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Delineation of behavioral phenotypes in genetic syndromes. Comparison of autism spectrum disorder, affect and hyperactivity.

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Abstract

We investigated the prevalence of autism spectrum disorder (ASD), hyperactivity and affect in seven genetic syndromes; Angelman (n =104), Cri du Chat (58), Cornelia de Lange (101), Fragile X (191), Prader-Willi (189), Smith-Magenis (42) and Lowe (56) syndromes (age range 4 to 51, 35% female). High levels of Autism (over 45%) were evident in Cornelia de Lange and Fragile X syndromes. High levels of impulsivity were seen in Smith-Magenis, Angelman, Cri du Chat, Fragile X and adults with Cornelia de Lange syndromes. Significant negative affect was evident in adults with Cornelia de Lange syndrome and significant positive affect was evident in adults with Cri du Chat and Prader-Willi syndromes. This comparative approach confirms and extends previously reported behavioral phenotypes.

Keywords: behavioral phenotype, autism spectrum disorder, hyperactivity, impulsivity, affect, genetic syndromes.

Delineation of behavioral phenotypes in genetic syndromes: 1. Autism Spectrum Disorder, Affect and Hyperactivity

Contemporary research into the effects of specific genetic disorders associated with intellectual disability now draws on a broad array of methods in addition to those used traditionally in clinical genetics. Recently published studies employ animal models (Lauterborn et al., 2007), neuro-imaging (Hinton et al., 2006; Campbell et al., 2006), 3D analysis of facial dysmorphology (Hammond et al., 2004) and hypothesis driven cognitive assessment (e.g. Scerif et al., 2007; Jarrold et al., 2007) to detail and explain phenotypic profiles. In combination these methods are revealing gene-brain-behavior relationships that are of interest to mainstream developmental psychology, particularly with regard to different and delayed developmental trajectories (Thomas & Karmiloff-Smith, 2005; Cornish et al., 2007), and psychiatry, given the comparatively high prevalence of psychological disorder in some genetic syndromes (Fine et al., 2005; de Vries et al., 2007; Holland et al., 2003; in review citation anonymised for blind review). The latter area of research is particularly promising as groups are defined by genetic status, as opposed to behaviorally, and this facilitates a developmental approach to the study of psychopathology with implications for early identification of disorder and modelling of pathways (Oliver & Hagerman, 2007).

The study of psychological disorder in genetic syndromes is of value in its own right but is also beginning to shed light on a number of psychiatric conditions. This is evident in the study of Alzheimer's disease in Down syndrome (Oliver et al., 1998), psychosis in velo-cardio facial and Prader-Willi syndromes (Murphy, 2005; Boer et al. 2002), and autism spectrum and attention deficit disorders in Tuberous Sclerosis Complex and Fragile X syndrome (de Vries et al., 2007; Cornish et al., 2004; Reiss & Hall, 2007). Similarly, study of clinically salient behavioral difference that might not be considered psychiatric disorder is also revealing the more subtle effects of genetic abnormality, and processes such as genomic imprinting, that are additional to intellectual disability.

Examples include social impairment in Turner's syndrome (Skuse et al., 1997), excessive sociability in Angelman syndrome (Oliver et al., 2007) and comparatively preserved and compromised cognitive development in Williams and Down syndrome (Karmiloff-Smith et al., 2004; Jarrold et al., 2002). Specific cognitive differences are likely to prove important in explaining clinically significant behavioral disorder with evidence of cognitive-behavioral-environment interactions emerging for Prader-Willi and Fragile X syndrome (in review citation anonymised for blind review; Hall et al., 2006). When studied within and between syndromes the associations between specific cognitive deficits and behavior might further contribute to understanding and disentangling the individual cognitive impairments that contribute to the behavioral profile in conditions such as Attention Deficit and Hyperactivity Disorder and Autism Spectrum Disorder.

The origin of many of these recent developments in the study of behavioral phenotypes is careful empirical description of behavioral phenomenology. To date the study of behavioral phenotypes has predominantly involved cohort descriptions or comparisons of syndromes, usually with a relatively limited number of participants. When this comparative strategy is used it is unusual for studies to include more than two syndrome groups at most and, inevitably, studies use different assessments of similar behavioral or cognitive constructs to achieve their aims (Jarrold & Brock, 2004; Hodapp & Dykens, 2001; 2005. The use of different assessments is also due to the difficulty of identifying assessments that are applicable, valid and reliable across a large range of disability. One consequence of the single comparison approach, in combination with the diversity of assessments, is that there is a paucity of directly comparable, empirical data on behavioral phenotypes across a number of syndromes. In this study we seek to generate these data.

A survey based approach to the description of a number of behavioral phenotypes simultaneously, confers some methodological and conceptual advantages over more limited comparisons. Comparatively large numbers, in combination with the use of measures with norms that identify

abnormally high or low scores, will produce data on clinically significant difference that are generalisable. Additionally, the approach helps to deal with the ubiquitous control group problem in behavioral phenotype research. The widely accepted definition of behavioral phenotypes proposed by Dykens (1995) emphasises the importance of description of a phenotype relative to those without the syndrome, normally a CA and MA comparable group. Another approach that would complement this strategy is comparison across genetic disorders or other aetiologies of intellectual disability. This approach would allow syndromes to be positioned relative to each other on given constructs. Although this strategy inevitably introduces the potential confound of degree of intellectual disability, this might be negated by the use of measures applicable across a range of disability and might be considered of less importance in a descriptive, as opposed to hypothesis driven, approach. These advantages and the need for a large, cross syndrome comparison study, arguably, outweigh the advantages of detailed behavioral assessment by observation and the disadvantage of a survey being unable to differentiate within syndrome genetic differences that might be related to the behavioral phenotype (see Edelman et al., 2007, Milner et al., 2005).

