Sleep Problems and Associations with Psychopathology and Cognition in Young People with 22q11.2 Deletion Syndrome (22q11.2DS)

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Background: Young people with 22q11.2 deletion syndrome (22q11.2DS) are at high risk for neurodevelopmental disorders. Sleep problems may play a role in this risk but their prevalence, nature and links to psychopathology and cognitive function remain undescribed in this population.

Method: Sleep problems, psychopathology, developmental coordination and cognitive function were assessed in 140 young people with 22q11.2DS (mean age=10.1, SD=2.46) and 65 unaffected sibling controls (mean age=10.8, SD=2.26). Primary carers completed questionnaires screening for the children's developmental coordination and autism spectrum disorder.

Results: Sleep problems were identified in 60% of young people with 22q11.2DS compared to 23% of sibling controls (OR=5.00, p<0.001). Two patterns best described sleep problems in 22q11.2DS: restless sleep and insomnia. Restless sleep was linked to increased ADHD symptoms (OR=1.16, p<0.001) and impaired executive function (OR=0.975, p=0.013). Both patterns were associated with elevated symptoms of anxiety disorder (restless sleep: OR=1.10, p=0.006 and insomnia: OR=1.07, p=0.045) and developmental coordination disorder (OR=0.968, p=0.0023, and OR=0.955, p=0.009). The insomnia pattern was also linked to elevated conduct disorder symptoms (OR=1.53, p=0.020).

Conclusions: Clinicians and carers should be aware that sleep problems are common in 22q11.2DS and index psychiatric risk, cognitive deficits and motor coordination problems. Future studies should explore the physiology of sleep and the links with the neurodevelopment in these young people.

Introduction

22q11.2 Deletion Syndrome (22q11.2DS) is a genetic disorder characterised by a hemizygous deletion of ~50 genes on the long arm of chromosome 22 (Swillen et al. 2015) and is one of the strongest known biological risk factors for development of schizophrenia (Monks et al., 2014; Schneider et al., 2014). It is associated with congenital physical abnormalities (e.g., heart defect, cleft palate) (McDonald-McGinn et al., 2001) and a range of neurodevelopmental problems (Schneider et al., 2014; Niarchou et al., 2015; Chawner et al., 2017; Cunningham et al., 2017) including an increased risk of ADHD (12-68%), anxiety disorders (in 40-76%), oppositional defiant disorder (ODD) (in 9-43%), autism spectrum disorder (ASD) (in 14-50%) (Schneider et al., 2014) and motor coordination problems (> 80%) (Cunningham et al., 2017) of young people with 22q11.2DS. Comorbid psychiatric presentation is common in individuals with 22q11.2DS, with 54% of children with 22q11.2DS reported to meet diagnostic criteria for one or more DSM-IV-TR psychiatric disorders (Niarchou et al., 2014) and a recent large-scale study has documented evidence of widespread structural brain abnormalities (Sun et al., 2018). In addition, the average IQ is ~30 IQ points lower than in typically developing children (Niarchou et al., 2014) and a range of deficits in specific cognitive functions have also been reported, including reaction time, sustained attention, processing speed, spatial working memory and executive function (Hooper et al., 2013; Niarchou et al., 2014).

Sleep problems have yet to be formally acknowledged as part of the 22q11.2DS phenotype despite anecdotal reports of their presence. The limited evidence of sleep problems that is available in 22q11.2DS has focused on sleep-related breathing disorders that arise from airway obstruction caused by craniofacial dysmorphia of the syndrome (Heike et al., 2007; Crockett et al., 2014; Kennedy et al., 2014). These small-scale studies and case reports have shown evidence for obstructive sleep apnoea in an estimated 10% of young people with 22q11.2DS, compared to only 2-4% in typically developing children (Chang et al., 2010; Kennedy et al., 2014). Furthermore, neurodevelopmental disorders (NDD) such as ADHD and Studies not specifically focussing on 22q11.2DS have provided evidence of elevated rates of

sleep problems in individuals with neurodevelopmental disorders (NDD) such as ADHD and ASD, with reported rates as high as 86% (Wiggs 2001; Robinson-Shelton and Malow. 2016). Rates of sleep problems between 40-80% have been reported in individuals with ASD (Souders et al., 2009), 25-50% in individuals with ADHD (Corkum et al. 1998; Spruyt et al. 2011) and 88% of those with anxiety disorders (88%) (Staner, 2003). These findings suggest that sleep problems could be prominent in individuals with 22q11.2DS.

To our knowledge this is the first study to address the prevalence and nature of sleep problems and their links with psychopathology and cognitive function in 22q11.2DS.

Specifically, we aimed to address the gap in the literature by: 1) quantifying the prevalence of sleep problems in a cohort of young people with 22q11.2DS compared to sibling controls; 2) describing the patterns of sleep problems in young people with 22q11.2DS and; 3) investigating the links between sleep problems and neurodevelopmental and cognitive outcomes in young people with 22q11.2DS.

Methodology

Participants

Participants were part of the ongoing Experiences of Children with cOpy number variants (ECHO) study (https://www.cardiff.ac.uk/mrc-centre-neuropsychiatric-genetics-genomics /research/themes/developmental-disorders/echo-study-cnv-research). Young people with 22q11.2DS were recruited through NHS Medical Genetics clinics in the UK, British 22q11.2DS charities (Max Appeal! 22qCrew and Unique), social media and family networks. Where available, a sibling without the deletion (sibling control) closest in age to the child with 22q11.2DS was also invited to take part in the ECHO study. The availability of this sibling control sample enabled us to conduct comparisons with a typically developing sample to quantify the extent of sleep problems in 22q11.2DS as well as conduct pairwise comparisons between case-control sibling pairs, therefore considering shared genetic background and family environmental factors. Carriers of the deletion and sibling controls were aged 6 or older and the presence (in carriers) or absence (in sibling controls) of the deletion was confirmed by a Medical Genetics laboratory and/or microarray analysis in the MRC Centre for Neuropsychiatric Genetics and Genomics laboratory at Cardiff University. The current study focussed on 140 young people with 22q11.2DS ($\bar{x}$ age =10.1, range = 6 years 3 month–17 years 1 month, SD= 2.45, 45.0% females) and 65 age-matched sibling controls ($\bar{x}$ age = 10.8, range = 6 years 1 month –16 years 7 months, SD= 2.26, 43.1% females). Family income information was obtained from questionnaires completed by the primary carer and can be found together with information of the age and gender of the participants in Table 1.

Of the participants with 22q11.2DS 17 were taking melatonin for sleep problems; one used antipsychotic medication aripiprazole for psychotic experiences; one risperidone for mood disorder and none were using ADHD medication. Parents reported a diagnosis of epilepsy in 10.7% (15/140) of participants with 22q11.2DS. Two children with 22q11.2DS were using sodium valproate for epilepsy. Prior to recruitment, primary carers consented for all participants and additional consent was obtained from participants aged ≥16 years with

capacity. The protocols used in this study were approved by NHS South East Wales Research Ethics Committee.

Assessments

Psychopathology and neurodevelopmental assessment

The semi-structured Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al., 1995) was conducted with the primary carer, and young people with capacity were themselves interviewed about their mood, anxiety and psychotic experiences with the child CAPA. All interviews were conducted by trained psychologists, and taped for monitoring and the scoring of symptoms. Attribution of diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) was discussed in consensus meetings led by child and adolescent psychiatrists.

The anxiety disorder symptom score included symptoms of generalised anxiety disorder, social phobia, specific phobia, separation anxiety, and panic disorder with and without agoraphobia, agoraphobia and obsessive-compulsive disorder. ADHD symptoms included the subscales of hyperactivity and impulsivity and inattention, ODD symptoms the subscales oppositional behaviour and deception, and conduct disorder (CD) symptoms the subscales of acts involving violence and violence against persons.

