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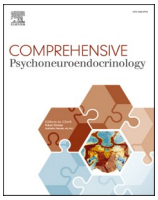

Exploring associations between diurnal cortisol, stress, coping and psychopathology in adolescents and young adults with 22q11.2 deletion syndrome

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ABSTRACT

Background: 22q11.2 deletion syndrome (22q11DS) is a neurogenetic condition associated to a high risk for psychiatric disorders, including psychosis. Individuals with 22q11DS are thought to experience increased levels of chronic stress, which could lead to alterations in hypothalamic-pituitary-adrenocortical (HPA)-axis functioning. In the current study, we investigated for the first time diurnal salivary cortisol profiles in adolescents and young adults with 22q11DS as well as their link with stress exposure, coping strategies and psychopathology, including psychotic symptoms.

Methods: Salivary cortisol was collected from adolescents and young adults with 22q11DS ($n = 30$, age = 19.7) and matched healthy controls (HC; $n = 36$, age = 18.5) six times a day for two days. Exposure to stressful life events, including peer victimization, coping strategies and general psychopathology were assessed with questionnaires. Psychotic symptoms and psychiatric comorbidities were evaluated with clinical interviews.

Results: We observed similar daily levels and diurnal profiles of salivary cortisol in adolescents and young adults with 22q11DS compared to HCs. However, participants with 22q11DS reported less frequent exposure to stress than HCs. In 22q11DS, we observed a significant association between the use of non-adaptive coping strategies and the severity of psychotics symptoms. Cortisol level was not associated to severity of psychotic symptoms, but elevated cortisol awakening response (CAR) was found in participants with 22q11DS with higher levels of general psychopathology.

Conclusions: Our results do not support earlier propositions of altered HPA-axis functioning in 22q11DS but highlight the need to further investigate diurnal cortisol as an indicator of HPA-axis functioning and its link with (earlier) stress exposure and psychopathology in this population. Interventions should target the development of adaptive coping skills in preventing psychosis in 22q11DS.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a neurogenetic condition resulting from a 1.5–3 megabase deletion on the long arm of chromosome 22. 22q11DS is associated with physical, social and cognitive impairments as well as high rates of psychiatric disorders. In particular, the syndrome is seen as a strong risk factor for developing psychosis; the prevalence of schizophrenia spectrum disorder (SSD) in 22q11DS is estimated to be up to 41% [1]. Moreover, similar clinical paths leading to transition to psychosis have been found in 22q11DS and other clinical high-risk (CHR) populations, which confirms that 22q11DS is a valuable human model for studying early risk factors for psychosis [2].

Individuals with 22q11DS often face a broad range of stressful

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experiences from childhood, including medical, cognitive and social problems, and are therefore thought to experience increased rates of chronic stress [3]. In the literature, (early-life) exposure to stress has constantly been associated to an increased risk for psychopathology, including psychosis, especially in vulnerable individuals [4,5]. In 22q11DS, the presence of negative life events, combined with an endogenous heightened vulnerability to stress and poorer coping skills, has been suggested to contribute to the increased risk for schizophrenia [3]. A mediating factor between stress and later psychopathology could be a dysregulation of the hypothalamic-pituitary-adrenocortical (HPA)-axis, a key biological stress response system in the human body [6]. In response to stressors, HPA-axis releases the glucocorticoid hormone cortisol, which typically shows a strong diurnal rhythm: the values peak within 30–45 min after waking (the cortisol awakening response, CAR) and decline throughout the day [7]. Chronic stress can shape the physiological stress response and lead to dysregulation of the HPA-axis [8]. Flatter cortisol diurnal rhythms have been related to poorer mental and physical health [9] and have been reported in various stress-related disorders, including depression and post-traumatic stress disorder (PTSD) [10,11]. Similarly, reduced CAR is reported in populations experiencing continuous stress, like fatigue or burnout, whereas enhanced CAR is associated with general life stress [12]. A dysfunction of the HPA-axis, as a result of chronic stress, has also been proposed to have a role in the development of schizophrenia [13]. Patients with psychosis present elevated cortisol levels [14] and attenuated CAR [15]. Elevated cortisol has also been reported in CHR populations (other than 22q11DS) but findings are less consistent [14], which could potentially be explained by the clinical evolution of CHR individuals. Indeed, a longitudinal study [16] reported elevated cortisol levels in CHR youth whose symptoms had reached a psychotic level within two years, compared to healthy controls (HCs) and CHR youth whose symptoms had remitted.

There is a paucity of studies on the topic of stress in 22q11DS. In adolescents and young adults, [17] recently showed an association between more frequent exposure to stress during the previous year and higher levels of subthreshold psychotic symptoms, which was mediated by dysfunctional coping strategies (e.g. rumination and dramatization). Moreover, they showed indirect evidence of altered HPA-axis functioning in 22q11DS, as they reported - together with [18] - a reduction of pituitary volume (PV) in 22q11DS that emerged during late adolescence/young adulthood. The PV reductions were associated with psychopathology in general but were not a specific marker of psychosis. The authors speculated that PV reductions could be caused by the chronic elevation of cortisol concentrations in adolescence leading to progressive exhaustion of HPA-axis in adulthood, as previously reported in various psychiatric disorders such as PTSD [19]. This argument is in line with seemingly contradictory findings regarding cortisol levels in children and adults with 22q11DS. Indeed, two studies ([20,21]) reported higher cortisol levels in children with 22q11DS, measured at a single time point either at 11am or in the afternoon, whereas [22] reported lower mean cortisol and attenuated cortisol response to daily stress in adults with 22q11DS compared to HCs. However, to date there are no studies investigating diurnal cortisol rhythms in 22q11DS in adolescence and young adulthood, even though this period is known to be particularly vulnerable for experiencing stress [23] and for the onset of psychopathology [24]. Moreover, despite the high prevalence of psychiatric disorders and chronic stress in 22q11DS [1,3], the role of cortisol in the pathway to psychosis or more general psychopathology has not yet been investigated in this population.

In the current study, we investigated for the first time diurnal salivary cortisol profiles and their link with exposure to stressful events (including peer victimization, which is relevant to study in 22q11DS as youth with special needs are in increased risk for bullying [25]), coping strategies and psychotic symptoms in adolescents and young adults with 22q11DS. Given the earlier findings of increased cortisol levels in children with 22q11DS [20,21] and in CHR youth [16], we hypothesized that participants with 22q11DS would show higher mean levels and altered diurnal profiles of cortisol compared to HCs. Furthermore, we hypothesized that more frequent exposure to stressful life events (including peer victimization) would be linked with higher mean cortisol levels, and expected this association to be mediated by the use of dysfunctional coping strategies. Also, considering the role of elevated cortisol levels and stress exposure in the development of psychosis [14,17], we hypothesized that participants with higher mean cortisol levels and participants with more frequent exposure to stress would show more severe symptoms of psychosis (positive and negative symptoms). We also expected that the relationship between stress exposure and psychotic symptoms would be mediated by mean cortisol level. Finally, we expected to find an association between altered cortisol and higher general psychopathology in participants with 22q11DS.

2. Methods

2.1. Participants

Thirty-three participants with a confirmed diagnosis of 22q11.2 deletion syndrome aged 12–28 years participated in the current study. Data were collected since August 2018 through the Swiss 22q11DS longitudinal cohort. 37 HCs aged 12–24 years were recruited within the siblings of the participants with 22q11DS and through the Geneva local community. The characteristics of participants are shown in Table 1. The groups were matched for age, sex and body mass index (BMI). Two participants with 22q11DS and three HCs reported smoking regularly. Of note, part of our sample (i.e., $n = 12$ 22q11DS and $n = 6$ HCs) overlapped with that of [17]. However, as participants were evaluated through longitudinal cohort, the participants included in the previous study of [17] were assessed at an earlier time point.

