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Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, Fragile X, and Cri du Chat syndromes: Results from a 2.5 year follow-up

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*Contrasting age related changes in autism spectrum disorder phenomenology in
Cornelia de Lange, Fragile X and Cri du Chat syndromes: Results from a 2.5 year
follow up.*

by

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ABSTRACT

Little is known about the way in which the characteristics of autism spectrum disorder (ASD) develop and manifest across the age span in individuals with genetic syndromes. In this study we present findings from a three year follow up of the characteristics associated with ASD in three syndromes: Cornelia de Lange (CdLS), Fragile X (FXS) and Cri du Chat (CdCS). Parents and carers of 251 individuals (CdLS= 67, CdCS= 42 and FXS=142) completed the Social Communication Questionnaire (SCQ) at Time 1 (T1) and again two and a half years later (T2). The FXS and CdLS groups were more likely to meet the cut-offs for both autism and ASD and show greater severity of ASD related behaviors, at both T1 and T2, compared to the CdCS group. Older individuals (>15yrs) with CdLS were more likely to meet the cut off for ASD than younger individuals (<=15yrs) with the syndrome and more likely to show greater severity of social impairments. In FXS repetitive behaviors were found to become less prominent with age and in CdCS social impairments were reported to be more severe with age. There were no significant changes between T1 and T2 in the severity of ASD characteristics in the CdCS and CdLS groups. The FXS group showed significantly fewer repetitive behaviors and less severe impairments in social interaction over this time frame. The findings suggest that while there may be similarities in overall severity and presentation of ASD characteristics in CdLS and FXS, these characteristics have divergent patterns of development within these groups.

Key words: Cornelia de Lange syndrome, Fragile X syndrome, Cri du Chat syndrome, autism spectrum disorder, autism, longitudinal, follow up, behavioral phenotype

INTRODUCTION

The association between autism spectrum disorder (ASD) and developmental disorders of genetic origin has recently become a source of great interest and debate within the behavioral phenotype and autism literatures. A large number of genetic syndromes have been reported to show a degree of association with ASD that is higher than expected including (amongst others): Tuberous Sclerosis Complex Williams, Fragile X, Rett, Cohen, Down and Cornelia de Lange syndromes (for reviews, see Fombonne, 1999; Gillberg & Coleman, 2000; Moss & Howlin, 2009; Moss et al., 2011). Studies that have evaluated the association between ASD and specific genetic syndromes in greater detail, have confirmed significant overlap with ASD but have also identified subtle differences in the way in which these characteristics manifest. However, little is known about how these characteristics develop across the age span and whether this is similar or different to that observed in those with idiopathic ASD. In the current study we examine age related changes in ASD symptomatology¹ in Cornelia de Lange syndrome (CdLS) compared to that of individuals with Fragile X (FXS) and Cri du Chat syndromes (CdCS). Both CdLS and FXS are considered to have a strong, but likely atypical, association with ASD whereas CdCS does not demonstrate significant overlap with ASD characteristics but does show similarities to CdLS with regard to degree of intellectual disability and communication skills.

Cornelia de Lange syndrome

CdLS is a multisystemic congenital syndrome that affects approximately one child in every 40,000-100,000 (O'Brien & Yule, 1995). The syndrome is caused by deletions

on chromosomes 5 (NIP-BL), 10 (SMC3) and X linked SMC1A and HDAC8 genes ([Deardorff et al., 2007](#); [Deardorff et al., 2012](#); [Gillis et al., 2004](#); [Krantz et al., 2004](#); [Musio et al., 2006](#); [Tonkin, et al., 2004](#)). It is a malformation disorder with a distinctive physical appearance, small stature, medical complications and variable developmental and behavioral presentation. There is a broad range of severity of intellectual disability ranging from mild to profound ([Kline et al., 2007](#)).

Studies have consistently reported a heightened prevalence of ASD in CdLS ranging from 50-67% ([Basile et al., 2007](#); [Berney, et al., 1999](#); [Bhuiyan et al., 2006](#); [Moss et al., 2008](#); [Moss et al., 2012](#); [Oliver et al., 2008](#); [Oliver et al., 2011](#)). Studies that have employed appropriate contrast groups have demonstrated that this heightened prevalence is not solely accounted for by degree of intellectual disability ([Moss et al., 2008](#); [Moss et al., 2012](#); [Oliver et al., 2008](#)). Comparison of individuals with CdLS to those with idiopathic ASD (matched for chronological age and nonverbal skills) confirms that while there are broad similarities between the two groups, subtle differences in specific areas of communication and social interaction are evident ([Moss et al., 2012](#)). Specifically, social anxiety and selective mutism are reported to be prominent ([Collis et al., 2006](#); [Goodban, 1993](#); [Moss et al., 2008](#); [Nelson et al., 2014](#); [Richard et al., 2009](#)).

