Overactivity, impulsivity and repetitive behaviour in males with fragile X syndrome: Contrasting developmental trajectories in those with and without autism

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Overactivity, impulsivity and repetitive behaviour in males with fragile X syndrome: Contrasting developmental trajectories in those with and without elevated autism symptoms

Suggested running head: Developmental trajectories in FXS

Abstract

Background: Hyperactivity and repetitive behaviour are characteristic features of fragile X syndrome (FXS). However, little is known about the influence of autism symptomatology on how these characteristics develop over time. We investigate the profiles and developmental trajectories of overactivity, impulsivity, and repetitive behaviour, in males with FXS over three time points spanning eight years. **Method**: Participants formed two subgroups, those who displayed elevated symptoms of autism at Time 1 (n=37; M_{age}=16.32; age range=6.61-43.51) and those who did not (n=32; M_{age}= 8.43; age range=8.94-47.49). **Results**: Participants without elevated symptoms of autism showed a reduction in impulsivity and repetitive questioning over time, whereas those with elevated symptoms of autism did not. Differences between the two subgroups in several topographies of repetitive behaviour emerged at Time 3 only. **Conclusions**: These results further understanding of the relationship between autistic phenomenology and behavioural characteristics in FXS.

Keywords: fragile X syndrome, autism, repetitive behaviour, attention deficit hyperactivity disorder, developmental trajectory

Background

Affecting approximately 1 in 4,000 males and 1 in 8,000 females, fragile X syndrome (FXS) is the most common cause of inherited intellectual disability (Turner, Webb, Wake, & Robinson, 1996). It is caused by abnormalities in the Fragile X Mental Retardation 1 (FMR1) gene located on the Xq27.3 site resulting in excessive cytosine-guanine-guanine (CGG) repeats. A recent meta-analysis indicated that approximately 30% of people with FXS meet criteria for a diagnosis of autism spectrum disorder (ASD; Richards, Jones, Groves, Moss, & Oliver, 2015), although some studies have cited higher prevalence rates of 50%-70% (e.g. Clifford et al., 2007; Lee, Martin, Berry-Kravis, & Losh, 2016). Many important advances have improved our understanding of ASD in FXS. For example, it is increasingly recognised that individuals with FXS, and even those with comorbid FXS and ASD, display a milder or atypical profile of ASD symptomatology than those with idiopathic ASD (Abbeduto, McDuffie, & Thurman, 2014). These subtle differences highlight the importance of delineating behavioural characteristics in individuals with FXS and exploring differences between those with and without ASD. However, little is known about the association between autism symptomatology and the development of behavioural characteristics over time. As a single gene disorder, FXS provides a useful model to further understand the way in which behavioural characteristics interact with co-morbid disorders over time, which can, in turn, inform the wider field of neurodevelopmental disorders. This study focuses on comparing the profiles, and delineating the developmental trajectories, of overactivity, impulsivity, and repetitive behaviour, in males with FXS who do and do not display elevated symptoms of autism.

Overactivity and impulsivity are often reported alongside inattention in the context of whether an individual meets criterion for an attention-related disorder, such as attention

deficit hyperactivity disorder (ADHD). The prevalence rate of ADHD in males with FXS is reported to be between 53-73% (Baumgardner, Reiss, Freund, & Abrams, 1995; Sullivan et al., 2006), which is substantially elevated in comparison to the prevalence rate of 5-7.1% reported in the general population (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012). In addition, individuals with FXS exhibit higher levels of overactivity and restlessness than individuals with other genetic syndromes (Oliver, Berg, Moss, Arron, & Burbidge, 2011; Turk, 1998). Most research points to a relatively stable trajectory of behavioural indicators of attention problems over time in individuals with FXS (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012; Hatton et al., 2002; Tonnsen, Grefer, Hatton, & Roberts, 2015; Turk, 1998). Cross-sectional research has identified an association between ADHD and ASD, with more pronounced broad attention problems occurring in individuals with FXS and ASD compared to those with a sole diagnosis of FXS or ASD (Smith, Barker, Seltzer, Abbeduto, & Greenberg, 2012). Given this association between ASD and ADHD in FXS, and reports that the co-occurrence of ASD and ADHD increases with age (Visser, Rommelse, Greven, & Buitelaar, 2016), it is important for longitudinal research to consider potential differences in the stability of overactivity and impulsivity in those with and without elevated autism symptomatology. Furthermore, literature exploring ADHD characteristics in individuals with FXS has often used the Attention Problems subscale of the Child Behavior Checklist (CBCL; Achenbach, 1991). Although the CBCL demonstrates good convergence with ADHD diagnoses (Biederman et al., 1993), this approach does not often offer a distinction between inattention, overactivity or impulsivity, and highlights the need for more fine-grained analyses of behavioural indicators of attention problems.