All participants had to have sufficient verbal and intellectual skills, and a parent or caretaker willing to participate in the study. Exclusion criteria for control group were 1) premature birth, 2) first-degree relative with developmental trouble, 3) neurological disorder, 4) history of psychical disorder requiring treatment, or 5) history of learning or language disorder requiring treatment. All participants and caretakers gave their written consent and participants received a financial compensation of 100CHF for participating in a large study including also additional measures. The study was approved by the Swiss Ethics Committee on research involving humans (CCER) of Geneva.

2.2. Materials

2.2.1. Questionnaires

Participants completed the Coddington Life Events Scales questionnaire (CLES) [26] that assesses previous important life events and their impact. Participants were asked to report if specific life events had happened to them in four different time frames (0–3, 4–6, 7–9, 10–12 months). Each event has a value in Life Change Units (LCUs) depending on the characteristics of the event (type, frequency, and time since occurrence). A total score of experienced stress in the past 12 months was calculated representing the weighted sum of the LCU scores.

Participants also completed the Multidimensional Peer Victimization Scale–Revised (MPVS-R) [27] that assesses the frequency of experienced peer victimization in the past year on a 3-point Likert scale (never, once, more than once).

To assess coping strategies, participants completed the Cognitive Emotion Regulation Questionnaire (CERQ) [28] that assesses the use of adaptive (acceptance, positive refocusing, refocus on planning, positive reappraisal, putting into perspective) and non-adaptive (self-blame, rumination, catastrophizing, and blaming others) strategies to regulate emotions in response to negative events. Furthermore, participants completed The Adolescent Coping Orientation for Problem Behaviors (A-COPE) [29]. Two scores, transformational coping and avoidance coping, were computed [29].

Table 1
Demographic characteristics, the variables of interest and the comparisons between groups.

	Healthy controls (n = 36)	22q11DS (n = 30)	Test statistic	P-value
Age in years, mean (S.D.)	18.54 (±3.23)	19.74 (±5.57)	$U = 513$	0.73
Sex (*n* M/F)	18/18	16/14	$X^2(1) = 0.07$	0.79
IQ, mean (S.D.)	111.24 (±11.63)	73.27 (±12.40)	$U = 1009$	<0.001**
Body mass index, mean (S.D.)	20.78 (±2.66)	23.49 (±5.30)	$U = 406$	0.17
Time of 1st sample in hours, mean (S.D.)	8:35 (±0:55)	8:49 (±0:42)	$T = 1.16$	0.25
Diagnosis, *n* (%)				
ADHD		14 (47%)		
Anxiety disorder		13 (43%)		
Mood disorder		5 (17%)		
Psychotic disorder		1 (3%)		
PTSD		1 (3%)		
Gambling disorder		1 (3%)		
Obsessive-compulsive disorder		1 (3%)		
Oppositional defiant disorder		1 (3%)		
Medication, *n* (%)				
Psychostimulants	0 (0%)	10 (33%)		
Antidepressants	0 (0%)	10 (33%)		
Neuroleptics	0 (0%)	8 (27%)		
Anxiolytics	1 (2%)	2 (6%)		
Omega-3	0 (0%)	6 (20%)		
Other medication[a]	3 (8%)	6 (20%)		
1st cortisol sample (nmol/L)	10.38 (±5.37)	9.77 (±3.16)	$T = -0.13$	0.89
Cortisol awakening response (nmol/L)	4.08 (±4.74)	3.70 (±5.38)	$T = -0.52$	0.61
Daily average cortisol (nmol/L)	7.99 (±2.62)	7.80 (±2.30)	$T = 0.24$	0.81
Diurnal slope (ß value)	−0.011 (±0.006)	−0.01 (±0.005)	$T = 0.88$	0.38
Stress exposure[b], mean (S.D.)	168.11 (±125.37)	107.43 (±149.70)	$U = 745$	0.008*
Peer victimization[c], mean (S.D.)	20.83 (±1.28)	21.78 (±3.52)	$U = 452.5$	0.6
Adaptive coping[d], mean (S.D.)	63.47 (±14.76)	57.93 (±13.18)	$U = 683.5$	0.064
Non-adaptive coping[e], mean (S.D.)	34.14 (±9.02)	35.17 (±10.51)	$U = 505$	0.65
Transformational coping[f], mean (S.D.)	89.97 (±16.88)	87.59 (±12.13)	$U = 527.5$	0.56
Avoidance coping[g], mean (S.D.)	57.89 (±11.42)	59.33 (±11.05)	$U = 458$	0.7
SIPS positive symptoms, mean (S.D.)		0.82 (±0.96)		
SIPS negative symptoms, mean (S.D.)		2.34 (±0.88)		
Total psychopathology[h], mean (S.D.)	45.66 (±9.99)	62.23 (±6.63)	$U = 82.5$	<0.001**
Externalizing psychopathology[i], mean (S.D.)	46.43 (±9.95)	54.97 (±8.78)	$U = 271$	0.001*
Internalizing psychopathology[i], mean (S.D.)	49.03 (±9.7)	66.10 (±7.04)	$U = 72$	<0.001**

*$p < .05$.
**$p < .001$.
nmol/L = nanomoles per litre.
β value = Beta value, calculated using nmol/L values.
[a] Other medication: medication that is not included in the above-mentioned categories, excluding glucocorticoids.
[b] Stress exposure: total score of CLES (past 12 months).
[c] Peer victimization: total score of MPVS-R.
[d] Adaptive coping: score of adaptive coping subscale of CERQ.
[e] Non-adaptive coping: score non-adaptive coping subscale of CERQ.
[f] Transformational coping: score of transformational coping subscale of A-COPE.
[g] Avoidance coping: score of avoidance coping subscale of A-COPE.
[h] Total psychopathology: T-score of ABCL/CBCL total score.
[i] Externalizing/Internalizing psychopathology: T-score of ABCL/CBCL subscale.

General psychopathology was assessed through parent-reported questionnaires with the Child Behavioral Checklist (CBCL) for children and adolescents and with the Adult Behavioral Checklist (ABCL) for adults aged 18 years or older [30]. The age-normalized T-scores of total psychopathology as well as of the externalizing and internalizing subscales were used.

Finally, parents completed a medical questionnaire that covers general information (such as height and weight) and medical history of participant as well as the use of current medication.

2.2.2. Clinical assessment

Participants with 22q11DS were assessed with The Structured Interview for Psychosis-Risk Syndromes (SIPS) [31] that covers four main dimensions of psychotic symptoms: positive, negative, disorganized, and general symptoms. The mean score (0–6) of five items measuring positive psychotic symptoms (delusional ideas, suspiciousness, grandiosity, hallucinations, and disorganized communication) as well as negative symptoms (social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, occupational functioning) were calculated.

A structured clinical interview (Diagnostic Interview for Children and Adolescents – Revised (DICA-IV); Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL); Structured Clinical Interview for Axis I DSM-IV (SCID-I)) was conducted with the participants with 22q11DS by a trained child psychiatrist (SE). We used the number of psychiatric diagnosis as an indicator of psychiatric comorbidity [18].

2.2.3. Cognitive assessment

Intellectual functioning was assessed with Weschler Intelligence Scale for Children for participants below 17 years and with the Weschler Adult Intelligence Scale for the participants aged 17 years or older.