ASD symptoms were screened for with the Social Communication Questionnaire (SCQ) (Rutter et al. 2003) completed by the primary carer (referred to as indicative ASD from here onwards). The total indicative ASD score comprised three subscales: social interaction, communication, and restrictive and repetitive traits. scQ total scores were available for a subsample of 128 young people with 22q11.2DS.

Symptom scores of psychopathologies were calculated by summing individual scores ranging from 0 to 26 for anxiety disorder, 0 to 16 for ADHD, 0 to 6 for ODD, 0 to 4 for CD and 0 to 34 for indicative ASD as in previous studies (Niarchou et al., 2014; Chawner et al., 2017;

Cunningham et al., 2017). A symptom score of ≥15 on the SCQ is considered to be indicative of ASD (Berument et al., 1999).

Sleep problems

Sleep problems over the preceding three months were established by interview with the primary carer using the sleep section of the CAPA. This section includes 11 questions (see Table 2): insomnias (trouble initiating sleep, trouble maintaining sleep and early morning awakening without being able to return to sleep); hypersomnia (excessive daytime sleepiness, extended sleep duration); restless sleep (inability to get comfortable and feel rested for the night); inadequately rested sleep (lack of restorative and maintained sleep); fatigue and tiredness (feelings of being tired at least half the time), and becoming tired or 'worn out' more easily than usual) and parasomnias (nightmares, night terrors and sleepwalking). This CAPA section screens for the presence of sleep problems but does not provide a sleep disorder diagnosis, which would require additional assessments including polysomnography conducted by clinicians. Items were coded "0 = absent" or "1 = present" and positive scores of the 11 items were summed to obtain an overall sleep problem score (Table 2) ranging from 0-7.

Developmental coordination problems

Indicative Developmental Coordination Disorder (DCD) was established using the DCD Questionnaire (DCDQ) (Wilson et al., 2009) completed by the primary carer. The DCDQ screens for motor coordination impairments with scores ranging from 15 to 75. Lower scores indicate greater coordination problems with discrimination thresholds based on age (Cunningham et al., 2017). We introduced this measure later in our study and therefore have available information from 97 young people with 22q11.2DS.

IQ

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was used to assess full-scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ).

Cognitive performance

The Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd, 2006) was used to assess of the following cognitive performances: spatial working memory (number of errors on the spatial working memory (SWM) task); spatial planning (number of problems solved on the Stockings of Cambridge (SOC) task); processing speed (reaction time in milliseconds on the Five-choice reaction time (RTI) task); visual attention (number of correct items on the Match-to-Sample Visual Search (MTS) task) and sustained attention (ability to distinguish the target stimuli from the distractor stimuli during the Rapid Visual Processing (RVP) task. All CANTAB scores were age- except for MTS where no CANTAB norms are available and raw scores were used. The Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993) was used to measure outcomes of perseverative (set-shifting) and non-perseverative (random) errors.

All measures in this study were selected because they are well-established and appropriate across the range of abilities of the participants (young people with 22q11.2DS and control siblings). Previous use of these instruments in similar contexts to the study sample is further outlined in the supplementary materials (see supplementary Table 2).

Statistical Analysis

Statistical analyses were conducted using STATA (version 13.1) (https://www.stata.com/stata-news/news28-4/stata13.1) and R (version 3.5.0) (R: The R Project for Statistical Computing, 2018).

To address aim 1, chi-squared tests and t-tests were used to determine any differences in the age and gender between the two groups. Where non-significant, we did not include these two variables as covariates in further analyses. Logistic regression analysis was used to establish whether group status (child with 22q11.2DS or control sibling) predicted total sleep problem score (the sum of positively endorsed sleep items of the CAPA) with age and family

relatedness (to indicate that a child with 22q11.2DS and their sibling came from the same family) as covariates.

To address aim 2, we first constructed two-by-two tables for each combination of the 11 sleep items in young people with 22q11.2DS, followed by tetrachoric correlation analysis (Pearson, 1900), which is suitable for dichotomous variables and assumes an underlying normal distribution (Ledesma et al. 2011). The 2x2 tables indicated that for several combinations of items the cell count for positive endorsement on both items (yes/yes) was zero and that therefore a correlation coefficient could not be calculated. This was the case for combinations between parasomnia items and several other items: night terrors and hypersomnia, sleep walking and hypersomnia; night terrors and tiredness; night terrors and fatigability; nightmares and fatigability; and sleep walking and fatigability. Furthermore, some 2x2 tables had very low yes/yes cell counts, resulting in low correlations and this involved several combinations with the parasomnia item sleep walking, i.e., sleep walking with initial insomnia (r=-0.036); sleep walking with early insomnia (r=-0.002); as well as fatigability with middle insomnia (r=-0.01). The parasomnia items were furthermore found to not correlate well (sleep walking with nightmares (r=0.06, p=0.620); sleep walking with night terrors (r=0.04, p=0.490), except for nightmares and night terrors (r=0.400, p<0.001). The parasomnia items also did not differ significantly between young people with 22q11.2DS and control siblings (Table 2), indicating that they do not represent sleep problems that are specific to young people with the deletion. We therefore removed the parasomnia items from the analysis. The items hypersomnia, tiredness and fatigability correlated quite strongly (hypersomnia with tiredness r=0.510; hypersomnia with fatigability r=0.370; tiredness with fatigability r=.560) and we combined these items into a single score capturing tiredness-related sleep problems. Similarly, the items early and middle insomnia also correlated quite strongly (r=0.522, p<0.001) and were combined (into an item capturing mid/early insomnia). Doing so addressed the almost zero correlation between middle insomnia and fatigability. Item combination was as follows: a dichotomous variable was created where a positive score on any of the items translated into

a positive score on the combined variable. Figure 1 provides a visualisation of the item combination procedure followed. This produced a 5-item tetrachoric correlation matrix (see supplementary Table 3), which was the basis for exploratory factor analysis (EFA) (Conway et al. 2003) to determine the patterns of sleep problems in young people with 22q11.2DS (see Table 2).Statistically, combining items that represent a single underlying construct is important because it reduces the number of comparisons that would be conducted if each individual item was analysed separately and enhances the robustness of the measured concept. Clinically, it is important to understand whether sleep problems cluster patterns and have different associations with other outcomes such as psychopathology as this can have implications for interventions. We decided on the number of factors to be retained from the EFA based on the scree plot of eigenvalues (values ≥0.6) (presented in supplementary Figure 2) and interpretation of meaningful patterns (Gorsuch, 1983). The factor solution was rotated using an oblique solution to maximise interpretation. The rotated factors were not normally distributed, determined by looking at the distribution plots and testing using Shapiro-Wilk test for normality and assessing Skewness of data. We subsequently calculated the sleep patterns by summing the binary sleep problem items that loaded on each factor ("1" = ≥1 positive item; "0" = no positive items) for use in further analysis. Spearman correlation analysis was used to determine the interrelationship between the resulting patterns of sleep problems.

For aim 3, hierarchical logistic regression analyses were used to examine the links between the patterns of sleep problems (presence or absence of a pattern) in young people with 22q11.2DS, taking age into account (step 1), with subsequent addition of psychiatric disorder symptoms (ADHD, anxiety CD, ODD and ASD), motor coordination problems (DCDQ) and cognitive performance (IQ, spatial working memory, sustained and visual attention, spatial planning and executive function) each individually (step 2).