As well as elevated hyperactivity, FXS is associated with repetitive behaviour. Interestingly, relationships between overactivity and impulsivity, and repetitive behaviour, have been reported in individuals with intellectual disabilities, suggesting that a common underlying

mechanism may be subserving these behaviours (Burbidge et al., 2010). Whilst repetitive behaviours and restricted interests form part of the diagnostic criteria for ASD, they are also characteristic of FXS (Turk & Graham, 1997). Indeed, both the frequency and number of topographies of repetitive behaviour are higher in FXS compared to other genetic syndromes and those with idiopathic intellectual disability (Moss, Oliver, Arron, Burbidge, & Berg, 2009). There is a growing body of evidence that highlights between-group differences when participants with FXS, with and without ASD, are compared. For example, higher levels of repetitive object use, compulsions and rituals, and circumscribed interests have been reported in individuals with FXS and comorbid ASD compared to those with FXS only (McDuffie et al., 2010). Studies investigating the developmental trajectory of repetitive behaviour have reported minimal change with chronological age for individuals with FXS (McDuffie et al., 2010; Thurman, McDuffie, Kover, Hagerman, & Abbeduto, 2015). However, age-related improvement in repetitive object use and hand and finger mannerisms has been reported for individuals with FXS and comorbid ASD (McDuffie et al., 2010). This emerging evidence, indicating subtle differences in the developmental trajectory of repetitive behaviour in these populations, highlights the critical importance of capturing behavioural change over time. The present study extends the current literature by using a longitudinal design to compare and contrast developmental trajectories of overactivity, impulsivity and repetitive behaviour over an eight-year time period in individuals with FXS who do and do not display elevated autism symptomatology.

Aims

The current study uses standardised measures of autism symptomatology, overactivity and impulsivity, and repetitive behaviour to address the following research questions:

1) Do individuals with FXS, with and without elevated symptoms of autism, differ in their profiles of overactivity, impulsivity, and repetitive behaviour? Based on existing literature indicating more severe behavioural indicators of attention problems (Smith et al., 2012), and repetitive behaviour (McDuffie et al., 2010) in individuals with co-morbid FXS and ASD versus those with FXS only, it was hypothesised that the group of individuals with FXS who also had elevated ASD symptomatology would show more severe atypicalities on measures of overactivity, impulsivity, and repetitive behaviour.
2) Does the developmental trajectory of overactivity, impulsivity and repetitive behaviour in individuals with FXS differ as a function of elevated autism symptomatology? As there is limited longitudinal research in FXS addressing change in behavioural characteristics over time and the impact of elevated autism symptomatology on potential behavioural change, no evidence-based hypotheses were generated. This study will explore the interplay between autism symptomatology and change in overactivity, impulsivity and repetitive behaviour over an eight-year period in males with FXS.
3) Are changes in overactivity and impulsivity associated with changes in repetitive behaviour, and does this association differ as a function of autism symptomatology? Based on research indicating an association between overactivity and impulsivity with repetitive behaviour (Burbidge et al., 2010), it was hypothesised that potential changes in these characteristics over time would also be associated.