2.2.4. Cortisol procedure

All participants collected saliva samples at home using the Salimetrics 2.0 mL passive-drool collection tubes. Participants and their parents received clear verbal and written instructions for collecting and storing the samples. To collect the samples, participants were instructed to place a cotton under their tongue for 90 s without touching it with their hands. The cotton was then placed in a tube that was put in the freezer. Samples were collected six times a day during two days: immediately after awakening, 30 min after awakening, 60 min after awakening and 120 min after awakening, in the afternoon at 4 p.m. and in the evening at 8 p.m. Participants were instructed to collect the samples preferably on two consecutive days during which they were spending most of the day at home, and to wake up before 10 a.m. on sampling days. They were also told not to eat or drink anything except water in the hour before sampling. Participants were instructed to indicate the exact time of collection of each sample and write down any problems they encountered during sampling. Participants stored the samples in their freezer until bringing them to lab. In the lab, saliva samples were stored at −20 °C until processed. Samples were then centrifuged at 3000 rpm for 15mn at 4 °C and salivary cortisol levels were quantified with the Salimetrics Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics) according to the manufacturer's instructions. The analytical sensitivity for the cortisol assay is 0.007 µg/dL with standard curve ranging from 0.012 to 3.00 µg/dL. Average intra- and

inter-assay coefficients of variation were 6.8% and 5.3% respectively.

Twenty-six participants took the cortisol samples on weekend days, 11 on weekdays, and 9 participants took the samples both on a weekday and a weekend day. Twenty-four participants did not report a date for either one or both sampling days. Most of the samples for which the dates were reported were taken on two consecutive days ($n = 42$). The groups were matched for the time they took the first sample (Table 1).

It should be noted that for the assessment of cortisol data and more specifically the CAR, we could not conform to all the consensus guidelines [32]. First of all, even though a self-reported diary system was used to verify the awakening time of participants, objective methods, such as actigraphy, were not available in the current study. Secondly, due to missing information, we were not able to control for all the recommended trait-like factors (e.g., oral contraceptive use) or covariates related to the sampling day (e.g., sleep duration or quality and prior day experiences) (see Stalder et al. [32]).

2.3. Data exclusion and handling of missing data

Two participants with 22q11DS and one HC subject were excluded from the analyses due to unsuccessful or insufficient sampling. One participant with 22q11DS was excluded because he reported taking glucocorticoid medication at the time of sampling, which is known to strongly influence functioning of the HPA-axis [33]. The analyses were therefore conducted with 66 valid participants. Moreover, eight cortisol samples were missing due to missing sampling or because there was not enough saliva, and seventeen samples were excluded because of poor adherence with sampling protocol. We also excluded 49 samples that participants took outside of specified windows of acceptable times (see Table 2) (adapted from Ref. [34] and one sample for which sampling time was not indicated. Furthermore, since even a 15-min delay after awakening in collecting morning saliva has a significant effect on cortisol value [32], we excluded two cortisol samples that were reported to be taken more than 10 min after waking up. Finally, the samples from one sampling day were excluded from three participants who had woken up after 10 a.m. at that day.

A data imputation strategy was applied to deal with missing data in order to be able to examine the diurnal variation of cortisol of all the valid participants. In case of a missing cortisol value for a certain time point in one of the days, the value of the same time point of the remaining day was used to replace the missing value ($n = 48$). This was done since there were no differences in cortisol values between the two sampling days (See Section 2.4.). If a participant had missing cortisol values at a certain time point in both days ($n = 18$), the missing values were replaced by using a stochastic regression data imputation [35] to allow for introducing a random error term. First, raw cortisol values were $\log_{10}$ transformed to correct skewness. The data was examined for potential outliers (>3SD) but no outliers were detected. Age, sex and diagnosis as well as all available $\log_{10}$ transformed cortisol values and times of measurement were then included into the model as predictive values and missing values were predicted using Rstudio [36] mice package [37] with number of multiple imputations set as 5. The imputed data-set was re-evaluated for outliers and no outliers were detected.

Table 2
Windows of acceptable times for cortisol samples.

Targeted Time	Window of Acceptable Times
Wake up + 30 min	Wake up + 25 - + 50 min
Wake up + 60 min	Wake up + 55 - + 80 min
Wake up + 120 min	Wake up + 115 - + 140 min
16 p.m.	15p.m.–17 p.m.
20 p.m.	19 p.m.–21 p.m.

2.4. Treatment of cortisol data

Cortisol data was treated in three ways to examine different outcomes of HPA activity (adapted from Ref. [38]. First, the cortisol awakening response (CAR) was computed by subtracting the cortisol value at waking from the cortisol value 30 min post-waking. Then, we computed the daily average cortisol value by summing all the six cortisol values and calculating the mean for each participant for each day. Finally, we computed the diurnal slope by doing a simple linear regression line that predicted the $\log_{10}$-transformed cortisol values from time since awakening. We excluded the cortisol 30 min post-waking to avoid the effect of CAR, in line with previous studies (e.g. Cohen et al. [34]). If a participant had not respected sampling time at certain time points, these missing values for sampling time were imputed as described above (Section 2.3). The imputation was done to have an estimate of diurnal cortisol slope for all participants.

The possible within-subject differences at each time point were examined in each group with repeated measures ANOVA. Indicating a typical rhythm over the day, cortisol showed a significant main effect of time in the 22q11DS group (F (5, 40) = 31.61, $p < .001$, $\eta 2 = 0.80$), and in HCs (F (5, 65) = 83.28, $p < .001$, $\eta 2 = 0.87$). Nevertheless, there were no significant effects of day in either group (F (1, 8) = 0.21, $p = .66$, $\eta 2 = 0.026$), (F (1, 13) = 0.48, $p = .50$, $\eta 2 = 0.036$). Similarly, there were no significant effect of day × time interaction in the 22q11DS group (F (5, 40) = 0.87, $p = .51$, $\eta 2 = 0.098$) nor in HCs (F (5, 65) = 0.41, $p = .84$, $\eta 2 = 0.03$). Furthermore, repeated measures ANOVA did not show any differences between days in CAR for participants with 22q11DS (F (1, 20) = 0.94, $p = .34$, $\eta 2 = 0.045$) or for HCs (F (1, 32) = 1.41, $p = .24$, $\eta 2 = 0.042$). Similarly, diurnal slope did not differ between the two days in either group (F (1, 10) = 0.15, $p = .71$, $\eta 2 = 0.014$) (F (1, 13) = 0.15, $p = .70$, $\eta 2 = 0.012$). Since there were no differences between the sampling days, cortisol values from the two days were averaged for the analyses.

2.5. Statistical analyses

The analyses were conducted with IBM SPSS Statistics 26. Between-group differences in cortisol measures (CAR, daily average cortisol and diurnal slope) were examined with an independent samples t-test. A mixed ANOVA was used to examine group differences in cortisol at each sampling point. For the other variables of interest, group comparisons were done using a Mann-Whitney U test or a chi-square test. Furthermore, in the group of participants with 22q11DS, we conducted a Spearman's rank correlation to examine associations between the variables of interest, after controlling for the effects of IQ and age.

The current study has been co-registered during the data collection (10.17605/OSF.IO/ZYGTA). However, we made two changes for the current study with respect to co-registration. Firstly, due to lot of missing cortisol data, we applied a data imputation strategy (See Section 2.3). Secondly, we conducted additional, not co-registered analyses about the associations between cortisol and general psychopathology in the 22q11DS group (See Section 3.5), thus our hypothesis about the link between cortisol and general psychopathology was not co-registered. The data set is publicly available through the YARETA data preservation system (https://doi.org/10.26037/yareta:y2dbjsabrvd3fmgptygjcsdgc4).

3. Results

3.1. Group differences in demographic variables

Group comparisons of demographic variables are shown in Table 1. Groups did not differ in terms of most demographic measures. In line with earlier findings of a lowered IQ in individuals with 22q11DS [39], IQ was significantly lower in the 22q11DS group compared to HCs.

3.2. Group differences in cortisol profiles

Independent *t*-test did not reveal significant differences in CAR between participants with 22q11DS and HCs (Table 1). Similarly, daily average cortisol or diurnal slope did not vary between the groups.