We conducted sensitivity analyses to determine whether relevant factors could explain these associations. We examined the links between the sleep patterns (presence or absence) and: maternal education level and the children's melatonin use; epilepsy diagnosis, and physical

health problems using logistic regression analyses. For the analyses of the sleep patterns and anxiety disorder symptoms, we also removed the sleep-related anxiety symptoms (i.e., ‘unable to sleep alone’ and ’separation nightmares’) from the total anxiety symptom score to establish if this changed the findings. Other potential confounders (e.g., other medication use) were not evaluated because of low prevalence within the sample.

To correct the analyses for multiple comparisons, we used a Benjamini–Hochberg false discovery rate (FDR) rate of 10% (Benjamini and Hochberg, 1995). The Benjamini-Hochberg method ranks the individual p-values from smallest to largest, with the smallest p-value ranking as 1. By comparing each individual p-value to the Benjamini-Hochberg critical value ((rank/total number of tests) * FDR (i.e., 10%)), if the largest p-value in our analyses before correction is smaller than its critical value, it is considered significant. Any p-values smaller than the largest p-value are also interpreted to be significant.

Results

Sociodemographic information is presented in Table 1. Individuals with 22q11.2DS were younger than sibling controls (t=2.09, p=0.040) but there was no difference in gender proportions (χ^2=0.125, p=0.724) but there were differences in age (t=2.09, p=0.04).

Prevalence of sleep problems in 22q11.2DS (Aim 1)

60% of young people with 22q11.2DS had experienced at least one sleep problem (22q11.2DS median=1 (range 0-7)) during the past 3 months, compared to 23.1% of sibling controls (controls median=0 (range 0-5)) (OR=5.00 p=<0.001) (Table 2). A paired t-test in the subsample of children with 22q11.2DS with a participating control sibling (n=63) showed a higher report of sleep problems in young people with 22q11.2DS compared to their siblings (t=4.56, p<0.001).

Analysis of the 11 individual CAPA items showed that compared with sibling controls young people with 22q11.2DS had higher rates of insomnias, restless and inadequately rested sleep, with a borderline trend for tiredness. There were no differences for hypersomnia, fatigability and the parasomnia items (nightmares, night terrors and sleepwalking) (Table 2).

Patterns of sleep problems in 22q11.2DS (Aim 2)

Exploratory factor analysis indicated that sleep problems in young people with 22q11.2DS were captured best by two patterns: restless sleep (see Table 2[a]) and insomnia (see Table 2[b]). The two factors deviated from normality (for restless sleep z=6.39, p<0.001 and p<0.001 (skewness); for insomnia z=3.53, p=0.0002 and p=0.03 (skewness)) and therefore were dichotomised. These patterns correlated (r=0.252, p=0.003), reflecting that children can have problems in both domains.

54.3% (76/140) of young people with 22q11.2DS scored on at least one sleep pattern. Of these 76 individuals, 44.7% (34/76) scored positive for the restless sleep pattern only; 21.1% (16/76) on the insomnia sleep pattern only and 34.2% (26/76) on both patterns. Neither pattern was associated with age (OR=1.01, p=0.912 for restless pattern; OR=0.865, p=0.069 for

insomnia pattern), or gender (OR=0.751, p=0.406 for restless pattern; OR=1.12, p=0.767 for insomnia pattern).

Links between sleep patterns and psychiatric symptoms, developmental coordination and cognitive function (Aim 3)

Young people with 22q11.2DS who scored positive for the restless sleep pattern compared to those with negative responses had higher rates of any psychiatric disorder, ADHD, anxiety disorder and ODD diagnoses (supplementary Table 1; n=0 young people reported CD diagnosis). No differences were found in the rates of diagnosis in those who scored positively on the insomnia sleep pattern compared to those who did not (supplementary Table 1).

The restless sleep pattern was associated with increased symptoms of ADHD, anxiety disorder, ODD, CD, indicative ASD and indicative DCD, as well as a poorer performance on the sustained attention and set shifting ability (perseverative errors on the WCST) tasks (see Table 3). following FDR correction (denoted by * in Table 3).

Post-hoc analysis of ADHD symptoms showed an association with the inattentive (OR=4.95, p<0.001), but not the hyperactive (OR=6.81, p=0.104) or combined (OR=1.76, p=0.307) subtypes.

The insomnia sleep pattern showed association with increased symptoms of anxiety disorder, CD and indicative DCD as well as impaired performance on the visual attention task (Table 3). The associations between the restless sleep pattern and sustained attention and the insomnia pattern and visual attention disappeared following FDR correction (denoted by * in Table 3).

Comorbid presentation of both sleep patterns with psychiatric symptoms was high (see figures 1 and 2). Of the 60 young people who scored on the restless sleep pattern, 86.7% (52/60) had at least one comorbidity as did 52.4% (22/42) of the young people scoring on the insomnia sleep pattern. The most common comorbid presentation for the restless sleep pattern (found in 18.6% scoring positive on this pattern) was in combination with symptoms of ADHD, anxiety

disorder, CD, ODD and indicative DCD and the most common comorbid presentation for the insomnia sleep pattern (35.7%) was in combination with anxiety, CD and DCD.

Sensitivity analyses

Neither sleep patterns were associated with family income (OR=0.929, p=0.418 for restless pattern; OR=0.925, p=0.432 for insomnia pattern).

Higher maternal education was associated with reduced risk of a positive score on the restless sleep pattern for young people with 22q11.2DS (OR=0.729, p=0.011), but not insomnia pattern (OR=0.979, p=0.866). Including maternal education as a covariate in regression analyses, the associations between restless sleep and indicative ASD (OR=1.04, p=0.101), conduct symptoms (OR=1.30, p=0.139) and oppositional symptoms were lost (OR=1.15, p=0.178) (b in Table 3).

12% (17/140) of young people with 22q11.2DS were using melatonin at the time of assessment and 94.1% (16/17) of these reported sleep problems. 68.8% (11/16) scored on both patterns; 18.8% (3/16) on the restless sleep pattern and 12.5% (2/16) on the insomnia pattern only. Children using melatonin had higher levels of sleep problems ($\bar{x}$=3.12) compared to those not using melatonin ($\bar{x}$=1.23) with elevated rates of restless sleep (OR=5.26, p=0.006) and insomnia (OR=15.8, p<0.001). The young people using melatonin for their sleep problems did not appear to have reported fewer sleep problems than young people not taking melatonin. Sleep problems were reported despite the melatonin use and furthermore, melatonin use appeared to be a proxy for sleep problem severity in our sample (where correcting for it would reduce the severity of sleep problems in the sample), we did not include it in our analysis as a covariate.

An epilepsy diagnosis (current or lifetime) was present in 10.7% (15/140) of participants with 22q11.2DS but was not found to be associated with sleep problems (restless; OR=1.38, p=0.457, and insomnia; OR=1.32, p=0.555).

Physical health problems did not associate with sleep problems: cardiac problems with restless sleep (OR=1.82, p=0.094) and insomnia (OR=1.13, p=0.748); respiratory problems with restless sleep (OR=1.10, p=0.807 and insomnia OR=0.765, p=0.536) and, skeletal problems with restless sleep (OR=1.46, p=0.295) and insomnia (OR=0.899, p=0.786).

Medication use in the young people with 22q11.2DS included antipsychotic medication aripiprazole (n=1) for psychotic experiences; risperidone for mood disorder (n=1); and sodium valproate for epilepsy (n=2). None were using ADHD medication. These prevalence's were too low to consider in sensitivity analysis.

Removal of the sleep-related anxiety symptoms did not change the findings for the links between either sleep pattern and anxiety disorder symptoms.