In this study we compare and detail the behavioral phenotypes for Angelman, Cri du Chat, Cornelia de Lange, Prader-Willi, Fragile X, Lowe and Smith-Magenis syndromes on assessments of Autism Spectrum Disorder (ASD), behavioral phenomena related to hyperactivity (overactivity and impulsivity) and negative and positive affect (mood and interest and pleasure). Detailed description of the behavioral phenotypes of each of these disorders is beyond the scope of this paper but, in brief, there is evidence that: 1. Fragile X and Cornelia de Lange syndromes are associated with ASD (Clifford et al., 2007; Moss et al., 2008; Oliver et al., 2008), 2. hyperactivity and impulsivity are associated with Angelman, Cri du Chat, Fragile X and Smith-Magenis syndromes (Clarke & Marston, 2000; Dykens & Clarke, 1997, Horsler & Oliver, 2006, Dykens & Smith, 1998) 3. significant negative affect is reported in Cornelia de Lange syndrome (Kline et al., 2007; Collis et

al., 2008) and 4. abnormally positive affect is evident in Angelman syndrome (Horsler & Oliver, 2006).

This study is part of a larger project comparing aspects of the behavioral phenotypes of the chosen syndromes. The comparison of the prevalence and phenomenology of self-injury and aggression are reported a companion paper (in review citation anonymised for blind review) and for a fine-grained analysis of repetitive behavior in Moss et al., (2008). The first aim of this study is to position these syndromes relative to each other and a group with heterogeneous cause of intellectual disability on measures of ASD and behavioral phenomena related to negative and positive affect and hyperactivity. The second aim is to quantify the proportion of each group that evidence abnormal scores, and thus potentially clinically significant levels, on these measures.

Methods

Recruitment

Participants with one of seven genetic syndromes (Angelman (AS), Cornelia de Lange (CdLS), Cri du Chat (CdCS), Fragile X (FXS), Lowe (LS), Prader Willi (PWS) and Smith Magenis (SMS) syndromes) were recruited for the study. A comparison group (Comp.) of participants with intellectual disability of heterogeneous aetiology was also recruited. Participants were recruited via the: Angelman Syndrome Support Education and Research Trust (membership of approximately 320), Cri du Chat Syndrome Support Group (180), Fragile X Society (male membership of over five years of 432), Prader-Willi Syndrome Association (571), Lowe Syndrome Trust UK (25), Lowe Syndrome Association USA (150) and Smith-Magenis Syndrome Foundation (95). 142 individuals with Cornelia de Lange syndrome and 151 individuals with intellectual disability of heterogeneous aetiology who had previously taken part in a study of the behavioral phenotype of Cornelia de Lange syndrome were contacted directly (Hyman, Oliver and Hall, 2002; in review citation anonymisedfor blind review). A further 234 individuals with Cornelia de Lange syndrome

were contacted via the Cornelia de Lange Syndrome Foundation UK. Thus, the total number of carers of individuals with Cornelia de Lange syndrome contacted was 376. Overall, approximately 2,300 individuals were contacted for participation in the study.

862 (35.24%) carers returned the questionnaires. Individuals under the age of four were excluded from the study as some measures were not appropriate for young children. Information regarding the diagnosis of genetic syndromes was obtained in order to establish the validity of diagnosis. Data on participants were excluded from the study if they did not have a specific diagnosis from a General Practitioner, Clinical Geneticist, Paediatrician, Neurologist and Psychiatrist or if a large proportion (more than 25% of items on individual questionnaires) of information was missing. After excluding participants, 797[1] individuals were included in the study. The overall return rate was 35% (range 27% (CdLS) to 44% (SMS and FXS).

Procedure

A covering letter, information sheet, questionnaire pack, consent form and prepaid return envelope were sent to carer's of prospective participants who were asked to complete and return questionnaires and the consent form.

Participants

Table 1 shows the number of participants, mean age and range, the percentage of males, verbal and mobile individuals in each group and estimates of ability. Participants ranged in age from 4 to 52 years (mean 16.46, SD 9.88) and 65.1% were male. The Wessex Scale, (Kushlick et al., 1973) was used to describe levels of ability (self help skills), mobility (ability to walk unaided), visual impairment and hearing impairment. Overall, 573 (71.9%) of participants were able or partly able, 468 (58.7%) were fully mobile, 575 (72.1%) had normal vision and 691 (86.7%) had normal hearing. 545 (68.4%) of participants were verbal (used more than 30 words or signs).

(place Table 1 about here)

Measures

The questionnaires sent to carers were: a demographic questionnaire, the Wessex Scale (Kushlick, Blunden & Cox, 1973), the Autism Screening Questionnaire (ASQ; Berument et al., 1999), The Activity Questionnaire (TAQ; Burbidge & Oliver, 2008) and an adapted version of the Mood, Interest and Pleasure Questionnaire (Ross & Oliver, 2003; Ross et al., 2008).

Demographic Questionnaire. The demographic questionnaire detailed age, gender, mobility, verbal ability, diagnostic status.

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 disabilities. Subscales include continence, mobility, self help skills, speech and literacy and information on vision and hearing is also included. The Wessex Scale has good inter-rater reliability at subscale level for both children and adults (Kushlick *et al*., 1973; Palmer and Jenkins, 1982).