There is emerging evidence indicating broad age-related changes in CdLS including increased anxiety, low mood and challenging behavior ([Berney et al., 1999](#); [Nelson et al., 2014](#); [Oliver et al., 2011](#)) alongside the early onset of physical signs of ageing ([Kline et al., 2007](#)). [Sarimski \(1997\)](#) reports significantly more social isolation and greater concern with changes in the environment in older children with the syndrome. However, there have been no studies to date that have explicitly evaluated age-related changes in ASD characteristics in this group. Biological processes that

occur downstream from the genetic mutations responsible for CdLS have been implicated in these described changes with age in the syndrome ([Gimigliano et al., 2012](#); [Kline et al., 2007](#)).

Fragile X syndrome

FXS is the most common cause of inherited intellectual disability ([Cornish, Turk, Hagerman, 2008](#)). The prevalence rate is approximately 1:4,000 males and 1:6,000 females ([Sherman, 2002](#)). FXS is caused by a trinucleotide (CGG) repeat expansion in the Fragile X Mental Retardation 1 (FMR1) gene located on the X chromosome ([Verkerk et al., 1991](#)). The size of the CGG repeat determines if the FMR1 allele is classified as either normal (5-44), premutation (55-200) or full mutation (>200) ([Maddalena et al., 2001](#)). Intellectual disability is reported to be within the mild to severe range in males, whereas females with the full mutation typically show a mild level of intellectual disability ([Cornish et al., 2008](#)). Behaviors associated with FXS include: gaze aversion, social anxiety, language impairment and stereotyped behaviors. Reported prevalence rates of ASD in FXS vary widely from 0% to 60% (see [Moss et al., 2011](#) and [Zafeiriou et al., 2013](#) for reviews). As for CdLS, the presentation is somewhat different to the social impairments that are characteristic of individuals with idiopathic autism, with social anxiety, selective mutism and gaze avoidance reported to be particularly characteristic of the syndrome alongside an apparently preserved motivation for social interaction ([Cornish et al., 2007](#); [Hall, et al., 2006](#); [Lesniak-Karpiak et al., 2003](#); [Moss et al., 2013](#); [Roberts et al., 2007](#); [Turk & Cornish, 1998](#)). Similarities to CdLS with regard to prevalence estimates and atypicalities in the nature of ASD characteristics make FXS an interesting contrast group in this study.

There are relatively few studies that have evaluated the trajectory of ASD symptomatology in individuals with FXS. Those that have suggest that the proportion of individuals meeting criteria for ASD is relatively stable over time ([Hatton et al., 2006](#); [Hernandez et al., 2009](#); [Sabaratnam et al., 2003](#)). However, there may be changes in specific characteristics such as increased preference for routine ([Sabaratnam et al., 2003](#)). [According](#) to [Hernandez et al. \(2009\)](#), the trajectory of ASD related characteristics may be different for those with FXS who have a diagnosis of ASD compared to those who do not meet these criteria.

Cri du Chat syndrome

CdCS is associated with similar levels of severe/profound ID, social communication deficits and stereotyped behavior to those with CdLS, hence enabling contrast. CdCS affects approximately 1 in 50,000 births ([Dykens et al., 2000](#)) and results from a deletion of chromatin from the short arm of chromosome 5. The deletion is present in 85% of cases; 10-15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of chromosome 5 ([Van Buggenhout et al, 2000](#)). Behaviors associated with CdCS include self-stimulatory/ repetitive behaviors, self-injurious behavior, aggression, temper tantrums, hyperactivity, poor concentration/ distractibility and impulsivity ([Collins & Cornish, 2002](#); [Cornish et al., 1998](#); [Cornish & Pigram, 1996](#); [Dykens & Clarke, 1997](#); [Dykens et al, 2000](#) and [Sarimski, 2003](#)).

ASD characteristics are not considered to be strongly associated with the CdCS ([Moss et al., 2008](#)) and have been reported to be less severe relative to a matched control group ([Claro et al., 2011](#)). In fact, several studies report social interaction skills as being a relative strength of individuals with CdCS ([Carlin, 1990](#); [Cornish & Pigram, 1996](#)).

Very little is known about the developmental profile of behaviors in CdCS and the outcome for adults with the syndrome. Consequently, it is not clear whether the reported strengths in social interaction skills remain stable over time or whether these areas of behavior demonstrate changes with age. Reports from parents and carers of individuals with CdCS suggest that there may be improvements in global behavioral profile over time in CdCS.

Aims

In this study, we aim to evaluate the course of ASD phenomenology with age and over time in CdLS compared to individuals with FXS and CdCS. Based on previous research findings the following hypotheses are proposed:

1. Individuals with CdLS and FXS will show a heightened prevalence for ASD characteristics compared to the CdCS group.
2. Older individuals with CdLS will be more likely to meet criteria for ASD and show increased severity of ASD compared to younger individuals with the syndrome.
3. Individuals with CdLS will show an increased severity and frequency of autism spectrum phenomenology over time.