Diurnal cortisol profiles for participants with 22q11DS and for HCs are shown in Fig. 1. Mixed ANOVA showed a significant main effect of time (F (3.37, 239.2) = 208.66, $p < .001$, $\eta 2 = 0.77$) indicating typical variation in cortisol during the day. However, there was no significant main effect of group (F (1, 64) = 0.06, $p = .81$, $\eta 2 = 0.001$) or time × group interaction (F (3.74, 239.2) = 0.82, $p = .5$, $\eta 2 = 0.013$), which indicated similar diurnal profiles of cortisol in both groups. Due to the data violating assumptions of sphericity, ANOVA test statistics were estimated using Greenhouse-Geisser method.

3.3. Effects of age and sex on cortisol

As age is known to have an effect on cortisol levels [40], we examined correlations between cortisol measures and age with Spearman rank correlation. Neither daily average cortisol (r_s (36) = 0.09, $p = .59$) (r_s (30) = 0.311, $p = .095$), CAR (r_s (36) = −0.101, $p = .56$) (r_s (30) = 0.085, $p = .65$) or diurnal slope (r_s (36) = −0.25, $p = .14$) (r_s (30) = −0.352, $p = .056$), correlated with age in HCs or in the 22q11DS group.

Sex differences in cortisol measures were examined in both groups with an independent samples *t*-test. In the control group, female participants showed significantly higher daily average cortisol levels (t (34) = −2.54, $p = .016$) and steeper diurnal slopes (smaller β-values; t (34) = 2.47, $p = .019$) than males. On the contrary, no sex difference was observed in the 22q11DS group either in daily average cortisol (t (28) = −0.26, $p = .80$) or in diurnal slope (t (28) = 0.86, $p = .40$). CAR did not show any sex differences in HCs (t (34) = 0.19, $p = .85$) or in the 22q11DS group (t (28) = −0.92, $p = .37$).

3.4. Group differences in stress exposure and coping

Participants with 22q11DS showed significantly less exposure to stressful life events in the past 12 months compared to HCs (Table 1). The frequency of peer victimization in the past 12 months was very low in both groups and therefore did not differ between the groups. On average, participants with 22q11DS reported using tendentially less adaptive coping strategies than HCs, measured by the CERQ, but the difference failed to reach a significant level. In examining different adaptive coping styles separately, participants with 22q11DS had generally lower scores than HCs, but the only significant difference was seen in the strategy of refocus on planning ($U = 726.5$, $p = .016$). On the contrary, the only adaptive strategy that participants with 22q11DS reported using more than HCs was positive refocusing ($U = 388.5$, $p = .05$). The total use of non-adaptive coping strategies did not differ between the two groups. However, when examining different non-adaptive coping styles separately, significant differences were observed in strategies of self-blame (with 22q11DS participants reporting less self-blame than HCs; $U = 729$, $p = .014$) and catastrophizing (with 22q11DS participants reporting more catastrophizing than HCs; $U = 340$, $p = .009$). Finally, the use of transformational or avoidance coping, measured by the A-COPE, did not differ between the groups (Table 1).

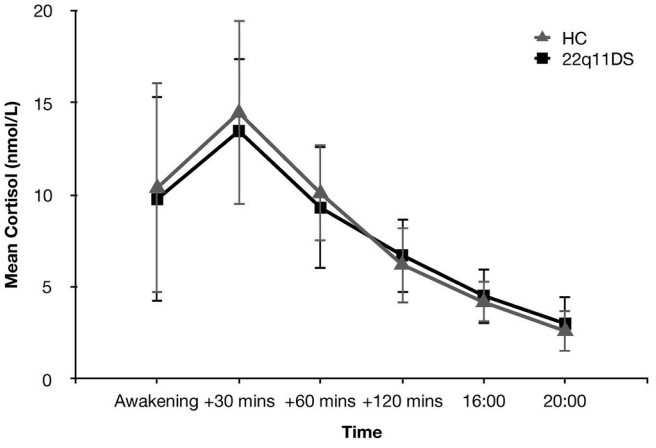

Fig. 1. Diurnal cortisol profiles for participants with 22q11DS (n = 30) and for healthy controls (n = 36).

3.5. Correlations

To examine correlations between cortisol, stress exposure, coping and psychotic symptoms in the 22q11DS group, we conducted a Spearman rank correlation, controlling for the effects of age and IQ (Fig. 2). Contrary to our hypothesis, the frequency of exposure to stress or peer victimization did not correlate with daily average cortisol, CAR or diurnal slope. Furthermore, mean cortisol level was not associated to the severity of positive or negative psychotic symptoms. This was also the case for CAR and diurnal slope, as well as for the frequency of stress exposure. Moreover, the use of coping strategies was not associated to cortisol levels or to stress exposure. However, the more frequent use of non-adaptive coping strategies was significantly associated to severity of positive (r_s (26) = 0.498, $p = .007$) and negative (r_s (26) = 0.548, $p = .003$) psychotic symptoms indicating that individuals with 22q11DS who reported using more non-adaptive coping strategies, showed more severe psychotic symptoms. Due to lack of correlations between stress, cortisol, coping and psychotic symptoms, we could not conduct mediation analyses.

Finally, due to low levels of psychotic symptoms presented by our sample as well as the fact that alterations in the HPA-axis functioning have been linked with various types of psychopathology [6], we conducted additional analyses to examine associations between cortisol and more general psychopathology in the 22q11DS group, which were no co-registered. To examine correlations between different cortisol measures and psychopathology as well as psychiatric comorbidity,

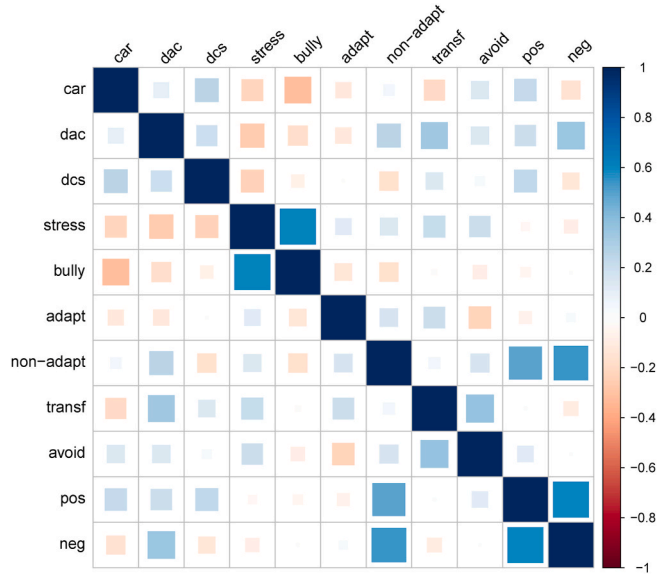

Fig. 2. Spearman correlations between cortisol measures and other variables of interest for participants with 22q11DS (n = 30), controlling for age and IQ. car = cortisol awakening response; dac = daily average cortisol; dcs = diurnal cortisol slope; stress = stress exposure (CLES); bully = peer victimization (MPVS-R); adapt = adaptive coping (CERQ); nonadapt = non-adaptive coping (CERQ); transf = transformational coping (A-COPE); avoid = avoidance coping (A-COPE); pos = positive psychotic symptoms (SIPS); neg = negative psychotic symptoms (SIPS).

Spearman rank correlation was used, controlling for the effects of age and IQ (Fig. 3). Total psychopathology had a significant correlation with CAR (r_s (26) = 0.522, p = .004): the participants who showed higher general psychopathology showed elevated CAR. This was also the case for the externalizing (r_s (26) = 0.555, p = .002) but not for the internalizing subscale (r_s (26) = 0.06, p = .76). Daily average cortisol and diurnal cortisol slope did not correlate with general psychopathology (all $p > .05$). We also observed that participants who had more lifetime psychiatric diagnoses showed elevated CAR (r_s (26) = 0.378, p = .047). Daily average cortisol or diurnal cortisol slope did not correlate with the number of psychiatric comorbidities.