Autism Screening Questionnaire (Berument et al., 1999). The Autism Screening Questionnaire was developed as a tool for screening for autism spectrum disorders in children and adults and is based on the Autism Diagnostic Interview (Lord et al., 1994). The measure consists of 40 items which are grouped into three subscales: communication; social interaction and repetitive and stereotyped patterns of behaviors. Items are scored for the presence of abnormal behaviors to yield a total score of between 0 and 39 (one item evaluates the current language level of the individual and is not included in the total score) with higher scores indicating the presence of a higher number of abnormal behaviors. The maximum possible score on the Communication, Social Interaction, and Repetitive Behavior domains are 13, 15, and 8, respectively. The authors identify a cut off score of

15 as the standard optimal cut off for distinguishing individuals with Pervasive Developmental Disorders (including autism) from other diagnoses (sensitivity = .85 and specificity = .75). In the current study this cut off is referred to as the Autism Spectrum Disorder cut off. A higher cut off of 22 is reported by the authors to differentiate between individuals with autism and those with other Pervasive Developmental Disorders (sensitivity = .75 and specificity = .60). The ASQ shows good concurrent validity with the Autism Diagnostic Interview and with the Autism Diagnostic Observation Schedule (Berument et al., 1999; Howlin & Karpf, 2004). Internal consistency is also good (α = .90 for the total scale; Berument et al., 1999). No inter-rater or test-retest reliability data have been reported by the authors.

Activity Questionnaire (Burbidge & Oliver, 2008). The Activity Questionnaire is an information-based questionnaire designed to evaluate hyperactivity and impulsivity and is appropriate for use with people with intellectual disability including those with severe or profound intellectual disability. The questionnaire comprises eighteen items grouped into three subscales: overactivity (score range 0=36), impulsivity (0-24) and impulsive speech (0-12). Factor analysis and internal consistency of subscales confirm the integrity of the subscales (in review citation anonymised). Items are scored on a five-point Likert scale with responses ranging from 0 (never/almost never) to 5 (always/almost all of the time). Item level inter-rater reliability ranges from .31 to .75 (mean .56) and test-retest reliability ranges from .60 to .90 (mean .75). Inter-rater and test-retest reliability indices for subscales and total score exceed .70. Different scoring protocols are used for non verbal and immobile individuals to ensure comparability of scores across a wide range of intellectual disability. Scores on the impulsivity subscale are prorated for immobile individuals as they are only able to score on four of the six items in this subscale. Burbidge and Oliver (2008) identify scores of 32 and 24 for the overactivity and impulsivity subscales respectively as abnormally high (at or above the 95th percentile) for children with intellectual disability aged 18 and under. Corresponding scores for over 18's are 26 and 22.

Mood, Interest and Pleasure Questionnaire (MIPQ; Ross & Oliver, 2003; Ross, et al., 2008). The Mood, Interest and Pleasure Questionnaire is an informant based questionnaire used to assess two constructs related to depression, mood and, interest and pleasure. It is designed for use with people with intellectual disability including those with severe or profound intellectual disabilities. Informants rate twenty five items describing operationally defined observable behaviors to give a total score, a Mood subscale score and an Interest and Pleasure subscale score. A shorter version of this measure was developed (MIPQ-S, in review citation anonymised for review) in which twelve items from the original measure were selected (six from each subscale) on the basis of their item total correlation and ensuring that all the original constructs of mood, interest and pleasure were included. This version shows good internal consistency (Cronbach's alpha coefficients: total = .88, Mood = .79, Interest and Pleasure = .87), test-retest (.97) and inter-rater reliability (.85). Each item is rated using a five point Likert scale to give a total score of between 0 and 48 where 48 is the maximum score indicating positive affect and elevated interest and pleasure. The two subscale scores range between 0 and 24. For the MIPQ-S, Ross *et al.* (2008) identify scores of 6 and 15 for the Interest and Pleasure and Mood subscales respectively as abnormally low (at or below the 5th percentile) for children with intellectual disability aged 18 and under. Corresponding scores for over 18's are 6 and 13. Similarly, scores of 23 and 24 for the Interest and Pleasure and Mood subscales respectively are identified as abnormally high (at or above the 95th percentile) for children with intellectual disability aged 18 and under. Corresponding scores for over 18's are 21 and 24.

Data analysis

To achieve the first aim of the study, a series of one-way ANOVA's and post hoc (Scheffe) tests were carried out in order to evaluate group differences on each subscale of the MIPQ, ASQ and TAQ. For the second aim of the study the proportion of each group attaining scores at or above the cut-off scores for the ASQ, abnormally low and high scores for the subscales of the MIPQ-S, and abnormally high scores for the overactivity and impulsivity subscales of the TAQ were identified

and compared across groups using Chi squared tests. Age group (18 and under vs. over 18) and gender were also examined for these data.

Results

Demographic Characteristics

The mean age of the 797 participants was 16.46 years (standard deviation, 9.88 years). 35% of the sample was female, with 69% verbal, 61% mobile and 32% able. 73% of the participants had normal vision and 88% had normal hearing. Descriptive data for the groups are presented in Table 1. A one-way ANOVA of the mean ages revealed significant differences across the eight participant groups ($F(7) = 2.08$, $p = .044$). Chi-square tests of gender ($\chi(7) = 208.72$, $p<.001$), speech ($\chi(7) = 349.57$, $p<.001$), mobility ($\chi(7) = 84.34$, $p<.001$), level of ability ($\chi(7) = 253.94$, $p<.001$), vision ($\chi(7) = 262.35$, $p<.001$) and hearing ($\chi(7) = 155.64$, $p<.001$) revealed significant differences between the groups. Post hoc contrasts were carried out for those demographic characteristics that differed significantly between the groups in order to determine the nature of these differences. Table 2 describes the results of these analyses.