METHODS

Recruitment

This study was conducted as part of a larger questionnaire survey study comparing aspects of behavioral phenotypes of multiple syndromes (Arron et al., 2011; Moss et al., 2009; Oliver et al., 2011). Individuals with CdLS, CdCS and FXS who had

participated in a previous study (Time one; T1) were invited to participate in the current follow up study two and a half years later.

At T1, 142 carers of individuals with CdLS who were already known to the research team and had provided consent to be contacted for further research were contacted directly and invited to take part in the questionnaire study. The remaining members of the Cornelia de Lange Syndrome Foundation (UK and Ireland; n= 234) were contacted and invited to take part in the study via the Foundation. Individuals with CdCS (n= 180) and FXS (n= 762), were contacted via the relevant support groups (the Cri du Chat Syndrome Support group and the Fragile X Society respectively) and invited to participate.

At T2, participants were invited to take part if they had participated at T1 and consented to be contacted for future research. In total, 385 individuals were invited to take part in the study at T2 (CdLS= 114, CdCS= 63 and FXS= 208). Of these, 274 caregivers completed and returned the questionnaire packs (CdLS= 80, CdCS= 46 and FXS= 148). The overall return rate at T2 was 71.1% (CdLS= 70.2%, CdCS= 73.0% and FXS= 71.1%).

All parents/carers were sent a letter, an information sheet, consent forms, a demographic questionnaire, questionnaire pack and a prepaid envelope at each time point.

Participants

Participants were included in this study if they met the following criteria:

1. A confirmed diagnosis of the relevant syndrome from an appropriate professional
2. No additional chromosomal abnormalities (other than those causing the syndrome);
3. Completion of at least 75% of the total questionnaire pack at both T1 and T2;

4. Aged four or over at T1. Participants were required to be at least four years at T1 because the Social Communication Questionnaire (Rutter et al, 2003) contains items regarding the participant's behavior when aged between four and five years.

In total, 251 individuals met the inclusion criteria and were included in the study (CdLS= 67, CdCS= 42 and FXS=142). Table I describes the participant characteristics at T1 and T2. At T1, participants were aged between 4 and 47 years (mean age= 17.31yrs; SD = 9.45), 184 (73.3%) were male, 226 (90%) were mobile and 193 (76.9%) were verbal (more than 30 words/signs in their vocabulary). At T2, participants were aged between 6 and 49 years (mean age= 19.83yrs; SD = 9.36), 230 (91.6%) were mobile and 200 (79.7%) were verbal. At both time points, significantly more individuals in the FXS group were mobile and verbal compared to the CdCS and CdLS groups. Self-help skills were also significantly higher in this group relative to the CdCS and CdLS groups (indicated by a higher proportion of individuals being reported as able or partly able).

(Insert Table I about here)

Measures

The questionnaire pack included multiple informant based questionnaire measures which are all appropriate for children and adults with intellectual disabilities. For the purpose of this study, a demographic questionnaire, Wessex Scale (Kushlick et al., 1973) and the Social Communication Questionnaire (SCQ; Rutter et al., 2003) was completed.

Demographic Questionnaire

A demographic questionnaire was used to obtain information regarding each participant's age, gender, verbal ability, mobility and diagnostic status. Specific questions in the demographic questionnaire address whether a formal diagnosis had been made, when this was made and by who in order to ensure the participant met inclusion criteria.

Wessex Scale (Kushlick et al., 1973). The Wessex Scale is an informant questionnaire designed to assess social and physical abilities in children and adults with intellectual disability. The scale comprises 15 items that rate the frequency of occurrence as frequent (more than once a week), occasionally, or never. Subscales include continence, mobility, self-help skills, and speech and literacy, and information on vision and hearing is also included. Items regarding the individual's ability to feed, wash and dress him- or herself compose the self-help skills subscale. The Wessex Scale has good interrater reliability at subscale level for both children and adults. Percentage agreement of responses at subscale level is reported to range from 78%–92% (Kushlick et al., 1973) and Kappa scores at item-level range from .37 to .89 (Palmer & Jenkins, 1982). The measure has been used to characterize levels of ability in a range of syndrome groups (i.e., Arron et al., 2011; Moss et al., 2009; Oliver et al., 2011)

The Social Communication Questionnaire (SCQ; Rutter et al., 2003)

The SCQ, previously known as the Autism Screening Questionnaire (ASQ), is a screening measure for autism spectrum disorder. Based on the Autism Diagnostic Interview-Revised (AID-R), the SCQ comprises 40 items completed by the main

caregiver. The items are grouped into three subscales: communication, social interaction and repetitive or stereotyped behaviors. The SCQ takes less than ten minutes to complete. All questions are yes-or-no with a score of one for 'Yes' (or the presence of abnormal behavior) and a score of zero for 'No'. In addition, all scores are summed to provide a total score between 1 and 39 (one question on the current language level is not included in the total score). According to the authors, the higher the score, the more autistic characteristics are present. The SCQ is reported to be accurate at discriminating between ASD and other conditions, including individuals with intellectual disabilities. The authors suggest a cut-off score of 15 or above to screen for ASD. A higher cut-off of 22 is used to screen for autism.

