant main multivariate effect of ELS ( $p = .44$ ), indicating there is no overall effect of ELS on language skills. Also, there is no significant multivariate group by ELS interaction,  $F(2, 143) = 1.4$ ,  $p = .24$ , indicating that this is similar for the control group and the extra X group.

### **Social Cognition**

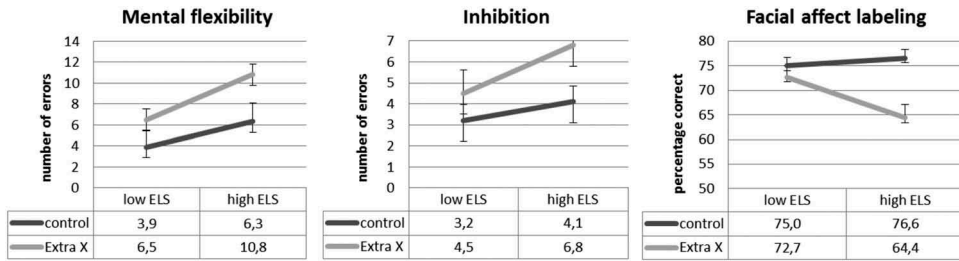
A MANOVA with group (control, extra X) and ELS (low, high) as the fixed factors and total scores for theory of mind and facial affect labeling as the independent factors showed no significant main multivariate effect of ELS ( $p = .24$ ), indicating that there is no overall effect of ELS on social cognition. However, there is a significant multivariate group by ELS interaction,  $F(2, 132) = 3.2$ ,  $p = .04$ , indicating that the effect of ELS is different for the control group and the extra X group. Univariate effects show that this interaction is significant for facial affect labeling,  $F(1, 133) = 5.7$ ,  $p = .02$ , but not for Theory of Mind,  $p = .72$ . Thus, only in the extra X group is facial affect labeling dependent on ELS, with a high ELS associated with more compromised social cognition (Figure 1).

### **Executive Functioning**

A MANCOVA (covaried for IQ) with group (control, extra X) and ELS (low, high) as the fixed factors and sustained attention regulation, inhibition, mental flexibility and working

**Table 3.** Cognitive Performance (Raw Scores) in Boys versus Girls with an Extra X Chromosome.

Cognitive domain	Boys with XXY, <i>M (SD)</i>	Girls with XXX, <i>M (SD)</i>	<i>p</i>
Receptive language	84.4 (16.3)	77.3 (19.8)	.14
Expressive language	53.8 (23.2)	54.0 (24.1)	.98
Facial affect labeling	70.7 (16.0)	70.4 (13.9)	.94
Theory of mind	96.4 (29.3)	82.6 (33.7)	.12
Attention regulation	2.5 (1.3)	2.8 (1.3)	.36
Inhibition	5.6 (5.9)	6.2 (7.0)	.72
Mental flexibility	8.6 (7.0)	9.3 (8.5)	.75
Working memory	44.9 (20.0)	40.3 (21.5)	.44



**Figure 1.** Scores on cognitive tests in the control group and extra X group, stratified to degree of early life stress (ELS).

*Note.* Both groups show deterioration in mental flexibility and inhibition with high ELS, but only the extra X group show deterioration in facial affect labeling with high ELS.

memory as the independent factors showed a significant main multivariate effect of ELS,  $F(4, 131) = 3.2, p = .01$ , indicating that ELS has an overall effect on executive functioning. Univariate effects show that the effect of ELS is significant for mental flexibility,  $F(1, 134) = 6.8, p = .01$ , borderline significant for inhibition, ( $p = .07$ , but not significant for sustained attention regulation,  $p = .20$ , or working memory,  $p = .35$ ). In other words, the effect of ELS is present for specific aspects of executive functioning. There is no significant multivariate group by ELS interaction,  $p = .87$ , indicating that the effects of ELS are similar for the control group and the extra X group (Figure 1).