(place Table 2 about here)

Table 2 reveals that individuals in the Angelman syndrome group were significantly younger than individuals in the comparison, Cri du Chat, Cornelia de Lange, Fragile X, and Prader-Willi syndrome groups. As only males with Fragile X and Lowe syndrome were recruited for the study, as expected, significant differences were found for gender in these groups. Fewer individuals with Angelman syndrome showed speech in comparison to all other groups and participants in this group were of lower ability than those in the comparison group and participants with Cri du Chat, Fragile X, Prader-Willi, Smith Magenis and Lowe syndromes. Fewer participants in the Cornelia de Lange syndrome group showed speech in comparison to other groups, excluding the Angelman and Cri du

Chat syndrome groups. A higher proportion of individuals with Cornelia de Lange and Smith Magenis syndromes evidenced poorer hearing than for other groups. Similarly, a higher proportion of individuals in the Lowe syndrome group had poorer vision than all other groups. Fewer individuals with Fragile X syndrome evidenced compromised vision than other groups. Compared to all other groups individuals in the Fragile X and Prader-Willi syndrome groups showed higher levels of ability and a higher proportion of individuals had speech.

Comparisons of behavioral difference

To achieve the first aim of the study comparisons across groups were undertaken at group mean level for each of the subscales for the Autism Screening Questionnaire, The Mood, Interest and Pleasure Questionnaire (Short version) and The Activity Questionnaire. The results of these analyses are shown in Table 3.

(place Table 3 about here)

To achieve the second aim of the study the proportion of individuals attaining abnormally high scores on the Overactivity and Impulsivity subscales of the TAQ and abnormally low and high scores on the Mood and Interest and Pleasure subscales of the MIPQ-S were calculated and broken down by both age group (18 and under vs. over 18) and gender. The proportion of each group attaining these scores for each subscale of the TAQ and MIPQ, broken down by age band is shown in Figure 1.

(place Figure 1 about here)

Communication, social interaction and repetitive behavior

Significant group differences are evident in mean scores on each of the three domains of the ASQ (communication, social interaction and repetitive behavior). Post hoc analyses revealed the sources of these differences (see Table 3). The FXS group score higher (indicating greater impairment) on the communication subscale than two other groups (CdCS and PWS) and the CdCS group score lower than the comparison group (Comp.). The FXS, CdLS and Comparison groups all scored higher on the social interaction subscale than the CdCS and PWS groups and the AS group also scored higher than the PWS group. On the repetitive behavior subscale the FXS scored higher than four other groups.

The proportions of each group scoring at or above cut-off scores for Autism and Autism Spectrum Disorder on the ASQ are shown in Table 4. The difference between the proportion in groups is significant for the Autism cut off score (($\chi(7) = 69.61$, $p<.001$). The data show a high prevalence of Autism in the CdLS and FXS (45.9% and 46.3% respectively) compared to 33.3% in the comparison group. The proportions of CdCS, AS and PWS are comparatively low (8.0%, 17.8% and 15.5%). The pattern for Autism Spectrum Disorder runs parallel to the profile for Autism and group differences are also evident ($\chi(7) = 77.81$, $p<.001$). In combination these analyses show high levels of Autism for Cornelia de Lange and Fragile X syndrome, with the latter evidencing high levels of repetitive behavior, and comparatively low levels of Autism, for CdCS, AS and PWS. No within group gender differences were identified.

(place Table 4 about here)

Mood, Interest and Pleasure

Significant group differences were found for scores on each of the MIPQ subscales (Mood and Interest and Pleasure). Post hoc analyses revealed the sources of these differences (see Table 2).

For the Mood subscale the AS group scored higher than three other groups (Comp., CdLS and PWS). The CdLS group scored lower than three other groups on the mood subscale (FXS, AS and LS) and the LS and AS groups scored higher than two other groups on the interest and pleasure subscale (Comp. and CdLS).

With regard to the data in figure 1 the proportions of individuals showing abnormally positive and negative affect differs across groups ($\chi(7) = 16.3$, $p<.05$ and $\chi(7) = 16.14$, $p<.05$ respectively). Proportions of individuals showing abnormal positive affect are highest for Angelman syndrome (children 13.6%, adults 18.2%, with no observed negative affect) and adults with Cri du Chat syndrome (28.6% significantly higher than for children, 0%). There are, notably, comparable levels of abnormally high positive affect for adults with PWS (16.9%, significantly higher than for children, 4.0%) to those seen in adults with AS (18.2%). For Lowe syndrome there is a high proportion of abnormally high levels of interest and pleasure in children (28.2%) with no observed negative affect in children or adults. By contrast abnormal negative affect is seen in 13.2% of adults, compared to 3.2% of children with CdLS (approaching statistical significance $p = .056$), and no evidence of abnormally high positive affect in adults. Finally, it is notable that in Smith-Magenis syndrome there is no evidence of abnormal positive or negative affect in children or adults. No within group gender differences were identified.

In combination these results show that in children and adults with Angelman syndrome and adults with Prader-Willi and Cri du Chat syndromes there is abnormally high positive affect evident in from 15% to 30% of individuals. There is also evidence of high levels of interest and pleasure in children with Lowe syndrome. Negative affect is evidenced by a significant proportion of adults with Cornelia de Lange syndrome (13.2%).

Impulsivity, overactivity and impulsive speech

Significant group differences were found in scores on all three subscales of the TAQ (impulsivity, overactivity and impulsive speech). Post hoc analyses show that the PWS group scored lower than all six syndrome groups on the overactivity scale and the FXS group scored higher than the PWS, Comp. and LS groups. The AS group scores higher than the comparison group. The PWS group also score lower than three groups (AS, FXS and SMS) on the impulsivity scale and the SMS group scores higher than three other groups (Comparison group, Lowe and Prader-Willi syndrome). The FXS group scored higher on the impulsive speech scale than two other groups (CdLS and CdCs).