Methods

Recruitment

This study was conducted as part of a large-scale questionnaire study investigating behaviour in children and adults with a range of different neurodevelopmental disorders. Participants were recruited over three time points. At Time 1 (2003-2004), parents and carers of 762 males with Fragile X syndrome were contacted through the Fragile X Society, the UK family support group, to participate in the study. Of the 762 prospective participants, 211 (27%) males took part in the study. At Time 2 (2006-2007) and Time 3 (2011), parents and carers of all 211 males with Fragile X syndrome who participated at Time 1 were directly invited to participate in the study. Of the 211 prospective participants, 148 (70%) males took part at Time 2 and 91 (43%) males took part at Time 3.

Participants were included in the present study if they had taken part at all three time-points. Participants who did not provide information regarding diagnosis, age or date of birth, had not completed the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003) at Time 1, or were missing information on over 75% of the 14 measures in the total questionnaire pack at any time point, were excluded from the study. Of the 91 participants that completed the measures at Time 3, 22 participants were excluded from the final analysis. Ten participants had not taken part at all three times points, three participants had not provided diagnostic information, eight participants had not completed the SCQ at Time 1, and one participant had not provided age or date of birth. Therefore, 69 participants were included in the final analyses.

Participants

Participants (N=69) were divided into two groups (FXS+Aut vs. FXS-Aut) based on the suggested cut-off scores for autism on the SCQ (Rutter et al., 2003) at Time 1 to reflect those with and without elevated autism symptomatology. Participants who scored 21 or lower on the SCQ at Time 1 formed the FXS-Aut group (N = 37) whereas participants who scored 22

or above at Time 1 formed the FXS+Aut group (N = 32). Table 1 provides details for participant characteristics for both groups at Time 1, Time 2 and Time 3. Between-group comparisons revealed that the two participant groups (FXS+Aut, FXS-Aut) were well-matched on chronological age, verbal ability and the self-help score of the Wessex (Kushlick, Blunden, & Cox, 1973) at all time points (all $p > .05$; see Table 1). This study was approved by the Coventry Research Ethics Committee, and written informed consent was obtained from all parents and carers of the participants.

[Insert Table 1 about here]

Measures

Demographic Questionnaire. A demographic questionnaire was used to collect participants' background information including their age, gender, verbal ability, and information on their diagnosis including who made the diagnosis and when.

The Wessex Scale. The Wessex scale (Kushlick et al., 1973) is an informant questionnaire designed to assess social and physical capabilities in children and adults with intellectual disabilities. The Wessex scale has good inter-rater reliability at subscale level for both children and adults with intellectual disabilities (Palmer & Jenkins, 1982). For the purposes of this study, and in line with previous literature (Arron, Oliver, Berg, Moss, & Burbidge, 2011; Cochran, Moss, Nelson, & Oliver, 2015; Moss et al., 2009; Oliver et al., 2011), the self-help subscale was used to characterise participants' level of ability.

The Social Communication Questionnaire. The SCQ (Rutter et al., 2003) is a 40 item informant questionnaire that assesses characteristics associated with autism spectrum disorder (ASD). There are three subscales: social interaction, communication and stereotyped and repetitive behaviour. For the purposes of the current study the communication subscale was

calculated in two ways. First, it was calculated in accordance to the instructions in the manual, where no scores were given for items 2-7 for non-verbal participants (Communication subscale). Secondly, it was calculated using a proportional formula for items 2-7 for non-verbal participants, with the principle that had non-verbal participants responded, they would have responded in this way (Proportional Communication subscale). The authors of this measure suggest a cut-off score of 15 to indicate the presence of an Autism Spectrum Disorder (ASD) and a cut-off score of 22 to indicate the presence of Autism. The SCQ's internal consistency is good ($\alpha = .90$). The SCQ also shows good concurrent validity with both the Autism Diagnostic Interview (Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), (Howlin & Karpf, 2004).