Discussion

This is the first study to systematically investigate the prevalence and nature of sleep problems in 22q11.2DS and establishing the links with psychopathology, motor and cognitive function. We find high rates of sleep problems affecting around two-thirds of young people with 22q11.2DS compared to around a quarter of sibling controls. Two patterns of sleep problems were found in 22q11.2DS: restless sleep and insomnia, which occurred at rates of 43% and 30%. Both patterns of sleep problems were associated with elevated symptoms of anxiety disorder and indicative DCD. The restless sleep pattern was also associated with increased ADHD symptoms and impaired executive function (set shifting ability), and the insomnia sleep pattern with conduct disorder symptoms.

Prevalence of sleep problems in 22q11.2DS

Young people with 22q11.2DS showed a higher prevalence of sleep problems at 60% than reported for young people in the general population (Owens and Mindell, 2011). Our findings add to a scarce literature of sleep problems in young people with genetic syndromes (De Leersnyder et al., 2001; Williams et al., 2006; Trickett et al., 2018). 23% of sibling controls reported sleep problems which is comparable to rates in neurotypical childhood of 25-50% (Owens and Mindell, 2011). Paired analysis in a subsample the of young people with 22q11.2DS with a participating sibling showed no association between their sleep problems. This is consistent with sleep problems in 22q11.2DS being specific to the syndrome and may suggest that environmental factors contributing to risk of sleep problems could specifically affect young people with 22q11.2DS with the same effect not shared by siblings. However, these hypotheses need to be evaluated in more detail.

Patterns of sleep problems in 22q11.2DS

Restless sleep and insomnia were identified as the two patterns of sleep problems in 22q11.2DS, with a subset of individuals scoring on both patterns. It is important to understand the particular sleep problems an individual is affected by for effective treatment. Young people

whose sleep problems manifest around tiredness could be treated differently to those experiencing delays in sleep onset (Kotagal and Pianosi, 2006; Malow et al., 2016).

Links between sleep patterns and psychiatric symptoms, developmental coordination problems and cognitive performance

ADHD symptoms were linked to increased likelihood of scoring on the restless sleep pattern. This results is in line with previous studies of idiopathic (Lycett et al., 2015) young people with ADHD showing that sleep problems including sleep-related breathing disorders (Chervin et al. 1997; Gozal et al. 2011) and restless legs syndrome (Chervin et al. 2002) are common in this population. We have previously reported a higher incidence of the inattentive ADHD subtype in 22q11.2DS compared to young people with idiopathic ADHD (Niarchou et al., 2018) and are now finding that the link between ADHD symptoms and restless sleep is driven by inattentive ADHD. These results should be interpreted with caution as only three individuals in our 22q11.2DS sample had the hyperactive ADHD subtype.

Anxiety symptoms were associated with both the restless and insomnia sleep patterns and these links remained in sensitivity analysis removing sleep-related anxiety symptoms from the total symptom score. There are reports of links between sleep problems and anxiety symptoms in young people with other genetic syndromes (Bassell et al., 2015) as well as in idiopathic samples. Insomnia is a common complaint in anxiety disorders (Vriend and Corkum, 2011) as is fatigue (Chorney et al., 2007) and prior studies have identified links between limb movements during sleep and generalised anxiety (Saletu et al. 2002; Staner 2003). Our findings are cross-sectional and cannot resolve whether anxiety symptoms preceded sleep problems, however they do highlight the need for increased awareness of sleep problems in this population and may be coupled with findings that early interventions may prevent sleep problems from continuing into later life (Benca et al. 1997; Staner 2003; Turnbull et al. 2013).

CD and ODD symptoms were associated with the restless sleep pattern (Eastabrook et al., 2003) and CD symptoms also with the insomnia pattern. Children with CD and ODD are reported to have more sleep problems than typically developing children including increased

nocturnal awakenings and delayed sleep onset, and conduct problems have also been reported to show particular links with sleep-related breathing disorders and periodic limb movements (Eastabrook et al., 2003). The associations between restless sleep pattern and symptoms of CD and ODD was lost considering the effects of maternal education.

22q11.2DS represents one of the strongest risk factors for the development of psychotic disorder and schizophrenia (Monks et al., 2014; Schneider et al., 2014). The current sample is too young to study how sleep problems relate to risk of psychosis and schizophrenia, however, this is an important topic for future research, including longitudinal studies (Ferrarelli et al. 2007; Pritchett et al. 2012; Wulff et al. 2012).

Elevated indicative ASD symptoms were associated with the restless sleep pattern. This is in line with previous reports of sleep problems being common in idiopathic samples of children with ASD (Reynolds and Malow 2011; Cohen et al. 2014; Robinson-Shelton and Malow 2016), including parasomnias, bedtime resistance, insomnia and daytime sleepiness (Johnson and Malow 2008; Souders et al. 2009). The association we found was lost in sensitivity analyses considering the effects of maternal education.

As we have previously reported, the rate of motor coordination problems in 22q11.2DS is very high (80%) (Cunningham et al., 2017). We now find that indicative DCD is associated with both restless and insomnia sleep patterns. There are few studies reporting sleep problems in DCD in general, with the exception of a few reports in children of disturbed sleep patterns (Wiggs et al. 2016) including bedtime resistance and daytime sleepiness (Barnett and Wiggs, 2012) and impaired sleep quality (Wiggs et al. 2005). Distinguishing these associations is important for improved understanding of the mechanisms that could link motor coordination with sleep.

The restless sleep pattern was associated with impairments in executive function and sustained attention and the insomnia pattern with impairment in visual attention. Only the link between the restless pattern and poor executive function remained after correction for multiple

testing. Cognitive flexibility and engagement of the frontal cortex is necessary for efficient executive function with studies observing a detrimental impact of sleep deprivation on set-shifting ability using the same test we used (WCST) in idiopathic samples (Maddox et al., 2009). Anatomical brain changes in 22q11.2DS (Sun et al., 2018) could affect normative frontal cortical engagement and potentially contribute to atypical sleep neurophysiology (Muzur et al. 2002).

Sensitivity analyses

Highest maternal education associated with reduced risk for restless sleep pattern

Higher maternal education level was associated with reduced risk of scoring on the restless sleep pattern. There is some evidence that parents with higher education attainment may be better informed on practices that can improve the quality of a child's sleep, with specific evidence of long-lasting effects in children with NDDs (Hiscock et al., 2015; Papadopoulos et al., 2015) including ASD (Trickett et al. 2017). There is clear evidence for higher maternal education to be linked to fewer childhood ODD (Rydell, 2010) and CD symptoms (Etherington et al., 2016). Capitalising on improving parental sleep education and family involvement to improve behaviour more generally but particularly sleep behaviours and hygiene in children with 22q11.2DS could help lessen sleep problems.

Melatonin use in 22q11.2DS

Melatonin is commonly prescribed in young people with insomnia-related problems as it mimics endogenous melatonin release, thought to positively influence sleep onset (Ivanenko et al., 2003). Of the individuals in our cohort on melatonin, all but one reported sleep problems. Sleep problems were higher in those on melatonin compared to those who were not, suggesting that melatonin was used by individuals with more severe problems and where sleep problems persist.

Sleep-related anxiety symptoms

Although a link between sleep problems and anxiety has been reported in genetic syndromes (Bassell et al., 2015) as well as idiopathic populations (Bélanger et al., 2004), but it was unclear to what extent the association is driven by sleep-related anxieties. We found the association between the restless pattern of sleep problems and symptoms of anxiety remained after excluding the anxiety-related sleep problem items, suggesting that sleep problems may not be driven by anxieties relating specifically to sleep such as co-sleeping and bedtime resistance.

Epilepsy diagnosis did not explain associations with patterns of sleep problems

An association between the patterns of sleep problems and an epilepsy diagnosis was not evident, suggesting that the sleep problems reported in this study population might not manifest directly from neurological problems attributable to epilepsy. However, the association between epilepsy and sleep problems is reported in some studies of neurodevelopmental disorders, suggesting that a high prevalence of sleep problems can associate with seizure-related activity especially during sleep onset and waking (Accardo and Malow, 2014).