### Role of Testosterone Treatment

To test for potential confounding effects of testosterone treatment, analyses were repeated with the 9 XXY boys on testosterone treatment excluded. The results show that the effects of ELS (mental flexibility,  $p = .008$ , and inhibition,  $p = .04$ ) and the group by ELS interactions (facial affect labeling,  $p = .04$ ) remain significant.

### Relation between Early Life Stress and Cognitive Performance

Within the extra X group, Spearman's correlational analyses showed that the number of negative life events is significantly correlated with the ability to label affective facial expressions ( $r = -.24, p = .04$ ), inhibitory control ( $r = -.26, p = .03$ ) and mental flexibility ( $r = -.27, p = .03$ ), with more negative life events associated with more compromised cognitive performance. No significant correlations were found for receptive language ( $p = .39$ ), expressive language ( $p = .40$ ), theory of mind ( $p = .41$ ), attention regulation ( $p = .39$ ) or working memory ( $p = .46$ ).

### Discussion

The results of this study show that high levels of ELS are associated with compromised executive functioning in the areas of mental flexibility and inhibitory control. This was found irrespective of group membership, suggesting that children with an extra X chromosome are equally vulnerable in this respect as typically-developing children. In

contrast, the children with an extra X chromosome are disproportionately vulnerable for deficits in facial affect labeling, depending on the level of ELS. In line with these observations, within the extra X group the degree of ELS is significantly correlated with more problems in inhibition, mental flexibility and facial affect labeling. Other cognitive domains—i.e., sustained attention regulation, working memory and receptive/expressive language skills—are not dependent on ELS.

The observation that executive functioning is affected by negative early life events fits with other studies reporting global deficits in executive functioning following ELS (Bos, Fox, Zeanah, & Nelson, 2009; Colvert et al., 2008; Pollak et al., 2010). It has been proposed that several developmental characteristics may contribute to this vulnerability (Pechtel & Pizzagalli, 2011). First, brain regions with extended postnatal development—as the frontal lobe areas supporting executive functions—are particularly vulnerable to long-term effects as a result of stress. Second, frontal lobe areas have a high density of dopaminergic projections and glucocorticoid receptors, which are influenced by stress.

The finding that the labeling of facial expressions of emotion is disproportionately compromised in children with an extra X who had experienced high levels of ELS is interesting considering that social dysfunction is a consistently reported area of vulnerability (Visootsak & Graham, 2009). A substantial body of work shows that perceiving and understanding emotions depends in part on brain regions such as the superior temporal gyrus (STG) and frontal brain areas (Adolphs, 2002), which are among the last to mature (Pechtel & Pizzagalli, 2011). Neuroimaging findings showing that the STG and frontal brain areas are compromised in individuals with an extra X chromosome (Lenroot, Lee, & Giedd, 2009), tentatively support the notion of a double-hit effect: ELS may impact upon the development of brain areas that are already more vulnerable to developmental disruptions.

To degree to which the increased vulnerability to stress of cognitive functioning is directly related to the effects that the extra X chromosome has on brain development remains unclear. It is hoped that the findings in this study stimulate the formulation and testing of genetic hypotheses in future studies, which could for example compare groups of children with varying degrees of additional X chromosomes to investigate if vulnerability to early life stress depends on X chromosomal mechanisms. Additionally, it would be interesting to focus on other environmental factors, including the clinical services received, the family history of learning disabilities and developmental delays, and socioeconomic status such as parental educational level. In this study, no significant correlation was found between parental educational level and ELS within the extra X group and within the control group. Furthermore, there are no significant differences in parental educational level between the high/low ELS subgroups. Based on these findings, it is concluded that SES has not contributed to the group effects that are observed. Another factor of interest is the potential role of androgen deficiency—and related medication—in boys with XXY. Unfortunately, the subgroup of 9 boys using testosterone supplements is too small to address this issue in the current study, which is a limitation. It would also be very interesting to assess the degree of stress in the extra X group in response to life events, and to what degree this results from limited coping skills, because this may also be one of the mechanisms that can account for the increased vulnerability in the extra X group.