Data analysis

The distribution of the SCQ data was tested for normality using Kolmogorov-Smirnov tests. The data were not normally distributed at subscale score level ($p < .05$). Therefore, non-parametric techniques were employed throughout the analysis. For some of the analyses, participants were subdivided into two age groups (≤ 15 years at T1 and > 15 years at T1). These age bands were chosen because they allowed for the most equal distribution of participants across these sub-groups.

RESULTS

Comparison of ASD phenomenology between syndrome groups

Chi-square tests were carried out to identify syndrome group differences in the prevalence of ASD phenomenology. Table II shows the proportion of individuals with CdLS, CdCS and FXS who met the SCQ cut off scores for ASD and autism at T1 and

T2. The FXS and CdLS groups had a significantly higher proportion of individuals meeting the cut offs for both autism and ASD than the CdCS group at both time points.

(Insert Table II about here)

In order to assess syndrome group differences in the severity of ASD phenomenology at T1 and T2, Kruskal-Wallis tests were conducted. Any significant differences identified, were further examined with pair wise Mann-Whitney tests to identify the source of the difference (See Table III).

(Insert Table III about here)

At T1, there was a significant group difference on all three domains of the SCQ (repetitive behavior: $X^2(2, N = 250) = 20.67, p < .001$; communication: $X^2(2, N = 250) = 32.66, p < .001$; social interaction: $X^2(2, N = 250) = 31.88, p < .001$). Post hoc tests showed that the FXS group scored significantly higher than the CdLS and CdCS groups on the repetitive behavior domain and both the FXS and CdLS groups scored significantly higher than the CdCS group on communication and social interaction domains. At T2, the pattern of findings had not changed.

In summary these analyses show that individuals with FXS and CdLS were more likely to meet the cut-offs for both autism and ASD, at both T1 and T2. At both time points, the FXS and CdLS groups showed greater severity of ASD related behaviors than the CdCS group in the communication and reciprocal social interaction domains while the FXS group showed the highest frequency of repetitive behaviors.

The effect of age on ASD phenomenology

Chi-square tests were used to compare the proportion of under/= fifteen year olds and over fifteen year olds within each syndrome group who scored above the cut-offs for autism and ASD on the SCQ at T1 (See Table IV).

(Insert Table IV about here)

At T1, a greater proportion of individuals with CdLS over the age of fifteen met the cut off for ASD compared to those under/= fifteen years old. ($p = .017$). Mann-Whitney U tests compared SCQ domain scores between older (>15) and younger (≤ 15) individuals within each syndrome (see Figure I). There was a significant difference within syndrome group, by age for CdLS and CdCS on the social interaction domain ($U = 267.00, p = .011$; $U = -98.50, p = .018$), and for FXS on the repetitive behavior domain ($U = 1574.50, p < .001$). The >15 s with CdLS and CdCS scored significantly higher on the social interaction domain than ≤ 15 s with these syndromes, while the reverse pattern was identified for the FXS group with regard to the repetitive behavior domain (i.e. ≤ 15 s scored significantly higher than >15 s).

(Insert Figure I about here)

In summary these analyses show that at T1, older (>15 s) individuals with CdLS were more likely to meet the cut off for ASD than younger (≤ 15 s) individuals with the syndrome. Similarly, older individuals with CdLS and were found to show greater severity of social impairments compared to younger individuals with the syndrome.

The same pattern was identified in the CdCS group, while in FXS repetitive behaviors were found to become less prominent with age.

The effect of time on ASD phenomenology.

In order to assess differences in the prevalence of ASD phenomenology over time, McNemar tests evaluated changes in the proportion of participants meeting the SCQ cut off scores between T1 and T2. Within each syndrome group, the proportion of participants showing absence, remission, incidence and persistence of meeting the cut-offs were examined (see Table V). There were no significant differences in the proportion of individuals meeting cut off for ASD and autism between T1 and T2.

(Insert Table V about here)

In order to assess any differences in the severity of ASD phenomenology over time, Wilcoxon Signed Ranks tests were used were conducted to examine whether SCQ scores changed significantly between T1 and T2, within each syndrome group (see Figure II).

(Insert Figure II about here)

The data in Figure II show that there were no significant differences on domain scores on the SCQ between T1 and T2 in the CdCS and CdLS groups. There was a significant difference identified for the FXS group on the repetitive behavior ($z = -2.38, p = .017$) and social interaction ($z = -2.64, p = .008$) domains of the SCQ. The

FXS group showed significantly lower scores on repetitive behavior and social interaction subscales of the SCQ at T2.

In summary individuals with CdCS and CdLS did not demonstrate significant changes in the severity of ASD characteristics over three year follow up. Those with FXS however, showed significantly fewer repetitive behaviors and less severe impairments in social interaction over this time frame.