4. Discussion

Our results indicate that adolescents and young adults with 22q11DS report significantly less frequent exposure to stressful life events than HCs. We also observed that the 22q11DS group used tendentially less adaptive coping strategies than HCs, and that more frequent use of non-adaptive coping was significantly associated to the severity of psychotic symptoms. However, stress exposure or coping were not associated to cortisol levels, and our results indicate, contrary to our hypotheses, that adolescents and young adults with 22q11DS show typical diurnal cortisol profiles. The severity of psychotic symptoms was not linked with cortisol levels, but elevated CAR was found in participants who showed higher levels of general psychopathology.

4.1. Stress exposure, peer victimization and coping strategies

Participants with 22q11DS reported less frequent exposure to stressful life events in the last 12 months compared to HCs. The finding is contradictory to what has been proposed about high levels of (chronic) stress in 22q11DS [3]. However, our results are in line with an earlier study using the same instrument [17] showing reduced stress exposure in 22q11DS compared to HCs. As the CLES scale assesses the frequency of important life events (like hospitalization or changing school) in the last 12 months, it may be the case that individuals with 22q11DS are actually more protected than HCs in their environment against this kind of major, external stressors. Alternatively, it is possible that participants with 22q11DS experienced more difficulties than HCs in responding retrospective questionnaires about stressful life events, given their cognitive difficulties [39]. Furthermore, on the contrary to our hypotheses, the frequency of stress exposure did not correlate with cortisol level or with the severity of psychotic symptoms. It is possible that the CLES scale, measuring only major and relatively non-frequent life events, does not capture well enough the subjective experience of stress of participants with 22q11DS in their daily lives. Indeed, experiences that are considered stressful for healthy individuals may not be the most essential source of stress for youth with a neurogenetic condition. In addition, it has been shown that not only the major life events, but also the minor stressors of daily life (daily hassles) are associated to psychopathology, including psychotic symptoms (e.g. Tessner et al. [41]). In adults with 22q11DS, [42] recently showed evidence of higher levels of perceived daily-life stress compared to HCs, suggesting an increased prevalence of minor events that are subjectively assessed as stressful in this population. The findings indicate that other methodologies, such as the Ecological Momentary Assessment (EMA) technique, may be more sensitive than retrospective questionnaires with a predefined list stressful events to capture stress, including daily hassles, experienced by the individuals with 22q11DS in their daily lives.

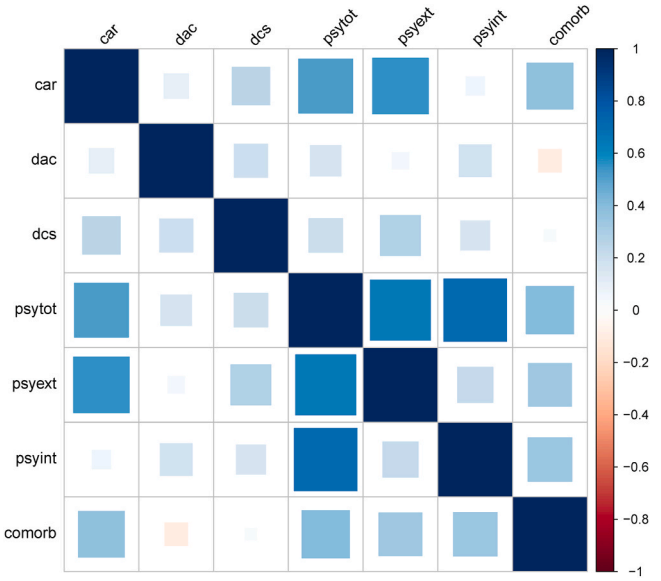

Fig. 3. Spearman correlations between cortisol measures and psychopathology as well as psychiatric comorbidity for participants with 22q11DS (n = 30), controlling for age and IQ. car = cortisol awakening response; dac = daily average cortisol; dcs = diurnal cortisol slope; psytot = total psychopathology (ABCL/CBCL); psyext = externalizing psychopathology (ABCL/CBCL); psyint = internalizing psychopathology (ABCL/CBCL); comorb = psychiatric comorbidity (number of psychiatric diagnoses).

In line with the results obtained with CLES, participants with 22q11DS reported very low levels of peer victimization in the last 12 months using the MPVS-R questionnaire, and the frequency of peer victimization was not associated to cortisol levels. These results are encouraging since earlier studies have showed an increased risk of bullying victimization in youth with special needs [25]. Childhood bullying has also been associated to increased psychotic symptoms in early adolescence [43]. In the current study, bullying was not associated to the severity of psychotic symptoms, which is probably due to the low levels of peer victimization reported by our participants. However, as only the period of the last 12 months is considered, the MPVS-R questionnaire does not capture earlier peer-related problems and their possible impact. Indeed, our sample included many young adults for whom the question of peer victimization was not currently relevant but might have been earlier in life. Given the earlier proposition of an interaction between early traumatic events and genetic vulnerability to explain the risk of psychosis in CHR individuals [44], future studies should also examine the potential impact of early-life stress and trauma on their clinical outcomes. As individuals with 22q11DS are at increased risk for both bullying victimization [45] and psychotic disorders [1], identifying early stressful, traumatic events could be particularly important in this vulnerable population.

Our results go to the same direction than previous findings reporting maladaptive coping in 22q11DS and in CHR individuals as well as an association between non-adaptive coping and the severity of psychotic symptoms in these populations [17,46]. Indeed, our results indicate that less efficient coping strategies can contribute to psychosis in 22q11DS, as earlier proposed by Beaton et al. [3]. Interventions should focus on developing adaptive coping strategies to prevent psychosis in this population.

4.2. Diurnal cortisol

Contrary to our hypotheses, adolescents and young adults with 22q11DS showed similar diurnal cortisol levels than HCs. The results are contradictory of previous findings showing higher cortisol levels in children with 22q11DS compared to HCs [20,21]. However, in these studies, cortisol was measured at a single time point either at 11am or in the afternoon, whereas the current study examined cortisol levels throughout the day during two days. In addition, these earlier studies collected cortisol in laboratory settings. As acute stress alters cortisol levels [8] and 22q11DS is characterized by high levels of anxiety, including social anxiety [1] it is possible that the evaluative situation in

laboratory could have increased children's stress levels leading to elevated cortisol values. In the current study, participants collected samples at home, which was likely a less stressful environment for them. However, potential differences in stress exposure during sampling days could have influenced cortisol levels in the current study. Indeed, [42] recently showed that adults with 22q11DS spent less time doing activities that require a substantial level of effort (e.g. work/school) and in the company of strangers in their daily lives than HCs. In the current study, information about activities or company of participants was not collected, but it is possible that participants with 22q11DS could have been less exposed to difficult situations and therefore experience less stress during the sampling days. Information about the subjective experience of stress during the cortisol sampling period should be collected in future studies. It is also possible that the context of the Covid-19 pandemic, during which a proportion of the participants was evaluated, had an impact on the stress and cortisol levels. Indeed, this prolonged period of isolation may have been a great cause of stress for certain participants, while for other participants (e.g., those with social anxiety), it may have been a relief to spend more time at home and less time with less familiar people. The effects of this period on clinical and biological manifestations in 22q11DS youth are currently unknown, even though individuals with special needs are seen to be particularly affected by the pandemic [47].