The Activity Questionnaire. The Activity Questionnaire (TAQ; Burbidge & Oliver, 2008; Burbidge et al., 2010) is an 18 item questionnaire designed to assess hyperactivity and impulsivity in individuals with intellectual disabilities. There are three subscales: overactivity, impulsivity and impulsive speech. Because immobile participants are only able to score on four of the six items on the impulsivity subscale, scores are prorated. Internal consistency and test-retest reliability is comparable to other standardised measures of activity (Burbidge et al., 2010).

The Repetitive Behaviour Questionnaire. The Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009) is a 19 item informant questionnaire that is used to assess the presence of repetitive behaviours in individuals with intellectual disabilities. There are five subscales: stereotyped behaviour, compulsive behaviour, repetitive speech, insistence on sameness and restricted preferences. Robust inter-rater reliability, test-retest reliability, concurrent validity, content validity and internal consistency are reported (Moss et al., 2009). Convergent validity

is also good between the RBQ and the Repetitive Behaviour subscale of the Autism Screening Questionnaire (Berument, Rutter, Lord, Pickles, & Bailey, 1999). Four items regarding repetitive questions, echolalia, restricted conversation and attachment to people are not scored for non-verbal individuals (less than 30 words or signs in their vocabulary).

Procedure

At all three time points, parents and carers of prospective participants were mailed a covering letter, an information sheet about the study, a questionnaire pack consisting of a number of measures, and a consent form. The measures were counterbalanced to account for any order effects.

Data Analysis

The distribution of the data was inspected for normality via the Kolmogrov-Smirnov test. Data were not normally distributed. Mann-Whitney tests were employed to assess group differences at each time point at full scale and subscale level of the TAQ and at full scale, subscale and item level of the RBQ. Friedmans tests were used to assess differences between time points for the FXS+Aut and FXS-Aut groups separately. Where differences existed, Wilcoxon Signed Ranks tests were used to locate the source of difference. Data are presented at a group level, but due to the large age range of the sample at Time 1, data are also reported for the FXS+Aut and FXS-Aut groups split into three age bands (6-11 years [FXS+Aut n = 12; FXS-Aut n = 13]; 12-18 years [FXS+Aut n = 9; FXS-Aut n = 11]; and 19+ years [FXS+Aut n = 11; FXS-Aut n = 13]).

This data analysis strategy offers the opportunity to explore between group comparisons of those with and without elevated autism symptoms. Alternative strategies using continuous variables that are typically employed for developmental trajectory analyses (regression,

multi-level modelling) require more statistical power than that available here for investigation at subscale or item level. However, due to multiple comparisons, a conservative alpha level of .01 was employed throughout the analyses.

Results

Change in Overactivity and Impulsivity over time

Figure 1 shows the mean scores for both the FXS+Aut group and FXS-Aut group for the Impulsivity (a), Overactivity (b), and Impulsive Speech (c) subscales of the TAQ.

[Insert Figure 1 about here]

Mann-Whitney Tests revealed no between-groups difference at any of the three time points on the Overactivity (all $p \geq .292$), Impulsivity (all $p \geq .126$) or Impulsive Speech (all $p \geq .202$) subscales of the TAQ. When these data were analysed by chronological age, participants aged 12-18 years at Time 1 in the FXS+Aut group scored significantly higher than the FXS-Aut group on the Overactivity subscales at Time 1 ($U = 11.000$, $p = .002$) and Time 2 ($U = 7.500$, $p = .001$), and on the Impulsivity subscale at Time 3 ($U = 15.500$, $p = .007$).