Strengths and Limitations

To our knowledge, this is the first study to systematically investigate sleep problems in 22q11.2DS. Our sample is large, including a valuable sibling control group, which allowed us to quantify the extent to which sleep problems are increased in 22q11.2DS and to conduct pairwise comparisons between sleep problems in young people with the deletion and their siblings, considering background genetic and environmental factors shared by family members. Available demographic and medication data allowed us to conduct sensitivity analyses to gain further insights into the nature of the relationships.

The measures we used, despite being gold-standard research diagnostic psychiatric tools, did not include objective monitoring of sleep problems or the young persons' own accounts of sleep problems. Parents might not be able to accurately report on all night-time activities and behaviours, particularly in older children, so using objective measures such as sleep

electroencephalography (EEG) and cardio-respiratory polygraphy would help to further explore sleep problems in 22q11.2DS. We did not include assessments of craniofacial abnormalities or sleep apnoea in this study and can therefore not account for the effect of these variables on our findings.

The current study established the rates of sleep problems in 22q11.2DS and the links with other problems these young people frequently face, but further research is now needed to elucidate the underlying causes. One or more of the genes within the deleted region may increase risk. It is also possible that structural brain abnormalities and atypical brain physiology (Flahault et al. 2012; Andrade et al. 2013; Scott et al. 2016; Sun et al. 2018) contribute to risk of sleep problems either directly, or indirectly through the consequences of psychiatric and cognitive deficits. Future genetic, longitudinal and brain studies (imaging, EEG) may shed light on these questions.

Clinical implications and Future Research Directions

Clinicians should be aware of the high rates of sleep problems in young people with 22q11.2DS and that these index several psychiatric, motor and cognitive problems. A sleep history could make it clearer which sleep problem a child has and could provide insights into the other problems they may experience. The restless sleep pattern may also explain to a degree the high rates of fatigue reported by other researchers in 22q11.2DS (Vergaelen et al., 2017).

Our findings have implications for better understanding sleep problems and the relationship with psychopathology in young people in non-high-risk samples. A dedicated sleep study examining 22q11.2DS neurophysiology during sleep would help contribute to understanding the origin of sleep problems and could inform better sleep interventions in this cohort.

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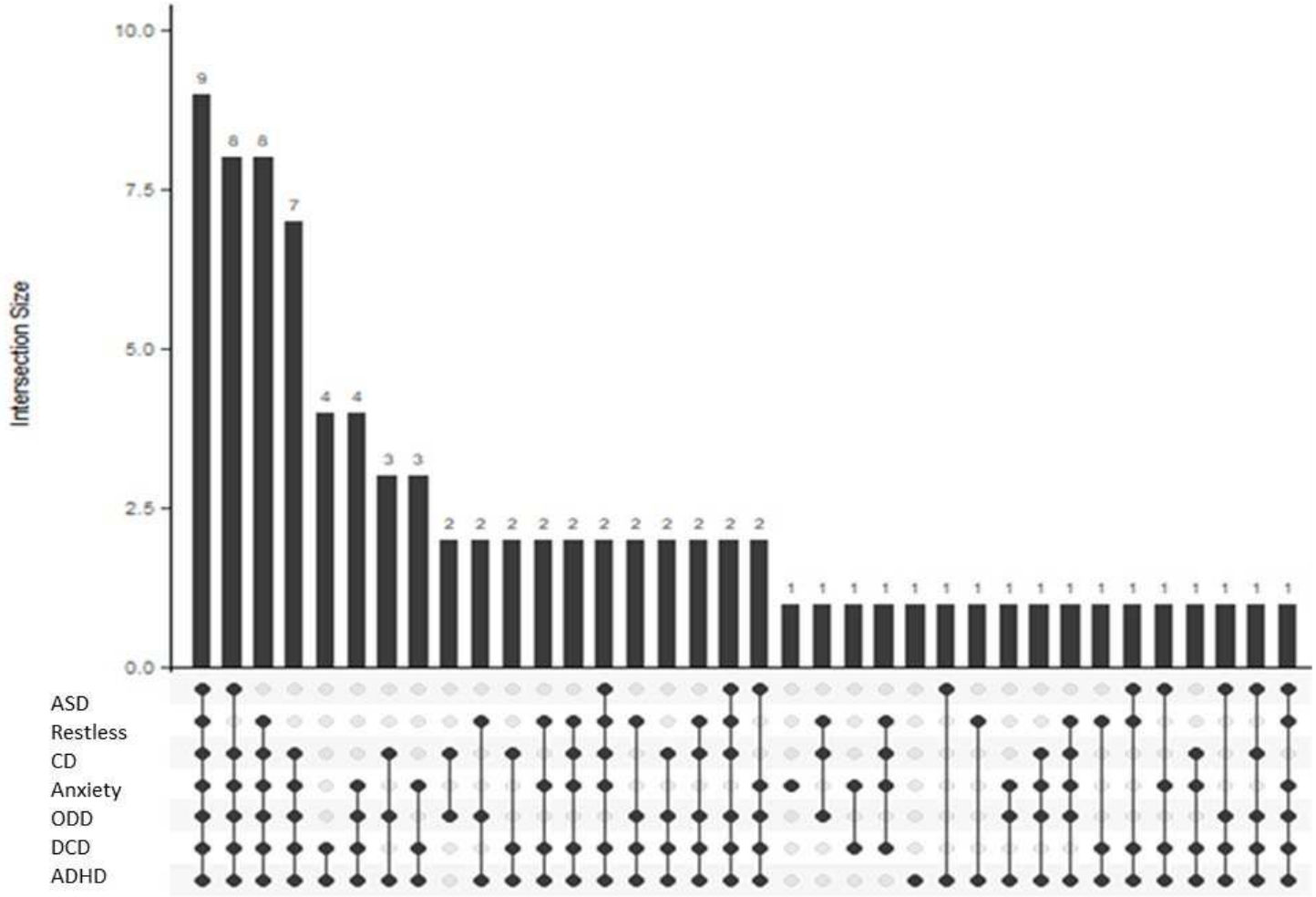

Figure 1 The UpSetR diagram based on the combined presentation of symptoms across the restless sleep pattern (restless sleep) and attention-deficit hyperactivity disorder (ADHD); indicative autism spectrum disorder (ASD); conduct disorder (CD); anxiety disorder (anxiety); oppositional defiant disorder (ODD); and indicative developmental coordination disorder (DCD). The filled black circles represent the presence of symptoms for each domain and empty circles show the absence of symptomology. This diagram includes n=88 young people with 22q11.2DS because of missingness in the SCQ (n=12) and DCDQ (which was introduced later on in our study; n=43).