Furthermore, contrary to our expectations, the results indicate that adolescents and young adults with 22q11DS show a typical CAR and diurnal cortisol slope. Previously, mixed results have been found in other at-risk populations. However, our results are consistent with some earlier findings in these individuals [15,48] as well as the only study investigating diurnal cortisol slope in 22q11DS with an adult sample [22]. In their study, however, [22] reported altered cortisol reactivity to stress in 22q11DS. Changes in cortisol reactivity have also been found in at-risk individuals, such as siblings of patients with psychotic disorder [48]. Future studies could include a measure of cortisol reactivity to examine changes in cortisol in relation to acute stress in youth with 22q11DS as well as its link with psychosis and more general psychopathology, as increased stress reactivity has been associated to development of psychopathology, especially psychotic disorders [49].

Our results do not support earlier propositions about altered HPA-axis functioning in 22q11DS [17,18,20–22]. However, the results could potentially be explained by the inter-individual variability of participants which may hide the fact that a subgroup of them could be characterized by atypical cortisol. Moreover, the possible differences (and possible abnormalities in 22q11DS) in pubertal development could have affected the current results. Indeed, we did not observe sex differences in the 22q11DS group in cortisol measures, contrary to our findings in HCs as well as earlier findings in typically developing adolescents [50]. As individuals with 22q11DS are known to present endocrine abnormalities [51] and delay in growth has also been reported [52,53], these differences could potentially be explained by a delay of puberty in 22q11DS, even though this topic has received little attention in the field. Further research is essential to expand our knowledge about the functioning of HPA-axis as well as maturational processes influencing its development in 22q11DS.

4.3. Associations between cortisol and psychopathology

Contrary to our hypotheses, cortisol level was not associated to the severity of positive psychotic symptoms in participants with 22q11DS. This can be due to the fact that our sample presented relatively low levels of psychotic symptoms and that only a small portion of these participants will develop a psychotic disorder later on. Indeed, [16] have found elevated cortisol levels at baseline in CHR youth whose symptoms later reached a psychotic level, compared to CHR youth whose symptoms remitted. Future longitudinal studies are needed to better understand the role of cortisol in the development of psychosis in 22q11DS.

As stress exposure has been associated to psychopathology [5], it is possible that participants with 22q11DS with higher levels of psychopathology present also higher levels of general life stress. This could explain the fact that participants with more general psychopathology showed an elevated CAR, since enhanced CAR has been associated to general life stress [12]. Moreover, the association between psychiatric comorbidity and elevated CAR in 22q11DS could be explained by the high prevalence of anxiety disorders in our sample, since higher CAR has been associated to chronic anxiety in adolescents as well as anxiety disorders in adulthood [54,55]. Finally, in a sample of older adults, [56] showed that higher CAR the next day was associated to greater prior-day feelings of sadness, loneliness and threat. It is possible that individuals with 22q11DS with higher levels of psychopathology and psychiatric comorbidity experience more frequent and intense negative affects in their daily-life, which could contribute to the observed CAR differences. However, this remains speculative since we did not collect information about the mood of participants during the sampling days.

4.4. Strengths, limitations and future directions

The current study is the first to investigate diurnal changes in salivary cortisol in adolescents and young adults with 22q11DS. Some methodological limits should however be considered. Firstly, cortisol samples were collected in the participants' naturalistic environment, which increases ecological validity, but can cause some challenges in interpreting the results. In particular, the CAR is particularly sensitive to sampling times, in the sense that even small delays after awakening can lead to imprecise measures of CAR [32]. In the present study, we did not use objective measures to verify sampling times and had to rely on participants' reports. The fact that the standard deviations of the two first cortisol values in the morning were higher than the other values suggests that there were some variations in the sampling times for these two measures. Future studies would benefit from objective measures of sampling times to control for the adherence to saliva sampling. Secondly, diurnal cortisol and especially CAR are known to be affected by the quality and quantity of sleep [32], which was not investigated in the current study. Future studies should collect information about sleep during the sampling period, for example through the use of actigraphy.

Given the large age range of the participants included in the current study, it is likely that they were in different stages of pubertal development. Previous studies have shown an influence of the stage of puberty on cortisol [40] but we were not able to specifically control for this variable. Note that age was used as a covariate in the analyses, which probably accounted for some of the variances related to pubertal development. Nevertheless, future studies should consider including a measure of pubertal development. Furthermore, information about the use of oral contraceptives was not specifically collected. However, as the participants or their parents were asked to report their current medication, we can assume that small part of female participants used oral contraceptives. The variety of medications used by the participants with 22q11DS should also be considered in interpreting the results of cortisol measures.

5. Conclusions

The results of the current study indicate that adolescents and young adults with 22q11DS show typical salivary cortisol levels and diurnal cortisol profiles. However, they reported less frequent exposure to stress and used tendentially less adaptive coping skills than HCs. Moreover, in participants with 22q11DS, more frequent use of non-adaptive coping was linked with more severe psychotic symptoms, indicating the importance of interventions to focus on developing adaptive coping strategies to prevent psychosis in this population. Neither cortisol or stress exposure was associated to psychotic symptoms, probably due to low levels of symptoms presented by our sample, but elevated CAR was found in participants with 22q11DS who showed higher levels of general

psychopathology. Our results do not support earlier propositions of altered HPA-axis functioning in 22q11DS but they highlight the need of future research to investigate diurnal cortisol as an indicator of HPA-axis functioning and its link with stress exposure as well as its role in the development of psychopathology in this population.

Author contributions

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2021.100103.

References

[1] M. Schneider, M. Debbané, A.S. Bassett, E.W. Chow, W.L. Fung, M. van den Bree, M. Owen, K.C. Murphy, M. Niarchou, W.R. Kates, K.M. Antshel, W. Fremont, D. M. McDonald-McGinn, R.E. Gur, E.H. Zackai, J. Vorstman, S.N. Duijff, P. W. Klaassen, A. Swillen, D. Gothelf, T. Green, A. Weizman, T. Van Amelsvoort, L. Evers, E. Boot, V. Shashi, S.R. Hooper, C.E. Bearden, M. Jalbrzikowski, M. Armando, S. Vicari, D.G. Murphy, O. Ousley, L.E. Campbell, T.J. Simon, S. Eliez, Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the international consortium on brain and behavior in 22q11.2 deletion syndrome, Am. J. Psychiatr. 171 (6) (2014, Jun) 627–639, https://doi.org/10.1176/appi.ajp.2013.13070864.

[2] M. Schneider, M. Armando, M. Pontillo, S. Vicari, M. Debbané, F. Schultze-Lutter, S. Eliez, Ultra high risk status and transition to psychosis in 22q11.2 deletion syndrome, World Psychiatr. 15 (3) (2016, Oct) 259–265, https://doi.org/10.1002/wps.20347.

[3] E.A. Beaton, T.J. Simon, How might stress contribute to increased risk for schizophrenia in children with chromosome 22q11.2 deletion syndrome? J. Neurodev. Disord. 3 (1) (2011) 68–75, https://doi.org/10.1007/s11689-010-9069-9.

[4] C. Corcoran, E. Walker, R. Huot, V. Mittal, K. Tessner, L. Kestler, D. Malaspina, The stress cascade and schizophrenia: etiology and onset, Schizophr. Bull. 29 (4) (2003) 671–692, https://doi.org/10.1093/oxfordjournals.schbul.a007038.

[5] R.C. Kessler, K.A. McLaughlin, J.G. Green, M.J. Gruber, N.A. Sampson, A. M. Zaslavsky, S. Aguilar-Gaxiola, A.O. Alhamzawi, J. Alonso, M. Angermeyer, Childhood adversities and adult psychopathology in the WHO world mental health surveys, Br. J. Psychiatr. 197 (5) (2010) 378–385, https://doi.org/10.1192/bjp.bp.110.080499.

[6] K.J. Koss, M.R. Gunnar, Annual Research Review: early adversity, the hypothalamic-pituitary-adrenocortical axis, and child psychopathology, JCPP (J. Child Psychol. Psychiatry) 59 (4) (2018) 327–346, https://doi.org/10.1111/jcpp.12784.