Friedman Tests revealed that scores on the Impulsivity subscale significantly changed over time in the FXS-Aut ($\chi^2 = 13.609$, $p = .001$) but not in the FXS+Aut group ($\chi^2 = 6.544$, $p = .038$). Follow up Wilcoxon Signed Ranks Tests confirmed that there was a decrease in Impulsivity scores between Time 1 and Time 2 (FXS-Aut: $Z = -2.813$, $p = .005$; Time 1 Mean: 15.51; Time 2 Mean: 12.97) and between Time 1 and Time 3 (FXS-Aut: $Z = -3.066$, $p = .002$; Time 1 Mean: 15.51; Time 3 Mean: 12.81) in the FXS-Aut group only. Friedman tests also revealed that scores on the Overactivity and Impulsive Speech subscales did not

change over time in the FXS-Aut group (Overactivity: $\chi^2 = 4.099$, $p = .129$; Impulsive Speech: $\chi^2 = .087$, $p = .957$), or in the FXS+Aut group (Overactivity: $\chi^2 = 3.048$, $p = .218$; Impulsive Speech: $\chi^2 = 2.753$, $p = .252$). When these data were analysed by age, the significant decrease in Impulsivity scores for the FXS-Aut group was only revealed for participants aged 12-18 years ($\chi^2 = 9.650$, $p = .008$). Impulsivity scores in the FXS+Aut group did not significantly change over time for any of the age groups (all $p > .01$). Overactivity and Impulsive speech subscales also did not change over time in either participant group when analysed by age band (all $p > .01$).

To summarise, these analyses showed no between-groups difference on any of the TAQ subscales. Impulsivity scores decreased over time in the FXS-Aut group (particularly for those in the 12-18 years' age band) but not in the FXS+Aut group. Overactivity and Impulsive Speech scores did not change over 8 years in either participant group.

Change in Repetitive Behaviour over time

Analysis of the RBQ scores was conducted at item level. Figure 2 shows the mean item level figures for the RBQ for the FXS-Aut and FXS+Aut groups at Time 1 (a), Time 2 (b) and Time 3 (c).

[Insert Figure 2 here]

Mann-Whitney Tests revealed no between-groups difference on any item of the RBQ at Time 1 (all $p > .028$) or Time 2 (all $p \geq .01$). However, at Time 3, participants in the FXS+Aut group obtained higher scores than participants in the FXS-Aut on object stereotypy ($p = .007$), lining up or arranging objects ($p = .003$), and 'just right' behaviour ($p = .003$). These between-group differences did not remain when analysing these data by age band.

Friedman Tests revealed that all item-level scores did not change over time in the FXS+Aut group (all $p > .017$). However, scores on repetitive questions decreased over time in the FXS-Aut group ($\chi^2 = .11.627$, $p = .003$; for all other items $p \geq .01$). Follow up Wilcoxon Signed Ranks Tests confirmed that there was a decrease in scores on repetitive questions between Time 1 and Time 3 (FXS-Aut: Z = -3.009, $p = .002$; Time 1 Mean: 2.85; Time 3 Mean: 2.29; maximum score of 4) and between Time 2 and Time 3 (FXS-Aut: Z = -2.626, $p = .009$; Time 2 Mean: 2.78; Time 3 Mean: 2.29) in the FXS-Aut group only. Analysing these data by age revealed that the decrease in repetitive questions over time in the FXS-Aut group only emerged in the 19+ years age group ($\chi^2 = 9.652$, $p = .008$). A decrease in restricted conversation also emerged for participants aged 19 years and above in the FXS+Aut group ($\chi^2 = 9.739$, $p = .008$).

Relationship between TAQ and RBQ change over time

Change scores were calculated for each subscale and the total score of the TAQ and RBQ by subtracting participant's scores at Time 3 from their scores at Time 1. A Spearman's correlation was conducted to investigate the relationship between change scores on the TAQ and RBQ for the FXS+Aut and FXS-Aut participant groups. These analyses revealed no significant correlations between the TAQ and RBQ subscales or total change scores in the FXS-Aut group (all $p > .054$) or in the FXS+Aut group (all $p > .021$). The correlation coefficients can be seen in Table 2.