The data presented in Figure 1 show differences across groups ($\chi(7) = 21.22$, $p<.01$) with a very high proportions of significant impulsivity in both children and adults with Smith-Magenis syndrome (40% and 58.3% respectively). High proportions are also evident in adults with Cri du Chat (21.7%), Angelman (30.4%) and Cornelia de Lange syndromes (25%, a significant increase from the proportion for children of 10%) and children with Fragile X syndrome (25.7%). The proportions in each group showing significant levels of overactivity (or hyperactivity) differ ($\chi(7) = 27.04$, $p<.01$) and are notably lower and for these syndromes varying for adults from 4.3% (Cri du Chat) to 16.7% (Smith-Magenis). No within group gender differences were identified.

In combination these data show significant impulsivity to be evident in a sizable proportion of adults with Cri du Chat, Angelman and Cornelia de Lange syndrome, children with Fragile X syndrome and both children and adults with Smith-Magenis syndrome. The significant increase in the proportion of people showing impulsivity between childhood and adulthood in Cornelia de Lange syndrome is notable, as is the comparatively lower proportion of each group that evidence significantly high levels of overactivity.

Discussion

This is the first study to contrast a range of syndromes with comparatively large numbers in each group using appropriately adapted measures. The patterns of findings from adapted measures are consistent with previous research and this increases confidence in the results of the comparative analysis and the reported proportions of each group showing abnormally high or low scores. More specifically, in Cornelia de Lange and Fragile X syndromes we identify high proportions scoring above the cut-off for ASD and this has been documented for CdLS (Berney et al., 1999; Bhuiyan et al., 2005; Moss et al., 2008; citation anonymised for blind review) and Fragile X syndromes (Rogers et al., 2001; Clifford et al., 2007). Additionally, we demonstrate that high proportions of people with Smith-Magenis, Fragile X, Angelman and Cri du Chat syndrome show excessive impulsivity and/or hyperactivity and this is consistent with previous reports Clarke and Marston, 2000; Dykens & Clarke, 1997; Dykens & Smith, 1998; Cornish et al., 2005). Finally, the excessive positive affect in Angelman, Cri du Chat and Lowe syndromes we have identified in this study are previously reported by Horsler and Oliver (2006) and Oliver et al. (2007).

The first aim of this study was to generate comparative data across syndromes in order to position syndromes relative to each other with regard to their behavioral phenotype. In Table 5 we have distilled the results from the comparative analysis presented in Table 3 to provide a single accessible presentation of the data. For each domain of each assessment for each syndrome, the table shows the number of other groups that the syndrome significantly differs from. This eases comparison across syndromes and across domains simultaneously.

(place Table 5 about here)

The importance of this summary presentation is that performance in more than one domain across and within syndromes can be appraised alongside an indication of the relative salience of that

domain for a syndrome. It is these combined qualities that comprise the behavioral signature of a syndrome. The signatures in the table, derived from the comparative approach, are broadly consistent with the data in Figure 1 which are derived from abnormally high and low scores. Applying an arbitrary criterion of difference from at least two other groups, the overall profiles in table 5 show that, in comparative terms: Angelman syndrome is characterised by elevated positive affect and hyperactivity; Cri du Chat syndrome by absence of social or communicative impairment; Cornelia de Lange syndrome by social impairment and negative affect; Fragile X syndrome by social and communicative impairment, repetitive behavior and hyperactivity; Prader-Willi syndrome by absence of repetitive behaviors and absence of social impairments; Lowe syndrome by positive affect as evidenced by interest and pleasure only and Smith-Magenis syndrome by impulsivity. In each case these characterisations of these syndromes in these domains that have been derived using empirical methods are supported by the broad cohort description and small group comparison group approaches (see O'Brien & Yule, 1995; Dykens et al., 2000). Having established this dataset and demonstrated its validity for well established syndromes it is now possible to extend the use of these assessments to other syndromes and place these syndromes within the same matrix.

There are a number of conceptual and methodological issues that are pertinent to the results of the study. It is possible that the samples in this study are in some way biased by recruiting from support groups. This seems unlikely given the similarity between behavioral profiles and extant literature. Additionally, these samples are likely to be significantly less biased than clinical samples. Given the emergent literature on difference for genetic subtypes in, for example, Angelman, Prader-Willi and Cornelia de Lange syndromes and deletion size in Cri du Chat syndrome (Milner et al., 2005; Bhuiyan et al., 2006; Zhang et al., 2005) clearly the characterisation at the syndrome level is crude and could be further refined by within group comparisons. Additionally, for statistical analyses the n varies between groups and thus power is differentially affected. This may mean that in smaller

groups a given level of difference, for example between age groups, might not be identified when it is evident for the same level of difference in larger groups. The only way to address this problem would be to discard large numbers of participants to equalise group sizes and this would have compromised generalisability.

The decision not to try to control for degree of intellectual disability across groups for the assessments that were used appears vindicated as phenotype profiles are consistent with existing literature. In the broader literature on autism spectrum disorder a greater degree of intellectual disability is associated with a higher prevalence of ASD (Nordin & Gillberg, 1996). If this effect had been evident in the dataset then syndromes associated with a greater degree of intellectual disability (such as Angelman syndrome, see Table 2) would have evidenced higher proportions reaching the cut-off for ASD than for more able groups (compare Prader-Willi syndrome with Angelman and Fragile X with Cri du Chat) but this was not the case. Finally, the assessments that have been used are clearly inferior to either observational assessments (e.g. ADOS) or validated interviews (e.g. ADI) and assessments of, for example, the cognitive substrate of the behavioral phenomena of impulsivity by tests of behavioral inhibition or delay gratification (Barkley, 1999). However, the data do clearly indicate which syndromes might usefully be explored with more refined assessments.