[7] D.E. Saxbe, A field (researcher's) guide to cortisol: tracking HPA axis functioning in everyday life, Health Psychol. Rev. 2 (2) (2008) 163–190, https://doi.org/10.1080/17437190802530812.

[8] B.S. McEwen, Protective and damaging effects of stress mediators, N. Engl. J. Med. 338 (3) (1998) 171–179, https://doi.org/10.1056/NEJM199801153380307.

[9] E.K. Adam, M.E. Quinn, R. Tavernier, M.T. McQuillan, K.A. Dahlke, K.E. Gilbert, Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis, Psychoneuroendocrinology 83 (2017) 25–41, https://doi.org/10.1016/j.psyneuen.2017.05.018.

[10] L.D. Doane, S. Mineka, R.E. Zinbarg, M. Craske, J.W. Griffith, E.K. Adam, Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion, Dev. Psychopathol. 25 (3) (2013) 629–642, https://doi.org/10.1017/S0954579413000060.

[11] G. Lauc, K. Zvonar, Z.e. Vuksić-Mihaljević, M. Flögel, Post-awakening changes in salivary cortisol in veterans with and without PTSD, Stress Health: J. Int. Soc. Investig. Stress 20 (2) (2004) 99–102, https://doi.org/10.1002/smi.1001.

[12] Y. Chida, A. Steptoe, Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis, Biol. Psychol. 80 (3) (2009) 265–278, https://doi.org/10.1016/j.biopsycho.2008.10.004.

[13] E.F. Walker, D. Diforio, Schizophrenia: a neural diathesis-stress model, Psychol. Rev. 104 (4) (1997) 667, https://doi.org/10.1037/0033-295x.104.4.667.

[14] M. Pruessner, A.E. Cullen, M. Aas, E.F. Walker, The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities, Neurosci. Biobehav. Rev. 73 (2017) 191–218, https://doi.org/10.1016/j.neubiorev.2016.12.013.

[15] M. Berger, A.K. Kraeuter, D. Romanik, P. Malouf, G.P. Amminger, Z. Sarnyai, Cortisol awakening response in patients with psychosis: systematic review and meta-analysis, Neurosci. Biobehav. Rev. 68 (2016) 157–166, https://doi.org/10.1016/j.neubiorev.2016.05.027.

[16] E.F. Walker, H.D. Trotman, B.D. Pearce, J. Addington, K.S. Cadenhead, B. A. Cornblatt, R. Heinssen, D.H. Mathalon, D.O. Perkins, L.J. Seidman, Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study, Biol. Psychiatr. 74 (6) (2013) 410–417, https://doi.org/10.1016/j.biopsych.2013.02.016.

[17] M. Armando, C. Sandini, M. Chambaz, M. Schaer, M. Schneider, S. Eliez, Coping strategies mediate the effect of stressful life events on schizotypal traits and psychotic symptoms in 22q11. 2 deletion syndrome, Schizophr. Bull. 44 (suppl_2) (2018) S525–S535, https://doi.org/10.1093/schbul/sby025.

[18] C. Sandini, M. Chambaz, M. Schneider, M. Armando, D. Zöller, M. Schaer, C. Sandi, D. Van De Ville, S. Eliez, Pituitary dysmaturation affects psychopathology and neurodevelopment in 22q11. 2 Deletion Syndrome, Psychoneuroendocrinology 113 (2020) 104540, https://doi.org/10.1016/j.psyneuen.2019.104540.

[19] R. Yehuda, M.H. Teicher, R.L. Trestman, R.A. Levengood, L.J. Siever, Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis, Biol. Psychiatr. 40 (2) (1996) 79–88, https://doi.org/10.1016/0006-3223(95)00451-3.

[20] D. Jacobson, M. Bursch, R. Lajiness-O'Neill, Potential role of cortisol in social and memory impairments in individuals with 22q11. 2 deletion syndrome, J. Pediatr. Genet. 5 (3) (2016) 150, https://doi.org/10.1055/s-0036-1584549.

[21] A.F. Sanders, D.A. Hobbs, D.D. Stephenson, R.D. Laird, E.A. Beaton, Working memory impairments in chromosome 22q11. 2 deletion syndrome: the roles of anxiety and stress physiology, J. Autism Dev. Disord. 47 (4) (2017) 992–1005, https://doi.org/10.1007/s10803-016-3011-2.

[22] E.D.A. van Duin, T. Vaessen, Z. Kasanova, W. Viechtbauer, U. Reininghaus, P. Saalbrink, C. Vingerhoets, D. Hernaus, J. Booij, A. Swillen, J. Vorstman, T. van Amelsvoort, I. Myin-Germeys, Lower cortisol levels and attenuated cortisol reactivity to daily-life stressors in adults with 22q11.2 deletion syndrome, Psychoneuroendocrinology 106 (2019, Aug) 85–94, https://doi.org/10.1016/j.psyneuen.2019.03.023.

[23] S.J. Lupien, B.S. McEwen, M.R. Gunnar, C. Heim, Effects of stress throughout the lifespan on the brain, behaviour and cognition, Nat. Rev. Neurosci. 10 (6) (2009, Jun) 434–445, https://doi.org/10.1038/nrn2639.

[24] T. Paus, M. Keshavan, J.N. Giedd, Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9 (12) (2008) 947–957, https://doi.org/10.1038/nrn2513.

[25] J.J. Blake, E.M. Lund, Q. Zhou, O.-m. Kwok, M.R. Benz, National prevalence rates of bully victimization among students with disabilities in the United States, Sch. Psychol. Q. 27 (4) (2012) 210, https://doi.org/10.1037/spq0000008.

[26] R.D. Coddington, Coddington Life Events Scales (CLES): Technical Manual, 1999.

[27] L.R. Betts, J.E. Houston, O.L. Steer, Development of the multidimensional peer victimization scale–revised (MPVS-R) and the multidimensional peer bullying scale (MPVS-RB), J. Genet. Psychol. 176 (2) (2015) 93–109, https://doi.org/10.1080/00221325.2015.1007915.

[28] N. Garnefski, V. Kraaij, P. Spinhoven, Negative life events, cognitive emotion regulation and emotional problems, Pers. Indiv. Differ. 30 (8) (2001) 1311–1327, https://doi.org/10.1016/S0191-8869(00)00113-6.

[29] J.M. Patterson, H.I. McCubbin, Adolescent coping style and behaviors: conceptualization and measurement, J. Adolesc. 10 (2) (1987, Jun) 163–186, https://doi.org/10.1016/s0140-1971(87)80086-6.

[30] T.M. Achenbach, L. Rescorla, Manual for the ASEBA Adult Forms & Profiles, University of Vermont, Burlington, VT, 2003.

[31] T.J. Miller, T.H. McGlashan, J.L. Rosen, K. Cadenhead, J. Ventura, W. McFarlane, D.O. Perkins, G.D. Pearlson, S.W. Woods, Prodromal assessment with the

structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability, Schizophr. Bull. 29 (4) (2003) 703, https://doi.org/10.1093/oxfordjournals.schbul.a007040.

[32] T. Stalder, C. Kirschbaum, B.M. Kudielka, E.K. Adam, J.C. Pruessner, S. Wüst, S. Dockray, N. Smyth, P. Evans, D.H. Hellhammer, Assessment of the cortisol awakening response: expert consensus guidelines, Psychoneuroendocrinology 63 (2016) 414–432, https://doi.org/10.1016/j.psyneuen.2015.10.010.

[33] U. Masharani, S. Shiboski, M.D. Eisner, P.P. Katz, S.L. Janson, D.A. Granger, P. D. Blanc, Impact of exogenous glucocorticoid use on salivary cortisol measurements among adults with asthma and rhinitis, Psychoneuroendocrinology 30 (8) (2005) 744–752, https://doi.org/10.1016/j.psyneuen.2005.03.003.