DISCUSSION

In this study, our primary aim was to evaluate the course of ASD phenomenology with age and time in CdLS. Two appropriate contrast groups were selected based on reported similarities within the literature to CdLS with regard to degree of intellectual disability and communication skills (CdCS) and severity of ASD symptomatology (FXS). We hypothesized that: 1. Individuals with CdLS and FXS will show a heightened prevalence for ASD characteristics compared to the CdCS group, 2. Older individuals with CdLS would be more likely to meet criteria for ASD and show increased severity relative to younger individuals with the syndrome and 3. Individuals with CdLS would show an increased severity and frequency of autism spectrum phenomenology over time.

In accordance with our first prediction, the CdLS and FXS groups were significantly more likely than the CdCS group to meet SCQ cut offs for autism and ASD at both T1 and T2. At both time points, the FXS and CdLS groups showed greater severity of ASD related behaviors than the CdCS group in the communication and reciprocal social interaction domains, while the FXS group showed the highest

frequency of repetitive behaviors than both groups. These findings are consistent with previous reports of a heightened prevalence of ASD phenomenology in CdLS compared to CdCS (Moss et al., 2008) and broad similarities with regard to severity of ASD characteristics in CdLS and FXS (Oliver et al., 2011; Moss et al., 2013). The increased weighting of repetitive behaviors within the profile of ASD characteristics in FXS has also been reported previously (Moss et al., 2013).

The results also supported our second prediction that older individuals with CdLS would show an increased prevalence and severity of ASD characteristics than younger individuals with the syndrome. Analysis confirmed that individuals over the age of fifteen years with CdLS were significantly more likely to meet the SCQ cut off score for ASD relative to those fifteen or younger. In CdCS and FXS, the proportion of individuals meeting SCQ cut off scores for autism and ASD remained stable across these age bands. Older individuals with CdLS were also significantly more likely to achieve a higher score on the social interaction domain of the SCQ compared to younger individuals, indicating increased severity of social impairments with age in this group. This change in social interaction scores was also identified in the CdCS group suggesting that this might, in part, be accounted for by degree of intellectual disability. However, the findings are consistent with previous studies that have reported increased social isolation in older children with CdLS ([Sarimski, 1997](#)) and broader changes in behavior, mood and anxiety (Berney et al., 1999; Nelson et al., 2014; Oliver et al., 2011). Further research is required to better understand the nature and etiology of this change. Some researchers have speculated that it may be related to biological effects that occur downstream from the genetic mutations responsible for CdLS ([Gimigliano et al. 2012](#); Kline et al., 2007).

Despite broad stability in the proportion of individuals with FXS meeting SCQ cut off scores, younger individuals with FXS scored significantly higher than older individuals on the repetitive behavior domain of the SCQ. Furthermore, there was a significant decrease on the repetitive behavior and social interaction domains between T1 and T2. Stability of diagnostic classifications of ASD in FXS has been reported in previous studies ([Hatton et al., 2006](#); [Hernandez et al., 2009](#); [Sabaratnam et al., 2003](#)). However, the apparent improvement in repetitive behaviors is in direct contrast to the findings from [Sabaratnam et al. \(2003\)](#) who described an increased preference for routine over a ten year period. These discrepancies might be accounted for by differences in the follow up length between these two studies or the level of specificity regarding repetitive behavior. Further research is required in order to better understand the trajectory of ASD characteristics in FXS.

Our final prediction, regarding change over time was not supported. There were no significant differences in the proportion of individuals with CdLS meeting ASD and autism SCQ cut off scores at T1 and T2 and no significant differences between T1 and T2 with regard to the severity of SCQ domain scores in this group. The significant age band differences identified in this study, alongside previous reports of age related changes with age in CdLS suggest that the follow up length in this study may not have been sufficient to detect changes over time in this group. Alternatively, it is possible that the age related changes identified in this study could be accounted for by a cohort effect. However, the consistency of these findings with previous reports within the CdLS literature suggests that this is unlikely to fully account for the observed changes. It would be beneficial for future research to include a wide enough age range to look at the effects of age in more detail and also increase the length of follow-up.

The findings from this study should be considered within the context of its limitations. Firstly, the findings rely upon the use of an informant screening tool and therefore provide a limited degree of detail regarding the nature of the behaviors reported. Observational tools such as the Autism Diagnostic Observation Schedule (Lord et al., 2000) should be considered in future studies. Secondly, while self-help skills are described in the study sample, it was not possible to control for this potentially confounding factor at a statistical level due to the reliance upon non-parametric analyses. However, the pattern of results indicates that any differences between the groups, with regard to degree of disability, was not likely to be a significantly confounding factor given that the most able group (FXS) was the group that scored significantly higher in all areas of the SCQ relative to the less able groups (CdCS and CdLS). Furthermore, the CdCS and CdLS groups were comparable with regard to self-help skills and mobility. Therefore any differences between these two groups is likely to be indicative of syndrome specific behaviors.