A significant construct validity issue is the extent to which scores on measures such as the ASQ appraise the construct they were designed to measure when applied to syndromes in which different forms of disorders of social and communicative behavior are evident. This is perhaps best demonstrated in Angelman syndrome in which communication is, almost, universally absent and the social impairment is characterised by sustained attempts at social engagement (Oliver et al., 2007) and excessive pleasure when social contact is ongoing (Horsler & Oliver, 2006). Despite this demonstrable difference from that normally seen in ASD, the group mean for social impairment on

the ASQ was higher than that for two other groups. This score profile might be generated for different reasons in different syndromes. There is clearly a need for caution in interpreting these data.

In addition to generating the empirical data to describe these syndromes there are a number of novel and interesting findings that warrant further research. The increase in impulsivity with age and the high levels of low mood in adults with Cornelia de Lange syndrome allude to syndrome specific, and possibly related, developmental trajectories for these phenomena. Similarly the possible double dissociation between overactivity and impulsivity in Fragile X and Smith-Magenis syndromes is of interest for models of ADHD as is the difference in the proportions across syndromes showing very high levels of impulsivity in comparison to hyperactivity. The similar proportions of people with Cornelia de Lange and Fragile X syndrome attaining the cut-off score for ASD is compelling, especially because the data in table 3 allude to a difference in the profile in the triad of impairments (see Moss et al., 2008). The very low level of overactivity (or activity generally) have been previously reported in Prader-Willi syndrome (Holland et al., 2003). The similarly low levels of impulsivity in the same syndrome suggest a continuum for this phenomenon and the lack of any impulsivity in PWS might be related to difficulties in attentional shift that have recently been reported in this syndrome (in review citation withheld for blind review). Finally, the possible increase in positive affect with age in Cri du Chat and Prader-Willi syndromes are notable and have not been previously reported, although mood fluctuations are reported in PWS (Holland et al., 2003). In each case these areas might be best explored using double dissociation strategies across syndromes showing same but different profiles and the emergent strategy of comparison of developmental trajectories across cognitive domains (Cornish et al., 2007).

As other authors have noted it is important to consider behavioral phenotypes within a developmental context and within the prevailing environment in which behavior is manifested.

Evidence for gene-environment interactions for genetic syndromes is beginning to emerge (Hall et al., 2007, Oliver et al., 2007, in review citation withheld for blind review) with transactional models suggesting complex relationships between cognitive and developmental variables and social exchanges (Moore et al., 2002). The results of this study can only identify the broad profile for each syndrome relative to other syndromes given the previous and current environments which the participants have experienced. Future research should seek to further describe the complexity of gene environment interactions whilst drawing on a developmental framework.

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Footnote

[1] The n may vary for the analysis due to missing data.

Table 1: Participant characteristics of each group.

		Comp.	**AS**	**CdCS**	**CdLS**	**FXS**	**PWS**	**LS**	**SMS**
N		56	104	58	101	191	189	56	42
Age*	Mean	18.25	13.40	17.20	17.49	16.57	17.04	16.20	15.45
	(SD)	(10.03)	(7.97)	(12.16)	(9.87)	(8.81)	(10.86)	(10.32)	(8.86)
	Range	6-38	4-45	4-44	4-40	6-47	4-51	4-51	4-38
Gender	Male (%)	64.3	55.8	36.2	40.6	100[6]	52.7	100[6]	40.5
Self [1] Help	Partly able/able[2] (%)	64.3	33.0	62.1	53.5	90.1	96.6	64.3	78.6
Mobility[1]	Fully mobile[3] (%)	36.4	46.1	53.7	59.2	70.4	73.0	46.4	73.2
Vision[1]	Normal (%)	67.3	87.5	84.5	67.3	88.9	71.9	12.7	65.9
Hearing[1]	Normal (%)	81.8	100	17.2	66.0	97.9	94.9	92.9	59
Speech[5]	Verbal (%)	60.0	1.9	67.2	45.5	88.9	96.3	74.5	81.0

***** In years

[1] Data derived from the Wessex questionnaire (Kushlick *et al.*, 1973; See section…for a description of the questionnaire).

[2] Those who score six or above on the total score of the self help subscale (items g-i).

[3] Those who score six on the total score of the mobility subscale (items e &f).

[4] Those who score 2 or above on item l of the questionnaire.

[5] Data derived from item 3 of the demographic questionnaire.

[6] All male due to X linked nature of syndrome. Females excluded from FXS group

Table 2: Post hoc contrasts for gender, speech, level of ability and impaired mobility vision and hearing. (Comp. = Comparison Group, AS = Angelman Syndrome, CdCS = Cri du Chat syndrome, CdLS = Cornelia de Lange syndrome, FXS = Fragile X syndrome, PWS = Prader-Willi syndrome, LS = Lowe syndrome, SMS = Smith-Magenis syndrome).

Demographic	**Post hoc analysis**
Age	Comp., CdCS, CdLS, FXS, PWS > AS
Gender	FXS, LS > Comp., AS, CdCS, CdLS, PWS, SMS.
Presence of speech	Comp., CdCS, CdLS, FXS, PWS, LS, SMS > AS.
	SMS, LS, PWS, FXS > CdLS.
	PWS > CdCS, LS.
	FXS > CdCS.
Impaired mobility	PWS < Comp., AS, LS.
	FXS < Comp., AS.
	SMS < Comp.
Level of ability	Comp., CdCS, FXS, PWS, LS, SMS > AS.
	PWS, FXS > Comp., CdCS, CdLS, LS.
	PWS > SMS.
Impaired vision	FXS < Comp., CdLS, PWS, SMS.
	Comp., AS, CdCS, CdLS, FXS, PWS, SMS < LS.
Impaired hearing	AS, FXS < Comp., CdCS, CdLS, SMS.
	PWS, LS < CdLS, SMS.