[34] S. Cohen, J.E. Schwartz, E. Epel, C. Kirschbaum, S. Sidney, T. Seeman, Socioeconomic status, race, and diurnal cortisol decline in the coronary artery risk development in young adults (CARDIA) study, Psychosom. Med. 68 (1) (2006) 41–50, https://doi.org/10.1097/01.psy.0000195967.51768.ea.

[35] M.S. Gold, P.M. Bentler, Treatments of missing data: a Monte Carlo comparison of RBHDI, iterative stochastic regression imputation, and expectation-maximization, Struct. Equ. Model. 7 (3) (2000) 319–355, https://doi.org/10.1207/S15328007SEM0703_1.

[36] RStudio Team, RStudio, Integrated Development Environment for R. *RStudio, PCB*, Boston, MA, 2021. URL, https://www.rstudio.com.

[37] S. Van Buuren, K. Groothuis-Oudshoorn, mice: multivariate imputation by chained equations in R, J. Stat. Software 45 (1) (2011) 1–67, https://doi.org/10.18637/jss.v045.i03.

[38] B. Lovell, M. Moss, M.A. Wetherell, Perceived stress, common health complaints and diurnal patterns of cortisol secretion in young, otherwise healthy individuals, Horm. Behav. 60 (3) (2011) 301–305, https://doi.org/10.1016/j.yhbeh.2011.06.007.

[39] B. De Smedt, K. Devriendt, J.P. Fryns, A. Vogels, M. Gewillig, A. Swillen, Intellectual abilities in a large sample of children with Velo-Cardio-Facial Syndrome: an update, J. Intellect. Disabil. Res. 51 (Pt 9) (2007, Sep) 666–670, https://doi.org/10.1111/j.1365-2788.2007.00955.x.

[40] W. Kiess, A. Meidert, R. Dressendörfer, K. Schriever, U. Kessler, A. Köunig, H. Schwarz, C. Strasburger, Salivary cortisol levels throughout childhood and adolescence: relation with age, pubertal stage, and weight, Pediatr. Res. 37 (4) (1995) 502–506, https://doi.org/10.1203/00006450-199504000-00020.

[41] K.D. Tessner, V. Mittal, E.F. Walker, Longitudinal study of stressful life events and daily stressors among adolescents at high risk for psychotic disorders, Schizophr. Bull. 37 (2) (2011, Mar) 432–441, https://doi.org/10.1093/schbul/sbp087.

[42] M. Schneider, T. Vaessen, E.D.A. van Duin, Z. Kasanova, W. Viechtbauer, U. Reininghaus, C. Vingerhoets, J. Booij, A. Swillen, J.A.S. Vorstman, T. van Amelsvoort, I. Myin-Germeys, Affective and psychotic reactivity to daily-life stress in adults with 22q11DS: a study using the experience sampling method, J. Neurodev. Disord. 12 (1) (2020, Nov 13) 30, https://doi.org/10.1186/s11689-020-09333-2.

[43] A. Schreier, D. Wolke, K. Thomas, J. Horwood, C. Hollis, D. Gunnell, G. Lewis, A. Thompson, S. Zammit, L. Duffy, Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years, Arch. Gen. Psychiatr. 66 (5) (2009) 527–536, https://doi.org/10.1001/archgenpsychiatry.2009.23.

[44] D. Mayo, S. Corey, L.H. Kelly, S. Yohannes, A.L. Youngquist, B.K. Stuart, T. A. Niendam, R.L. Loewy, The role of trauma and stressful life events among individuals at clinical high risk for psychosis: a review, Front. Psychiatr. 8 (2017) 55.

[45] D. Mayo, K.A. Bolden, T.J. Simon, T.A. Niendam, Bullying and psychosis: the impact of chronic traumatic stress on psychosis risk in 22q11. 2 deletion syndrome-a uniquely vulnerable population, J. Psychiatr. Res. 114 (2019) 99–104, https://doi.org/10.1016/j.jpsychires.2019.04.011.

[46] L. Mian, G.M. Lattanzi, S. Tognin, Coping strategies in individuals at ultra-high risk of psychosis: a systematic review, Early Interv. Psychiatr. 12 (4) (2018, Aug) 525–534, https://doi.org/10.1111/eip.12492.

[47] D. Dukes, J. Van Herwegen, M. Alessandri, F. Al Nemary, J.A. Rad, P.B. Lavenex, N. Bolshakov, S. Bölte, P. Buffle, R.Y. Cai, Introducing the COVID-19 crisis special education needs coping survey. https://doi.org/10.31234/osf.io/rtswa, 2021.

[48] D. Collip, N.A. Nicolson, M. Lardinois, T. Lataster, J. van Os, I. Myin-Germeys, Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis, Psychol. Med. 41 (11) (2011, Nov) 2305–2315, https://doi.org/10.1017/s0033291711000602.

[49] I. Myin-Germeys, J. van Os, Stress-reactivity in psychosis: evidence for an affective pathway to psychosis, Clin. Psychol. Rev. 27 (4) (2007, May) 409–424, https://doi.org/10.1016/j.cpr.2006.09.005.

[50] E.A. Shirtcliff, A.L. Allison, J.M. Armstrong, M.J. Slattery, N.H. Kalin, M.J. Essex, Longitudinal stability and developmental properties of salivary cortisol levels and circadian rhythms from childhood to adolescence, Dev. Psychobiol. 54 (5) (2012, Jul) 493–502, https://doi.org/10.1002/dev.20607.

[51] Y. Levy-Shraga, D. Gothelf, Z. Goichberg, U. Katz, R. Somech, O. Pinhas-Hamiel, D. Modan-Moses, Growth characteristics and endocrine abnormalities in 22q11. 2 deletion syndrome, Am. J. Med. Genet. 173 (5) (2017) 1301–1308, https://doi.org/10.1002/ajmg.a.38175.

[52] S. Jyonouchi, D.M. McDonald-McGinn, S. Bale, E.H. Zackai, K.E. Sullivan, CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: a comparison of immunologic and nonimmunologic phenotypic features, Pediatrics 123 (5) (2009, May) e871–877, https://doi.org/10.1542/peds.2008-3400.

[53] S. Turan, N. Özdemir, T. Güran, F. Akalın, T. Akçay, C. Ayabakan, Y. Yılmaz, A. Bereket, Constitutional growth delay pattern of growth in Velo− Cardio− facial syndrome: longitudinal follow up and final height of two cases, J. Clin. Res. Pediatr. Endocrinol. 1 (1) (2008) 43, https://doi.org/10.4008/jcrpe.v1i1.13.

[54] K. Greaves-Lord, R.F. Ferdinand, A.J. Oldehinkel, F.E. Sondeijker, J. Ormel, F. C. Verhulst, Higher cortisol awakening response in young adolescents with persistent anxiety problems, Acta Psychiatr. Scand. 116 (2) (2007, Aug) 137–144, https://doi.org/10.1111/j.1600-0447.2007.01001.x.

[55] S.A. Vreeburg, F.G. Zitman, J. van Pelt, R.H. Derijk, J.C. Verhagen, R. van Dyck, W. J. Hoogendijk, J.H. Smit, B.W. Penninx, Salivary cortisol levels in persons with and without different anxiety disorders, Psychosom. Med. 72 (4) (2010) 340–347, https://doi.org/10.1097/PSY.0b013e3181d2f0c8.

[56] E.K. Adam, L.C. Hawkley, B.M. Kudielka, J.T. Cacioppo, Day-to-day dynamics of experience–cortisol associations in a population-based sample of older adults, Proc. Natl. Acad. Sci. Unit. States Am. 103 (45) (2006) 17058–17063, https://doi.org/10.1073/pnas.0605053103.