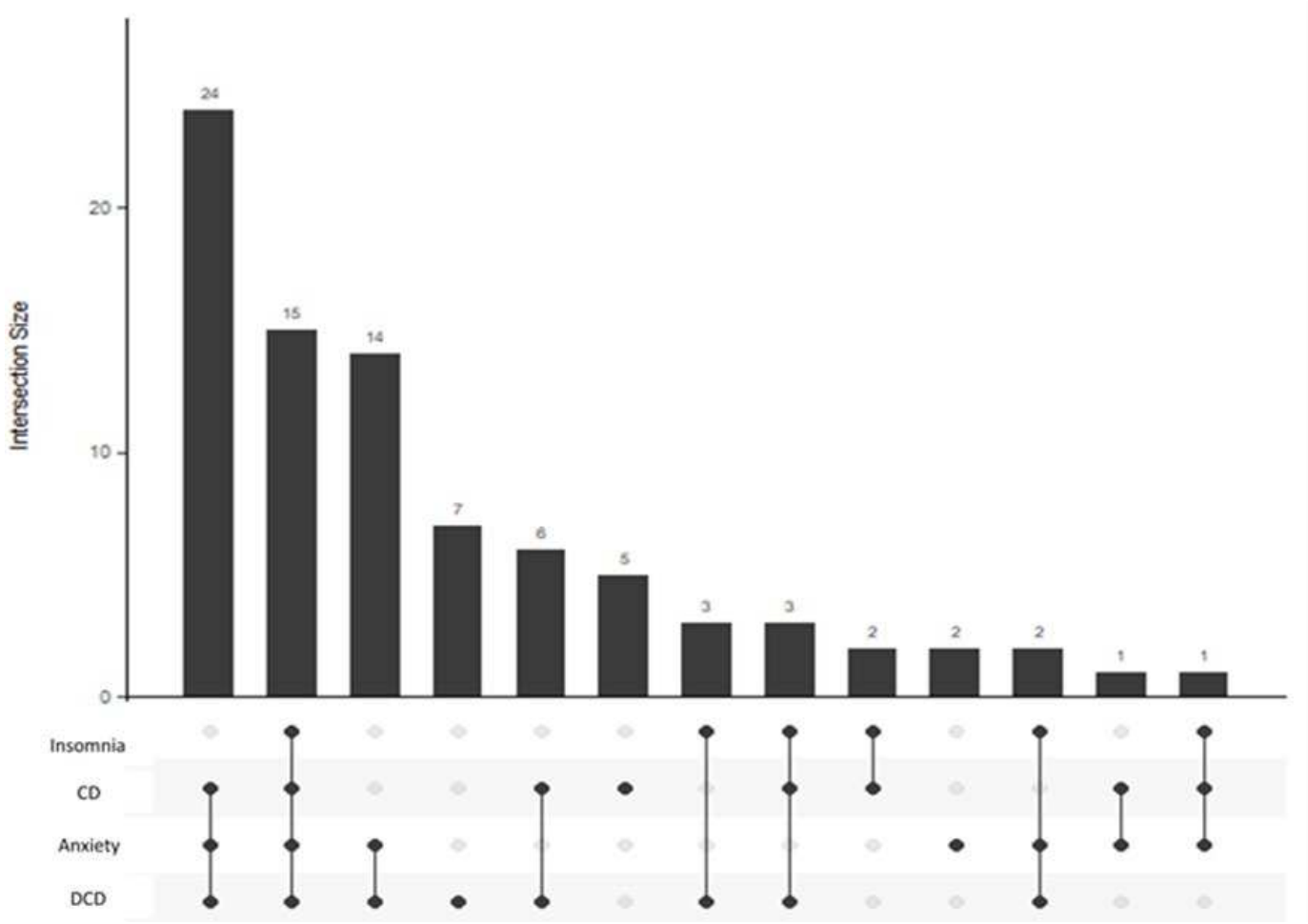

Figure 2 The UpSetR based on the combined presentation of symptoms across the insomnia sleep pattern and conduct disorder (CD); anxiety disorder and indicative developmental coordination disorder (DCD). The filled black circles represent the presence of symptoms for each domain and empty circles show the absence of symptomology. This diagram includes n=97 young people with 22q11.2DS because of missingness in the DCDQ (which was introduced later on in our study).

Table 1 Demographic information on participating families

					%
Family ethnic background					
	European				85.9
	Mixed				4.23
	Non-European				2.11
	Unknown				10.6
Highest maternal education qualification					
	No qualifications				8.57
	Low: O-levels or GCSEs				22.9
	Middle: A-levels/Highers or vocational training				23.6
	High: University degree and/or other higher postgraduate qualification				36.4
	Other				3.52
	Unknown				3.57
Family income					
	≤19,999				20.4
	20,000-39,000				23.9
	40,000-59,000				18.3
	≥60,000				23.9
	Unknown				13.4
Age, years: mean (s.d.) range					p
	Probands	10.1 (2.46) 6.02-17.1	Siblings	10.8 (2.26) 6.29-16.6	**0.04**
Gender, *n* (%)					
	Probands	63/140 F (45%)	Siblings	28/65 F (43.1%)	0.796

Table 2 Prevalence of sleep problems items in young people with 22q11.2DS and sibling controls

Sleep items, *n* (%)		**22q11.2DS**	**Sibling controls**	**OR**	**95% CI for means/medians differences**	**p**
At least one sleep problem		60% (84/140)	23.1% (15/65)	5.00	2.56-9.76	**<0.001**
Total number of sleep problems		Median score (s.d., range)	Median score (s.d., range)			
		1 (1.76, 0-7)	0 (1.05, 0-5)	1.86	1.34-2.57	**<0.001**
			Total, n (%)			
Hypersomnia[a]		8 (5.71)	1 (1.54)	3.88	0.475-31.7	0.206
Restless sleep[a]		45 (32.1)	4 (6.15)	7.22	2.47-21.1	**<0.001**
Inadequately rested[a]		27 (19.3)	1 (1.54)	15.3	2.03-115	**0.008**
Tiredness[a]		15 (10.7)	1 (1.54)	7.68	0.992-59.4	0.051
Fatigability[a]		7 (5.00)	1 (1.54)	3.37	0.406-28.0	0.261
Insomnias						
	Initial[b]	32 (22.9)	7 (10.8)	2.46	1.02-5.91	**0.045**
	Middle[b]	23 (16.4)	1 (1.54)	12.6	1.66-95.3	**0.014**
	Early[b]	13 (9.29)	0 (0.00)	-		-
Parasomnias						
	Nightmares	16 (11.4)	6 (9.23)	1.27	0.472-3.41	0.637
	Night terrors	8 (5.71)	2 (3.08)	1.91	0.384-9.25	0.422
	Sleepwalking	11 (7.86)	4 (6.15)	1.30	0.398-4.25	0.664

Age was included as a covariate in the regression analyses. [a]Sleep problems indexing restless sleep/tiredness sleep pattern; [b]Sleep problems indexing insomnia pattern (see aim 2).

Table 3 Associations between patterns of sleep problems, symptom counts of psychopathology, IQ and cognitive performance in young people with 22q11.2DS

Measure	**Restless sleep pattern**			
Psychopathology (symptoms counts)				
	OR	S.E.	95% CI	p
Attention–deficit hyperactivity disorder	1.16	0.047	1.07-1.25	**<0.001**
Anxiety disorder	1.10	0.039	1.03-1.19	**0.006**
Conduct disorder	1.41	0.237	1.02-1.96	**0.038**[a]
Oppositional defiant disorder	1.29	0.137	1.05-1.59	**0.015**[a]
Indicative autism-spectrum disorder	1.05	0.027	1.00-1.10	**0.048**[a]
Indicative developmental coordination disorder[b]	0.968	0.014	0.940-0.996	**0.023**
IQ				
Full-scale IQ	0.980	0.0151	0.951-1.01	0.194
Performance IQ	0.984	0.0156	0.953-1.01	0.296
Verbal IQ	0.981	0.0137	0.955-1.01	0.175
Cognitive processing				
Processing speed (five-choice reaction time)	0.938	0.096	0.769-13.14	0.525
Sustained attention (rapid visual processing)	0.832	0.076	0.696-0.995	**0.044**[*]
Visual attention (match to sample)	0.997	0.026	0.948-1.05	0.900
Spatial planning	0.950	0.192	0.640-1.41	0.800
Spatial working memory	0.909	0.174	0.625-1.32	0.616
Set shifting ability	0.973	0.001	0.954-0.993	**0.008**
Errors on the Wisconsin Card Sorting Task	1.02	0.010	0.998-1.04	0.074
Measure	**Insomnia pattern**			
Psychopathology (symptoms counts)				
	OR	S.E.	95% CI	p
Attention–deficit hyperactivity disorder	1.04	0.042	0.961-1.12	0.338
Anxiety disorder	1.07	0.036	1.00-1.14	**0.045**
Conduct disorder	1.53	0.278	1.07-2.18	**0.020**
Oppositional defiant disorder	1.22	0.133	0.980-1.51	0.075
Indicative autism-spectrum disorder	1.04	0.027	0.992-1.10	0.095
Indicative developmental coordination disorder[a]	0.955	0.017	0.922-0.989	**0.009**
IQ				
Full-scale IQ	0.988	0.017	0.956-1.02	0.467
Performance IQ	0.982	0.018	0.949-1.02	0.315
Verbal IQ	0.992	0.015	0.963-1.02	0.595
Cognitive processing				
Processing speed (five-choice reaction time)	1.15	0.157	0.881-1.50	0.303
Sustained attention (rapid visual processing)	0.995	0.061	0.882-1.12	0.941
Visual attention (match to sample)	0.945	0.026	0.895-0.998	**0.042**[*]
Spatial planning	1.21	0.277	0.771-1.89	0.410
Spatial working memory	1.09	0.227	0.729-1.64	0.663
Set shifting ability	0.989	0.010	0.970-1.01	0.301
Errors on the Wisconsin Card Sorting Task	1.01	0.010	0.989-1.03	0.381