Table 3. Means (SD's) for subscales of the MIPQ, TAQ and SCQ with results for analyses of variance and post hoc analyses. (Comp. = Comparison Group, AS = Angelman Syndrome, CdCS = Cri du Chat syndrome, CdLS = Cornelia de Lange syndrome, FXS = Fragile X syndrome, PWS = Prader-Willi syndrome, LS = Lowe syndrome, SMS = Smith-Magenis syndrome).

	Comp.	AS	CDCS	CDLS	FXS	PWS	LS	SMS	ANOVA df	F	P level	Post Hoc ≤.01
N	56	103	58	101	190	187	56	42				
Mean MIPQ-S Mood score (SD)	19.23 (3.32)	21.42 (1.91)	20.11 (2.82)	18.58 (3.63)	20.74 (2.78)	19.60 (3.39)	20.87 (1.98)	19.17 (2.82)	7,785	10.53	<.001	AS > Comp., CdLS, PWS LS, FXS > CdLS
Mean MIPQ-S Interest & Pleasure score (SD)	14.73 (5.20)	18.07 (3.86)	17.53 (3.77)	15.00 (4.35)	16.76 (4.04)	16.35 (4.32)	19.04 (3.32)	15.79 (4.84)	7,785	8.97	<.001	LS, AS > Comp., CdLS
Mean ASQ Communication score (SD)	6.39 (2.30)	5.59 (1.74)	4.10 (2.09)	5.83 (2.18)	6.80 (2.41)	5.17 (2.53)	5.72 (2.74)	5.57 (2.68)	7,699	10.65	<.001	FXS > CdCS, PWS Comp. > CdCS
Mean ASQ Social Interaction score (SD)	8.36 (4.05)	7.29 (3.08)	5.02 (2.99)	8.99 (3.89)	8.14 (3.26)	4.83 (3.61)	6.69 (3.79)	7.00 (3.17)	7,697	19.52	<.001	CdLS, FXS, Comp. > CdCS, PWS AS > PWS
Mean ASQ Repetitive Behavior score (SD)	2.99 (2.15)	3.44 (1.81)	3.25 (1.87)	3.91 (1.91)	4.74 (2.19)	3.36 (2.11)	4.42 (2.19)	4.70 (2.10)	7,784	10.87	<.001	FXS > Comp., AS, CdCS, PWS
Mean TAQ Overactivity score (SD)	12.53 (9.21)	19.02 (8.06)	16.42 (8.95)	14.56 (9.83)	18.77 (10.34)	6.94 (6.95)	12.91 (8.97)	18.18 (9.40)	7,788	31.25	<.001	AS, CdCS, CdLS, FXS, LS, SMS > PWS FXS > Comp., LS AS > Comp.
Mean TAQ Impulsivity Score (SD)	12.90 (7.42)	17.48 (6.16)	16.14 (6.47)	14.75 (6.59)	16.21 (6.89)	13.00 (7.03)	13.29 (7.56)	19.95 (4.79)	7,785	9.82	<.001	AS, FXS, SMS > PWS SMS > Comp., LS
Mean TAQ Impulsive Speech score (SD)	4.01 (2.98)	*	2.56 (3.03)	2.13 (2.53)	5.56 (3.70)	4.33 (3.41)	4.55 (3.09)	5.89 (3.67)	7,536	8.39	<.001	FXS > CdCS, CdLS SMS > CdLS

Table 4: Proportions of each group attaining cut–off scores on the Autism Screening Questionnaire indicative of Autism Spectrum Disorder (ASD) or Autism . (Comp. = Comparison Group, AS = Angelman Syndrome, CdCS = Cri du Chat syndrome, CdLS = Cornelia de Lange syndrome, FXS = Fragile X syndrome, PWS = Prader-Willi syndrome, LS = Lowe syndrome, SMS = Smith-Magenis syndrome).

		Comp.	AS	CdCS	CdLS	FXS	PWS	LS	SMS	Total
ASD	*n*	*24*	*67*	*20*	*67*	*148*	*77*	*37*	*26*	*466*
	%	72.7	66.3	40.0	78.8	83.6	45.8	71.2	68.4	66.2
Autism	*n*	*11*	*18*	*4*	*39*	*82*	*26*	*18*	*14*	*212*
	%	33.3	17.8	8.0	45.9	46.3	15.5	34.6	36.8	30.1