The findings that children with an extra X chromosome seem particularly vulnerable in terms of social cognitive skills may have clinical implications, as these children may require closer monitoring and extra support when experiencing stressful life events compared to other children. In particular, the consistently-reported increased tendency in children with an extra X chromosome to show social withdrawal (Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010; Tartaglia, Howell, Sutherland, Wilson, & Wilson, 2010) warrants special attention, as this coping strategy may make children even more prone to the effects of stress on social cognition due to social isolation and a related reduction in social learning experiences.

Thus, early and timely monitoring and support of children with an extra X chromosome is warranted in case of ELS factors. Executive functioning and related problems in the regulation of emotion, thought and behavior—and social cognition which is important for social adaption—should be targets in clinical care. At the same time, this study also underscores that genetic make-up is not the only determinant of developmental outcome in children with an extra X, but that environmental factors may also have a substantial impact—not only in terms of vulnerability but also in terms of opportunities to positively shape development through training, support and intervention.

## Disclosure Statement

No potential conflict of interest was reported by the authors.

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## References

- Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington, VT: University of Vermont Department of Psychiatry.
- Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology*, 12(2), 169–177. doi:10.1016/S0959-4388(02)00301-X
- Bos, K. J., Fox, N., Zeanah, C. H., & Nelson, C. A., III. (2009). Effects of early psychosocial deprivation on the development of memory and executive function. *Frontiers in Behavioral Neuroscience*, 3. doi:10.3389/neuro.08.016.2009
- Campbell, J. M. (1998). Internal and external validity of seven Wechsler Intelligence Scale for Children – Third Edition short forms in a sample of psychiatric inpatients. *Psychological Assessment*, 10(4), 431–434. doi:10.1037/1040-3590.10.4.431
- Colvert, E., Rutter, M., Kreppner, J., Beckett, C., Castle, J., Groothues, C., ... Sonuga-Barke, E. J. S. (2008). Do theory of mind and executive function deficits underlie the adverse outcomes associated with profound early deprivation? Findings from the English and Romanian adoptees study. *Journal of Abnormal Child Psychology*, 36(7), 1057–1068. doi:10.1007/s10802-008-9232-x
- Crawford, J. R., Allan, K. M., & Jack, A. M. (1992). Short-forms of the UK WAIS-r: Regression equations and their predictive-validity in a general-population sample. *British Journal of Clinical Psychology*, 31, 191–202. doi:10.1111/bjc.1992.31.issue-2