[a]Associations were lost following sensitivity analyses; [b]Developmental coordination disorder is reversed scored; [*]Associations were lost following correcting FDR correction for multiple testing

Supplementary material

Table 1 Associations between the restless and insomnia sleep patterns and psychiatric disorder diagnoses in young people with 22q11.2DS

	Restless sleep			**Insomnia**			**Both patterns vs. No pattern**		
Psychiatric Disorder (research diagnosis)	**Scored, n (%)**	**No score, n (%)**	**p**	**Scored, n (%)**	**No score, n (%)**	**p**	**Scored, n (%)**	**No score, n (%)**	**p**
Any Psychiatric Disorder	48 (80.0)	38 (52.8)	**0.001**	29 (74.4)	57 (61.3)	0.151	20 (76.9)	29 (49.2)	**0.017**
ADHD diagnosis	33 (55.0)	21 (26.3)	**0.001**	18 (42.9)	36 (36.7)	0.495	13 (50)	16 (25)	**0.021**
Any anxiety diagnosis	20 (33.3)	15 (18.8)	**0.049**	12 (28.6)	23 (23.5)	0.523	8 (30.8)	11 (17.2)	0.152
CD diagnosis	0 (0)	0 (0)	**-**	0 (0)	0 (0)	**-**	0 (0)	0 (0)	**-**
ODD diagnosis	17 (28.8)	8 (10.5)	**0.007**	11 (28.2)	14 (14.6)	0.065	9 (34.6)	7 (11.5)	**0.011**
Indicative ASD*	25 (43.9)	20 (29.4)	0.094	18 (47.4)	27 (31.0)	0.080	10 (41.7)	12 (22.2)	0.078
Indicative DCD*	38 (88.4)	41 (76)	0.117	24 (88.9)	55 (78.6)	0.241	16 (88.9)	33 (73.3)	0.180
IQ	**Mean score (s.d)**	**Mean score (s.d)**	**p**	**Mean score (s.d)**	**Mean score (s.d)**	**p**	**Mean score (s.d)**	**Mean score (s.d)**	**p**
Full-scale IQ	74.9 (12.1)	77.9 (12.3)	0.194	75.3 (10.6)	77.1 (12.8)	0.471	75.3 (11.2)	78.4 (12.8)	0.313
Performance IQ	77.1 (11.4)	79.3 (12.0)	0.298	76.6 (9.85)	79.0 (12.4)	0.317	77.9 (10.6)	80.5 (12.5)	0.403
Verbal IQ	76.5 (13.4)	79.9 (13.5)	0.176	77.4 (12.3)	78.8 (14.0)	0.598	76.6 (12.0)	80.2 (13.6)	0.287
Cognitive processing	**Median score (s.d)**	**Median score (s.d)**	**p**	**Median score (s.d)**	**Median score (s.d)**	**p**	**Median score (s.d)**	**Median score (s.d)**	**p**
Processing speed (five-choice reaction time)	0.290 (2.31)	0.380 (1.59)	0.995	0.090 (1.21)	0.380 (2.15)	0.825	0.090 (1.12)	0.040 (1.64)	0.717
Sustained attention (rapid visual processing)	-2.18 (4.82)	-1.31 (2.01)	**0.03**	-2.22 (2.42)	-1.71 (3.95)	0.823	-2.26 (2.53)	-1.26 (1.95)	0.116
Visual attention (match to sample)	42 (7.58)	42 (39.7)	0.780	41 (8.67)	42 (6.88)	**0.043**	41 (7.90)	42 (6.63)	0.179
Spatial planning	-1.05 (0.963)	-1.05 (1.06)	0.847	-1.05 (0.994)	-1.05 (1.03)	0.578	-0.816 (0.915)	-0.910 (1.05)	0.528
Spatial working memory	-1.18 (0.948)	-1.04 (0.922)	0.989	-1.37 (0.919)	-1.04 (0.936)	0.390	-1.07 (0.906)	-0.990 (0.913)	0.675
Set shifting ability	82.0 (19.4)	90.5 (22.0)	**0.011**	84 (22.1)	88 (21.3)	0.430	84.5 (19.0)	92 (20.9)	0.088
Errors on WCST	101 (21.6)	93.5 (20.1)	0.096	98 (19.3)	97.5 (21.7)	0.496	101 (18.0)	94 (20.1)	0.128

Table 2 The assessments conducted in the study and reliability measures/articles in similar populations

Assessment	**Reliability measures**
Child and Adolescent Psychiatric Assessment (CAPA)	The Child and Adolescent Psychiatric Assessment (CAPA), Angold, Adrian et al. Journal of the American Academy of Child & Adolescent Psychiatry, Volume 39, Issue 1, 39 – 48; Wamboldt MZ, Wasmboldt FS, Gavin L & McTaggart S (2001) A parent-child relationship scale derived from the Child and Adolescent Psychiatric Assessment (CAPA). *Journal of the American Academy of Child and Adolescent Psychiatry*, 40:945-953.
Social Communication Questionnaire (SCQ)	Berument, S.K., M. Rutter, C. Lord, A. Pickles & A. Bailey. 1999. Autism screening questionnaire: diagnostic validity BrJ psychiatry 175: 444-51.
Developmental Coordination Disorder Questionnaire (DCDQ)	Einfeld, S.L. & B.T. Tonge. Manual for the Developmental Behaviour Checklist (Second Edition) - Primary Carer Version (DBC-P) and Teacher Version (DBC-T). 2002. Melbourne and Sydney, Monash University Centre for Developmental Psychiatry and Psychology and School of Psychiatry, University of New South Wales.
The Cambridge Neuropsychological Test Automated Battery (CANTAB)	http://www.cantab.com. Accessed 26/03/2008; Matsuura N, Ishitobi M, Arai S, Kawamura K, Asano M, Inohara K, Narimoto T, Wada Y, Hiratani M, Kosaka H. Distinguishing between autism spectrum disorder and attention deficit hyperactivity disorder by using behavioral checklists, cognitive assessments, and neuropsychological test battery. Asian J Psychiatr. 2014 Dec; 12:50-7.
The Weschler Abbreviated Scale of Intelligence (WASI)	Wechsler D. Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: Psychcorp; 1999; Bishop SL, Farmer C, Thurm A. Measurement of nonverbal IQ in autism spectrum disorder: scores in young adulthood compared to early childhood. *J Autism Dev Disord*. 2015;45(4):966-74.
The Wisconsin Card Sorting Task (WCST)	Ozonoff, S. (1995). Reliability and validity of the Wisconsin Card Sorting Test in studies of autism. *Neuropsychology, 9*(4), 491-500; Stephen C. Bowden, Kylie S. Fowler, Richard C. Bell, Gregory Whelan, Christine C. Clifford, Alison J. Ritter & Caroline M. Long (1998) The Reliability and Internal Validity of the Wisconsin Card Sorting Test, Neuropsychological Rehabilitation, 8:3, 243-254, DOI: 10.1080/713755573