Discussion

Here, we highlight contrasting developmental trajectories of overactivity, impulsivity, and repetitive behaviour in males with FXS with and without elevated symptoms of ASD over three time points within an eight-year period. Impulsivity decreased over time only in the males with FXS who did not display elevated symptoms of autism. In addition, most

repetitive behaviours remained stable in both subgroups, with the exception of repetitive questioning, which, again, decreased over time only in the individuals without elevated symptoms of autism. Participants with FXS who did have elevated symptoms of autism demonstrated a heightened severity of object stereotypy, lining up or arranging objects, and 'just right' behaviour, compared to those with FXS without elevated symptoms of autism at Time 3 but not at any other time points. Finally, there was no association between change over time in overactivity or impulsivity, and change in repetitive behaviour, in either group suggesting that the previous association reported between these two constructs in individuals with intellectual disability (Burbidge et al., 2010) may not extend to those with FXS. When chronological age was accounted for in the age band analyses, primary results, indicating that individuals with FXS without elevated symptoms of autism displayed a decrease in impulsivity and repetitive questioning, were upheld in the 12-18 years and 19+ years age groups, respectively, suggesting that the results of the study may be primarily driven by adolescents and adults.

Existing literature has indicated that broad attention problems remain largely stable over time in FXS (Cornish et al., 2012; Grefer, Flory, Cornish, Hatton, & Roberts, 2016; Hatton et al., 2002; Tonnsen et al., 2015). Interestingly, the results of the present study indicate that, although impulsivity is a phenotypic feature of FXS, it decreases over time. However, when impulsivity presents alongside elevated ASD symptomatology, it is a more persistent trait. This corroborates existing literature indicating a higher co-occurrence of ASD and ADHD with increasing age (Visser et al., 2016), and suggests that those with ASD may be at higher risk of ADHD and vice versa. Furthermore, the results reported here may indicate differences in the underlying mechanisms associated with impulsivity in those with and without ASD, which subsequently determines the developmental course of behaviour.

The current study also found higher levels of particular topographies of repetitive behaviours in males with FXS who displayed elevated symptoms of autism compared to males who did not. Given that repetitive behaviour is a feature of ASD, it is unsurprising that there are group differences in repetitive behaviours. However, it is interesting that these differences emerged at Time 3 but were not present at Time 1 or Time 2, which suggests potentially subtle differences in the way in which repetitive behaviour emerges over time in these two subgroups. The approach adopted in the present study also afforded the opportunity to highlight differences between the participant groups in the trajectories of repetitive behaviour at a fine-grained level. Specifically, a decrease in repetitive questioning was revealed in males with FXS who displayed elevated symptoms of autism whereas no change was reported in those who did not display elevated symptoms of autism. This suggests that the developmental course of repetitive behaviour in individuals with FXS shifts as a function of ASD symptomatology. Specifically, individuals with FXS demonstrate repetitive behaviour regardless of ASD status and then, over time, pathways for those with and those without elevated symptoms of ASD diverge resulting in less severe repetitive behaviour in those without elevated symptoms of ASD, and more severe repetitive behaviour in those with elevated symptoms of ASD. As with the results regarding impulsivity, these results may indicate subtle differences in the mechanisms and functions of these behaviours between those with and without ASD. Importantly, the within group analyses conducted in the present study only yielded a decrease in one item of the RBQ (repetitive questions) over the eight-year period in individuals without elevated autism symptoms, highlighting the utility of conducting fine-grained analysis to investigate the profiles and developmental trajectories of repetitive behaviour (Moss et al., 2009).

There are some limitations to the present study. While obtaining ability levels through measures of adaptive functioning and intellectual quotient would have been beneficial, an