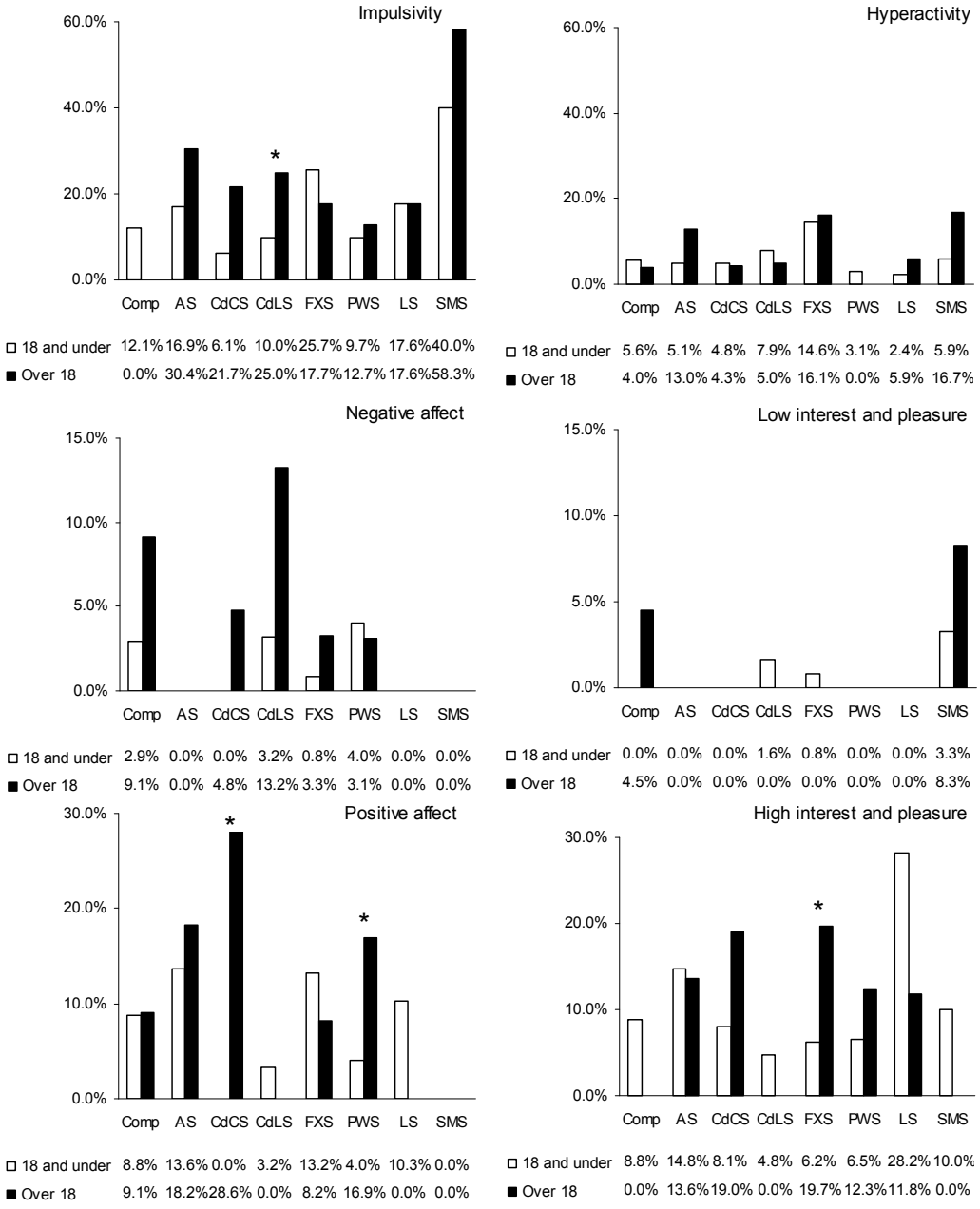
Table 5. Relative position of syndrome groups on assessments of Autism Spectrum Disorder, Affect and Hyperactivity (+ = scores higher than one other group, - = scores lower than one other group, o = no difference from other groups).

	Autism Spectrum Disorder			**Affect**		**Hyperactivity**	
Syndrome	**Social**	**Communication**	**Repetitive Behavior**	**Interest & Pleasure**	**Mood**	**Over-activity**	**Impulsivity**
None	++	+	-	--	-	--	-
Angelman	+	O	-	++	+++	++	+
Cri du Chat	---	--	-	O	O	+	O
Cornelia de Lange	++	O	O	--	---	+	O
Fragile X	++	++	++++	O	+	+++	+
Prader-Willi	----	-	-	O	-	------	---
Lowe	O	O	O	++	+	O	--
Smith Magenis	O	O	O	O	O	+	+++

Figure Captions

Figure 1: The percentage of each group scoring abnormally high on measures of hyperactivity and impulsivity and abnormally high or low on measures of affect and interest and pleasure, broken down by age bands. (Comp = Comparison Group, AS = Angelman Syndrome, CdCS = Cri du Chat syndrome, CdLS = Cornelia de Lange syndrome, FXS = Fragile X syndrome, PWS = Prader-Willi syndrome, LS = Lowe syndrome, SMS = Smith-Magenis syndrome).

Figure 1 Top


Impulsivity
60.0%
40.0%
20.0%
0.0%
*
Comp AS CdCS CdLS FXS PWS LS SMS
18 and under 12.1% 16.9% 6.1% 10.0% 25.7% 9.7% 17.6% 40.0%
Over 18 0.0% 30.4% 21.7% 25.0% 17.7% 12.7% 17.6% 58.3%
Hyperactivity
60.0%
40.0%
20.0%
0.0%
Comp AS CdCS CdLS FXS PWS LS SMS
18 and under 5.6% 5.1% 4.8% 7.9% 14.6% 3.1% 2.4% 5.9%
Over 18 4.0% 13.0% 4.3% 5.0% 16.1% 0.0% 5.9% 16.7%
Negative affect
15.0%
10.0%
5.0%
0.0%
Comp AS CdCS CdLS FXS PWS LS SMS
18 and under 2.9% 0.0% 0.0% 3.2% 0.8% 4.0% 0.0% 0.0%
Over 18 9.1% 0.0% 4.8% 13.2% 3.3% 3.1% 0.0% 0.0%
Low interest and pleasure
15.0%
10.0%
5.0%
0.0%
Comp AS CdCS CdLS FXS PWS LS SMS
18 and under 0.0% 0.0% 0.0% 1.6% 0.8% 0.0% 0.0% 3.3%
Over 18 4.5% 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 8.3%
Positive affect
30.0%
20.0%
10.0%
0.0%
*
*
Comp AS CdCS CdLS FXS PWS LS SMS
18 and under 8.8% 13.6% 0.0% 3.2% 13.2% 4.0% 10.3% 0.0%
Over 18 9.1% 18.2% 28.6% 0.0% 8.2% 16.9% 0.0% 0.0%
High interest and pleasure
30.0%
20.0%
10.0%
0.0%
*
Comp AS CdCS CdLS FXS PWS LS SMS
18 and under 8.8% 14.8% 8.1% 4.8% 6.2% 6.5% 28.2% 10.0%
Over 18 0.0% 13.6% 19.0% 0.0% 19.7% 12.3% 11.8% 0.0%