In summary, consistent with previous findings, individuals with CdLS demonstrated a heightened prevalence for ASD relative to individuals with CdCS. The severity of these characteristics was similar to that observed in individuals with FXS, although the profile of impairments was slightly different, with repetitive behavior being a more prominent feature in FXS. Despite the broad similarities in CdLS and FXS, the presentation of ASD characteristics in these two groups showed different trajectories. In FXS, the proportion of individuals meeting SCQ cut off scores was stable, although repetitive behavior scores showed a significant decline with age and over time, indicating improvements in this domain. In CdLS, social interaction skills were reported to be more impaired in older compared to younger individuals and this contributed to a greater proportion of older individuals meeting

SCQ cut off scores for ASD compared to younger individuals. Although there was no significant effect of time in this group, this may be accounted for by the relatively short follow up period. Further studies, evaluating ASD characteristics over a longer period of time are required to fully understand these changes. If ASD phenomenology is, indeed, getting increasing with age in CdLS, this could have important implications for planning support services and advice given to families about what to expect in the future. [O'Brien](#) (2000), Howlin et al., (1995) and Moss & Howlin (2009) all stress the importance of this type of information to help the families gain vital early intervention services, especially in education settings.

FOOTNOTE

¹The terms ‘ASD phenomenology’ or ‘ASD symptomatology’ will be used interchangeably throughout this manuscript to refer to the behaviors and impairments that are considered to be characteristic of individuals with ASD, as described in the DSM- IV-TR (APA; 2000) and ICD-10 (WHO; 1992) manuals.

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Table I. Participant characteristics at T1 and T2

		CdLS (n=67)	CdCS (n=42)	FXS (n=142)	F/ χ^2	df	p value	Post hoc tests
Time 1								
Age ¹	M	17.33	17.65	17.23	.01	2	.99	-
	(SD)	(9.22)	(11.75)	(8.84)				
	Range	4-40	4-44	6-47				
Gender	% Male (n)	41.8 (28)	33.3 (14)	100 ³ (142)	120.01	2	<.001	FXS>CdLS,CdCS
Speech ²	% Verbal (n)	52.2 (35)	73.8 (31)	89.4 (127)	35.70	2	<.001	FXS>CdCS>CdLS
Mobility ²	% Mobile (n)	83.6 (56)	76.2 (32)	97.2 (138)	20.17	2	<.001	FXS>CdCS,CdLS
Self-help skills ⁴	% Able/ partly able (n)	50.7 (34)	64.3 (27)	90.8 (129)	43.36	2	<.001	FXS>CdCS,CdLS
Time 2								
Age ¹	M	20.08	19.89	19.63	.09	2	.92	-
	(SD)	(9.25)	(11.79)	(8.60)				
	Range	6-43	6-47	9-49				
Speech ²	% Verbal (n)	53.7 (36)	78.6 (33)	92.3 (131)	41.76	2	<.001	FXS>CdCS>CdLS
Mobility ²	% Mobile (n)	86.6 (58)	78.6 (33)	97.9 (139)	18.83	2	<.001	FXS>CdLS,CdCS
Self-help skills ⁴	% Able/ partly able (n)	37.31 (25)	80.95 (34)	93.66 (133)	58.36	2	<.001	FXS>CdCS,CdLS

¹ In years

² data derived from the demographic questionnaire (see measures section)

³ Only male participants with Fragile X syndrome were recruited

⁴ Data derived from the Wessex Scales (see measures section)

Table II: Percentage of individuals who scored above the cut-off for autism (AU) and autism spectrum disorder (ASD) on the Social Communication Questionnaire at T1 and T2.

	CdLS %	CdCS %	FXS %	χ^2	df	p value	Post hoc tests
T1- AU cut-off	45.8	8.1	45.8	18.38	2	<.001	FXS, CdLS > CdCS
T1- ASD cut-off	79.7	37.8	85.5	36.67	2	<.001	FXS, CdLS > CdCS
T2- AU cut-off	43.1	10.5	45.3	15.53	2	<.001	FXS, CdLS > CdCS
T2- ASD cut-off	74.1	44.7	83.6	23.33	2	<.001	FXS, CdLS > CdCS

Table III: Median values of syndrome group scores on the SCQ at time1 and time 2.

	CdLS (n=67)*	CdCS (n=41)*	FXS (n=142)*	X²	df	p value (<.02)	Post Hoc (<.01)
Time 1							
Communication	7.00	4.00	7.00	32.66	2	<.001	FXS, CdLS > CdCS
Restricted, Repetitive and stereotyped behaviours	4.00	3.00	5.00	20.67	2	<.001	FXS > CdCS, CdLS
Reciprocal social interaction	9.00	4.00	8.00	31.88	2	<.001	FXS, CdLS > CdCS
Time 2							
Communication	7.00	4.00	7.00	28.51	2	<.001	FXS, CdLS > CdCS
Restricted, Repetitive and stereotyped behaviours	4.00	3.50	5.00	10.92	2	.004	FXS > CdCS
Reciprocal social interaction	9.00	4.29	8.00	30.67	2	<.001	FXS, CdLS > CdCS

* Ns varied due to missing data

Table IV: Percentage of individuals (Under/=15years (U15) and Over 15 years (O15)) within each syndrome group who scored above the cut-off for autism (AU) and autism spectrum disorder (ASD) on the Social Communication Questionnaire.