informant measure of self-help was used to indicate ability levels due to practical limitations of large, longitudinal postal surveys. Importantly, participant groups were statistically comparable on both self-help skills and the percentage of participants who were verbal (defined as being able to speak or sign 30 words), suggesting that ability levels were unlikely to have influenced the results reported here. In addition, participants with FXS were characterised as having elevated symptoms of autism based on their SCQ scores at Time 1. The cut-off used was that indicated by the authors of the SCQ to indicate that increased autism would likely be detected with more in-depth measures, but this is not a diagnostic tool. Rather, it is a well-standardised and robust informant-report measure, which demonstrates good validity with more detailed measures of autism symptomatology, such as the ADOS (Lord et al., 1999), that can be administered within the scope of a large postal survey. This method does not account for the possibility that autism status or severity may change over time. In this study, a total of 19 out of 69 participants changed autism status between Time 1 and Time 3. This is unsurprising as the Lifetime version of the SCQ was used at Time 1, which indicates whether an individual has ever displayed symptoms of autism, and the Current version of the SCQ was used at Time 3, to indicate whether they currently display symptoms of ASD. It is beyond the scope of the current study to measure change of autism status over time. All analyses that compared scores across time on impulsivity, overactivity and repetitive behaviour, were conducted again after excluding the 19 participants that changed autism status. These analyses confirmed the results reported here, which demonstrates that change in autism status was not masking potential changes over time within the current study.

In addition, information on medication use was not available for all participants included in the present study. However, retrospective information on medication use was obtained from 23 participants. Ten of these participants were reported to have taken psychoactive

medication in their lifetime, and five participants were reported to have taken such medication within six months of the data collection period (medication prescribed for anxiety [n = 2], epilepsy [n = 2] and ADHD [n = 1]). Due to these small numbers, medication use was not accounted for in the statistical analyses reported here. However, more detailed information on medication use and comorbid diagnoses is important for the interpretation of the results and future research should explore these factors and their influence in the developmental trajectories of behavioural characteristics in males with FXS with and without elevated autism symptoms.

Finally, although the large age range of participants is not necessarily a limitation of the study due to the benefits of studying behaviour across the lifespan, this posed challenges when accounting for chronological age in the analyses. Chronological age was accounted for by conducting secondary analyses, which involved creating subgroups of participants in different age bands. This resulted in small sample sizes for these subgroups, which reduced the statistical power. However, reduced power is more likely to mask, rather than inflate, significant differences. These age-band analyses did reveal interesting findings regarding the extent to which impulsivity and repetitive questioning develops over time in adolescence and adulthood but these should be interpreted with caution. These preliminary results require confirmation with larger sample sizes, which will enable the effects to be explored using more sophisticated statistical techniques such as multi-level modelling.

It is a challenge to retain large sample sizes whilst conducting longitudinal research in rare genetic syndromes. Despite this, there are several strengths to the current study. To our knowledge, this is the first study to assess behavioural characteristics associated with FXS over an eight-year time period in individuals ranging in age from early childhood to mid-adulthood. This expands on previous studies that have offered rich information using cross-

sectional designs and longitudinal designs over shorter time frames. In addition, previous studies have long been extrapolating differences in characteristics of individuals with FXS with and without ASD. This has served to identify the utility of investigating these subgroups separately, which has been achieved here using a cross-sectional approach to differentiate between subgroups at three different time points, and a longitudinal approach to trace the developmental trajectories of overactivity, impulsivity, and repetitive behaviour in these groups. The current study points to potential differences in mechanisms subserving overactivity, impulsivity, and repetitive behaviour in those with and without ASD. Existing literature has indicated that hyperarousal plays a role in repetitive behaviour in ASD, whereby repetitive behaviour serves as a self-regulating coping mechanism in situations of elevated arousal (see Leekam, Prior, & Uljarevic, 2011 for a review). As atypical physiological arousal has been reported in FXS (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Roberts, Boccia, Bailey, Hatton, & Skinner, 2001), future research should explore hyperarousal as one avenue for further understanding the potential mechanisms governing behavioural characteristics in this population.

Conclusions

The present study documents a difference in the trajectories of overactivity and impulsivity, and repetitive behaviour, in males with FXS, in those with elevated symptoms of ASD compared to those without. Although we identified no group differences in overactivity or impulsivity, impulsivity improved over time in a group of males with FXS without elevated symptoms of autism but remained persistent in those with elevated symptoms of autism. In addition, subtle differences in the profile of repetitive behaviours emerged over time between these two subgroups. Repetitive behaviour and impulsive behaviour have previously been associated with self-injurious behaviour in males with FXS (Arron, Oliver, Moss, Berg, &

Burbidge, 2011), highlighting the critical importance of further understanding these behaviours. The findings of the present study, which further our understanding of overactive, impulsive and repetitive behaviour in males with FXS, and highlight the compounding effects of ASD in FXS, are of critical importance for the development of early, targeted interventions.