Table 3 Factor loadings and variance for the exploratory factor analysis (EFA) after rotation of the matrix

Variables	Restless (factor 1)	Insomnia (factor 2)
Initial insomnia	-0.0157	0.8027
Middle and Early insomnia	0.0492	0.8261
Tiredness, Fatigue and Hypersomnia	0.7860	-0.0569
Restless sleep	0.7578	0.0.342
Inadequately rested	0.6406	0.1549

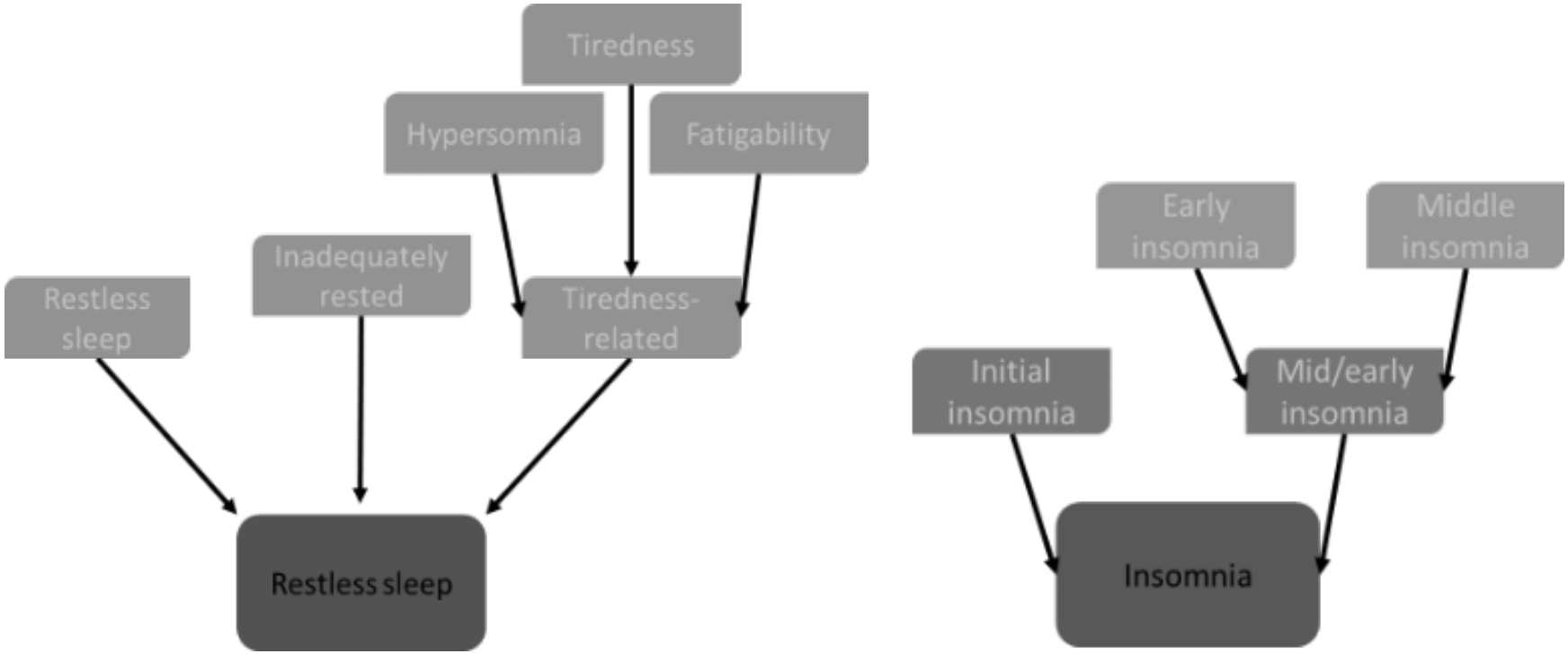

Figure 1 Visualisation of the two-factor outcome from the exploratory factor analysis (EFA). After exclusion of the parasomnia items (nightmares, night terrors and sleep walking), the hypersomnia, tiredness and fatigability were combined into one item 'tiredness-related' because they correlated strongly. Similarly, early and middle insomnia were combined. EFA indicated that a structure of two patterns 'restless sleep' and 'insomnia' best described the sleep problems of children with 22q11.2DS.

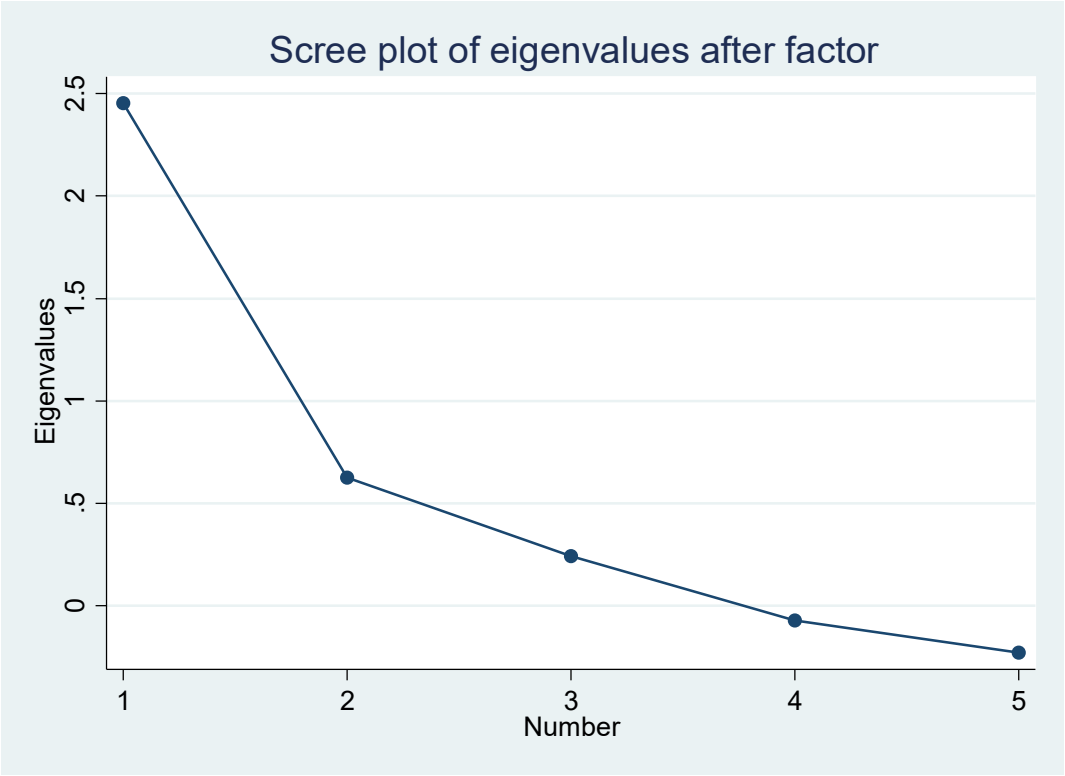

Figure 2 Scree plot showing evidence to support the decision to use two factors in the exploratory factor analysis