	Under/= 15 % (n)	Over 15 % (n)	<i>x</i> ²	<i>df</i>	<i>p</i> value
T1- AU cut-off					
CdLS	35.5 (31)	57.1 (28)	2.78	1	.095
CdCS	5.0 (20)	11.8 (17)	.564	1	.452
FXS	49.4 (77)	40.7 (54)	.948	1	.330
T1- ASD cut-off					
CdLS	67.7	92.9	5.73	1	.017
CdCS	35.0	41.2	.149	1	.699
FXS	87.0	83.3	.347	1	.556

Table V: Percentage and number of participants (in parentheses), by syndrome group, in absent, remission, incidence and persistence of meeting the cut-offs for AU and ASD on the Social Communication Questionnaire and analysis examining the persistence of meeting cut-off between T₁ and T₂.

SCQ Cut-off	Absent (Below at T ₁ ,	Remission (Above at T ₁ ,	Incidence (Below at T ₁ ,	Persistent (Above at T ₁ ,	p
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	Below at T₂)	Below at T₂)	above at T₂)	Above at T₂)	
AU Cut-off					
CdLS	93.8 (30)	7.7 (2)	6.3 (2)	92.3 (24)	1.00
FXS	86.2 (56)	19.7 (12)	13.8 (9)	80.3 (49)	.66
CdCS	94.1 (32)	33.3 (1)	5.9 (2)	66.7 (2)	1.00
ASD Cut-off					
CdLS	91.7 (11)	10.9 (5)	8.3 (1)	89.1 (41)	.22
FXS	61.1 (11)	7.4 (8)	38.9 (7)	92.6 (100)	1.00
CdCS	86.4 (19)	13.3 (2)	13.6 (3)	86.7 (13)	1.00