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Table 1. *Participant characteristics at Time 1, Time 2 and Time 3 assessments for participants scoring above and below cut-off for autism on the Social Communication Questionnaire at Time 1 (N=69)*

		Time 1			Time 2			Time 3		
		FXS-Aut (n = 37)	FXS+Aut (n = 32)	*P*	FXS-Aut (n = 37)	FXS+Aut (n = 32)	*p*	FXS-Aut (n = 37)	FXS+Aut (n = 32)	*p*
Chronological age (years)	Mean (SD)	16.32 (8.07)	18.43 (10.34)	.346	18.96 (7.94)[a]	20.97 (10.41)[b]	.379	23.76 (7.86)	25.45 (10.28)	.445
	Range	6.61-43.51	8.94-47.49		9.18-45.45[a]	11.49-49.41		14.2-50.54	15.67-54.43	
Self-help skills[1]	Mean (SD)	7.43 (1.56)	7.17 (1.55)	.451	7.89 (1.05)	7.31(1.55)	.164	7.84 (1.42)	7.53 (1.39)	.277
	Range	4.00-9.00	4.00-9.00		5.00-9.00	4.00-9.00		3.00-9.00	4.00-9.00	
Speech[2]	% verbal	89.19	87.5	.827	91.89	87.50	.547	94.59	90.63	.526
SCQ total score	Mean (SD)	16.32 (3.68)	25.77 (2.88)	<.001	15.71 (4.16)	25.03 (3.59)	<.001	16.01 (5.07)	20.96 (5.40)	<.001
	Range	6.00-21.60	22.00-33.00		6.00-25.00	19.00-31.86		7.25-27.00	11.00-33.00	

[1]Data derived from the Wessex Scales (see Measures section); [2]Data derived from the demographic questionnaire (see Measures section); [a]data missing from two participants; [b]data missing from one participant

Table 2. Correlation coefficients for the relationship between TAQ and RBQ subscale and total change scores for the FXS+Aut and FXS-Aut participant groups.

	FXS +Aut	FXS -Aut	FXS +Aut	FXS -Aut	FXS +Aut	FXS -Aut	FXS +Aut	FXS -Aut
	Impulsivity		Overactivity		Impulsive Speech		Total Activity Score	
Stereotyped Behaviour r_s	.150	.064	.407	.247	.140	.164	.420	.234
p	.430	.706	.025	.140	.494	.362	.021	.163
Compulsive Behaviour r_s	.193	-.028	.114	-.061	-.014	.187	.215	.066
p	.306	.867	.550	.720	.946	.296	.254	.696
Insistence on Sameness r_s	.316	.014	.210	.003	.272	.105	.346	.060
p	.083	.934	.256	.985	.171	.567	.057	.728
Restricted Preferences r_s	-.072	-.058	.003	-.009	.091	.187	-.013	.046
p	.728	.747	.989	.962	.658	.298	.950	.799
Repetitive Language r_s	.163	.101	.209	.094	.176	.120	.281	.167
p	.427	.576	.305	.604	.389	.506	.164	.353
Total RBQ Score r_s	.195	.011	.208	.112	.157	.344	.305	.218
p	.302	.950	.269	.515	.442	.054	.102	.201

Figure Legends

Figure 1. The mean scores for participants with FXS with ASD and participants with FXS without ASD on each subscale of The Activity Questionnaire. Error bars represent standard error of the mean.

Figure 2. The profile of item-level scores of the Repetitive Behaviour Questionnaire for participants with FXS with ASD and for participants FXS without ASD at Time 1 (Figure 2a), Time 2 (Figure 2b) and Time 3 (Figure 2c).