- De Sonneville, L. M. J. (1999). Amsterdam neuropsychological tasks: A computer-aided assessment program. In B. P. L. M. Den Brinker, P. J. Beek, A. N. Brand, S. J. Maarse, & L. J. M. Mulder (Eds.), *Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in psychology* (Vol. 6). Lisse, The Netherlands: Swets & Zeitlinger.
- Giltay, J. C., & Maiburg, M. C. (2010). Klinefelter syndrome: Clinical and molecular aspects. *Expert Review of Molecular Diagnostics*, 10(6), 765–776. doi:10.1586/erm.10.63
- Groth, K. A., Skakkebaek, A., Host, C., Gravholt, C. H., & Bojesen, A. (2013). Clinical review: Klinefelter syndrome—a clinical update. *The Journal of Clinical Endocrinology & Metabolism*, 98(1), 20–30. doi:10.1210/jc.2012-2382
- Lenroot, R. K., Lee, N. R., & Giedd, J. N. (2009). Effects of sex chromosome aneuploidies on brain development: Evidence from neuroimaging studies. *Developmental Disabilities Research Reviews*, 15(4), 318–327. doi:10.1002/ddrr.v15:4
- Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: An integrated review of human literature. *Psychopharmacology*, 214(1), 55–70. doi:10.1007/s00213-010-2009-2
- Pollak, S. D., Nelson, C. A., Schlaak, M. F., Roeber, B. J., Wewerka, S. S., Wiik, K. L., ... Gunnar, M. R. (2010). Neurodevelopmental effects of early deprivation in postinstitutionalized children. *Child Development*, 81(1), 224–236. doi:10.1111/j.1467-8624.2009.01391.x
- Semel, E., Wiig, E. H., & Secord, W. A. (2003). *Clinical evaluation of language fundamentals, fourth edition (CELF-4)*. Toronto, Canada: The Psychological Corporation/A Harcourt Assessment Company.
- Simms, M. D. (2007). Language disorders in children: Classification and clinical syndromes. *Pediatric Clinics of North America*, 54(3), 437–467. doi:10.1016/j.pcl.2007.02.014
- Tartaglia, N., Cordeiro, L., Howell, S., Wilson, R., & Janusz, J. (2010). The spectrum of the behavioral phenotype in boys and adolescents 47,XXY (Klinefelter syndrome). *Pediatric endocrinology reviews*, 8(Suppl 1), 151–159.
- Tartaglia, N., Howell, S., Sutherland, A., Wilson, R., & Wilson, L. (2010). A review of trisomy X (47, XXX). *Orphanet Journal of Rare Diseases*, 5, 9. doi:10.1186/1750-1172-5-8
- van Bon, W. H. J. (1982). *Handleiding Taaltests voor Kinderen TvK* [Manual Language Tests for Children]. Lisse, The Netherlands: Swets & Zeitlinger B.V.
- van Manen, T. G., Prins, P. J. M., & Emmelkamp, P. M. G. (2009). *Manual for the Social Cognitive Skills Test*. Houten, The Netherlands: Bohn Stafleu van Loghum.
- van Rijn, S., Stockmann, L., Borghgraef, M., Bruining, H., van Ravenswaaij-Arts, C., Govaerts, L., ... Swaab, H. (2014). The social behavioral phenotype in boys and girls with an extra X chromosome (Klinefelter syndrome and Trisomy X): A comparison with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 44(2), 310–320. doi:10.1007/s10803-013-1860-5
- van Rijn, S., Stockmann, L., van Buggenhout, G., van Ravenswaaij-Arts, C., & Swaab, H. (2014). Social cognition and underlying cognitive mechanisms in children with an extra X chromosome: A comparison with autism spectrum disorder. *Genes Brain and Behavior*, 13(5), 459–467. doi:10.1111/gbb.12134
- van Rijn, S., & Swaab, H. (2015). Executive dysfunction and the relation with behavioral problems in children with 47,XXY and 47,XXX. *Genes, Brain, and Behavior*, 14, 200–208. doi:10.1111/gbb.12203
- Veerman, J. W. (1992). Assessing the family environment of clinically admitted children. Life events, total family functioning and parental coping styles. In J. D. van Der Ploeg, P. M. van den Bergh, M. Klomp, E. J. Knorth, & M. Smit (Eds.), *Vulnerable youth in residential care. Part I. Social competence, social support and social climate* (pp. 207–224). Apeldoorn: Garant.
- Visootsak, J., & Graham, J. M. (2009). Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY. *Developmental Disabilities Research Reviews*, 15(4), 328–332. doi:10.1002/ddrr.v15:4
- Wechsler, D. (2003). *Wechsler Intelligence Scale for Children – Fourth Edition*. San Antonio, TX: Psychological Corporation.

## Appendix

### Overview of life events, as measured with the Questionnaire of Life Events.

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A brother or sister was added to the family.  
The child was admitted to hospital.  
The child acquired a permanent physical disability due to illness or accident.  
One of the parents was admitted to hospital.  
A sibling was admitted to hospital.  
The child reached a milestone in school or sports.  
Death of a pet.  
One of the grandparents died.  
A sibling died.  
One of the parents died.  
A close friend died.  
The child joined a new club or society.  
One of the parents was unemployed for more than six months.  
One of the parents started a new employment for at least two days per week.  
The child changed schools.  
A close friend moved away.  
The family moved.  
The child acquired a new friend.  
An adult was added to the family.  
The child got a stepfather or stepmother.  
A brother or sister left the family.  
One of the parents left the house permanently due to divorce or parents no longer wishing to live together.  
The child was involved in a road traffic accident.  
One of the family members developed an alcohol or drug addiction.

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