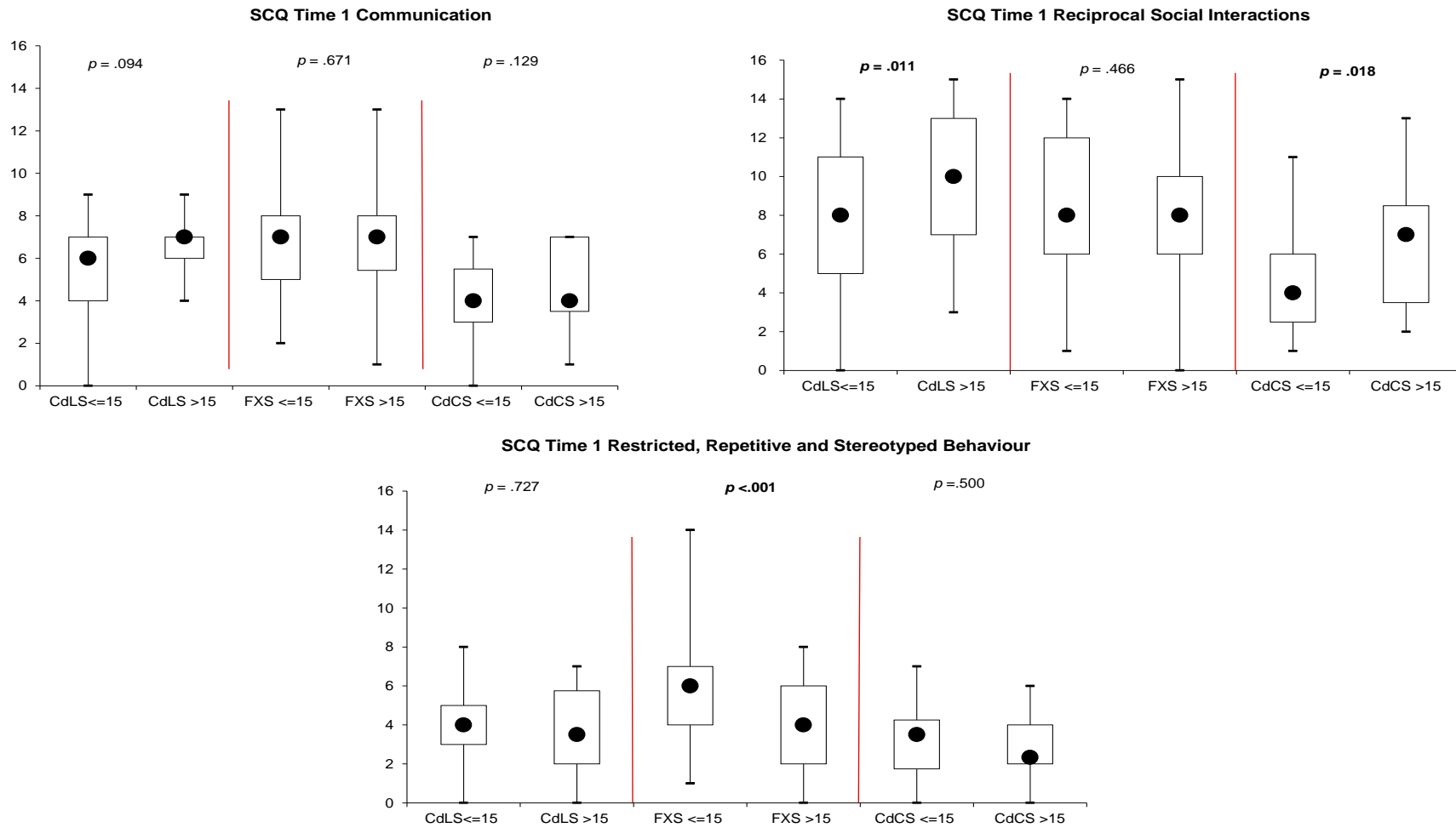


Figure I: SCQ domain scores at T1 by syndrome group (CdLS, FXS and CdCS) and age group (<=15 and >15).

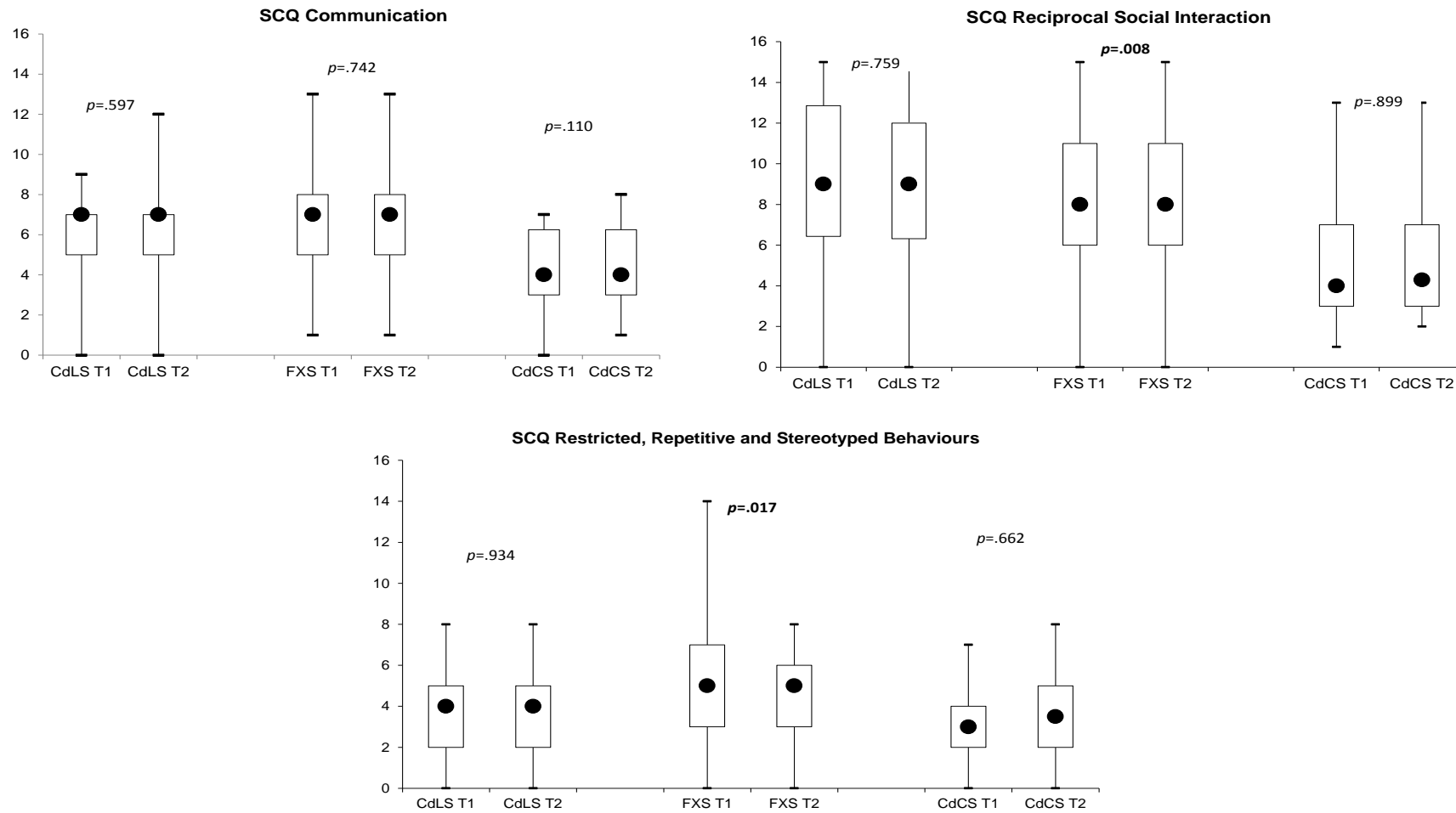


Figure II: SCQ domain scores at T1 and T2 in CdLS, FXS and CdCS.