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INVITED ARTICLE FOR THEMED ISSUE

Coping Strategies Mediate the Effect of Stressful Life Events on Schizotypal Traits and Psychotic Symptoms in 22q11.2 Deletion Syndrome

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Converging evidence suggests that psychosis emerges from the complex interaction of genetic and environmental factors. Stressful life events (SLEs) play a prominent role in combination with coping strategies and with a dysfunctional hypothalamus-pituitary-adrenal axis (HPAA). It has been proposed that the framework of schizotypy might help disentangle the interaction between genetic and environmental factors in the pathogenesis of psychosis. Similarly, 22q11.2 deletion syndrome (22q11DS) is considered as a genetic model of psychosis vulnerability. However, SLE and coping strategies remain largely unexplored in 22q11DS. Moreover, the HPAA has not been systematically investigated in this population. Here, we explored the correlation between SLE, emotional coping strategies, schizotypal personality traits, subthreshold psychotic symptoms in a sample of 43 healthy controls (HCs) compared with 59 individuals with 22q11DS. In the latter, we also explored the correlation with pituitary volume as estimated from structural magnetic resonance imaging. We found that SLE and negative coping strategies were correlated with schizotypal personality traits in both HCs and 22q11DS, and with psychotic symptoms in the 22q11DS group only, whereas reduced pituitary volume correlated with general psychopathology. Moreover, dysfunctional coping mediated the effect of SLE on schizotypal personality traits and psychotic symptoms in 22q11DS. Our findings recapitulate evidence in nonsyndromic patients and confirm the central role of stress and coping in the pathogenesis of psychosis. More broadly, they highlight the importance of environmental factors in the pathway to psychosis in 22q11DS, suggesting a strong rationale for the implementation of stress and particularly coping-oriented interventions in this population.

Key words: schizotypy/schizophrenia/22q11DS/stress exposure/coping strategies/pituitary volume

Introduction

Psychotic disorders are responsible for the sixth largest share of disability-adjusted life years in adults in Europe,[1] and the third largest of all main psychiatric disorders worldwide.[2] As a consequence, many efforts have been directed to understanding the causes of schizophrenia.

Research has led to the identification of a large number of candidate genes that have been associated with schizophrenia.[3] However, each of these genes confer only a small effect on the phenotype.[4] Hence, alongside genetic research, efforts have focused on identifying additional risk factors that could amplify the impact of this genetic predisposition. In this sense, the influence of stress and coping strategies on the emergence/exacerbation of psychotic symptoms has been suggested as a fruitful venue of investigation that merits further research.

Stressful Events and Psychosis

To date, evidence of increased exposure to stressful life events (SLE) in schizophrenia patients is contrasting.[5]

In individuals with psychosis, several studies have demonstrated that an increased number of SLE precedes psychotic relapse.[6,7]

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More recently, researchers have investigated the role played by SLE on the phases preceding the first-episode psychosis (FEP), namely the clinical high risk (CHR) for psychosis state.[8] A first meta-analysis showed that recent SLE are associated with a higher risk of FEP.[9] Moreover, some evidence pointed to a threshold effect, so that when the recurrent experience of SLE exceeds the individual's coping capacity, symptom onset or exacerbation occurs.[10,11]

However, a more recent meta-analysis[12] concluded that, while childhood trauma was highly prevalent among CHR individuals, recent SLE rates were significantly lower in CHR individuals compared with healthy controls.

The Role of Reactivity to Stress as a Mediator between Stress and Psychotic Symptoms

A possible explanation for this nonconverging evidence is that, besides the number and type of SLE, CHR patients tend to experience SLE and daily stressors as more subjectively stressful.

In this regard, it has been hypothesized that individuals with poor coping skills might have an underlying vulnerability to the development of psychosis.[13] Accordingly, CHR research indicates that the number of reported daily stressors does not differ between controls and CHR individuals, but the latter reports those daily stressors as more stressful or upsetting.[5,14] Moreover self-reported chronic stress levels were associated with greater positive and depressive symptom severity in CHR patients. In line with these evidences, a prospective study using experience sampling method (ESM) found that CHR individuals were more emotionally reactive to daily stressors than controls and manifested a stress-linked exacerbation of symptoms comparable to that shown by psychotic patients.[15]

An opportunity to better understand the interaction between SLE and reactivity to stress in the development of psychotic symptoms comes from the schizotypy construct which is considered as a dynamic continuum from personality to psychosis and is characterized by a multidimensional structure comprising cognitive–perceptual (positive), interpersonal (negative), and disorganized dimensions.[16,17] Schizotypy is considered as a risk factor for schizophrenia and schizophrenia-spectrum disorders,[18,19] suggesting that overlapping etiological factors underlie both phenotypes. Both positive and negative schizotypal traits have been associated with social dysfunctions. Schizotypy has also been described in association with affective anomalies, such as social anhedonia and more in general with abnormalities in subjective experience of emotion.[20] Cognitive deficits are also observed, especially in inhibitory control, selective and sustained attention, incidental learning, and memory.[21]

It was recently suggested that schizotypy might help to disentangle the interaction of predisposing factors (eg, genetic risk), resilience (eg, coping strategies), and sensitization factors (eg, SLE) in the pathway to psychosis.[22,23] Indeed, evidence suggested that the relationship between genetic predisposition and schizotypal traits is mediated by exposure to SLEs.[24] Moreover, several studies have shown a correlation between schizotypal traits and dysfunctional coping strategies.[25–27]

The Role of Dysfunctional Hypothalamus-Pituitary-Adrenal Axis

The hypothalamus-pituitary-adrenal axis (HPAA) is critical in governing adaptive responses to stress that depend upon the phasic and timely release of glucocorticoids by the adrenal cortex.[28] It was proposed that HPAA dysfunction, induced by chronic stress, could play a role in the pathogenesis of schizophrenia.[29,30] Indeed psychotic patients consistently present elevated basal cortisol concentration[31] that has toxic effects on brain structures highly affected by the disease, such as the hippocampus.[32,33] Moreover, psychotic patients present reduced phasic HPAA responsiveness, such as cortisol awakening response (CAR)[34] and cortisol stress reactivity,[35] which could mediate increased susceptibility to daily life stressors.[36]

Pituitary volume (PV) is considered as an indirect maker of HPAA function,[37] as the gland can undergo proliferation in response to functional demands.[38,39] Several studies have reported PV alterations in psychosis with a recent meta-analysis highlighting PV increases selectively in earlier disease stages (CHR and FEP).[40] The literature also reports several inconsistencies with multiple reports of PV reductions, particularly in chronic schizophrenia.[37,41] Taken together findings of PV alterations in psychosis point to a dynamic pattern of alteration with diverging findings at different disease stages.[36] However, to date evidence of correlations between HPAA dysfunction and symptom severity remains scarce.[31]

22q11DS as a Potential Model to Understand the Interaction between Stress and Risk for Psychosis

The main limitation of studies investigating stress in the pathogenesis of psychosis is the inability to unravel the interactions between genetically determined risk/resilience factors and environment (GXE) because of confounding processes, pleiotropy, or reverse causation.[42]

An opportunity to address this concern may be found in populations where the genetic load for psychosis is strong, well-defined, and homogeneous within the population.[43]

In this sense, 22q11.2 deletion syndrome (22q11DS) is particularly valuable.[43] This syndrome is caused by a microdeletion of 1.5–3 million base pairs on chromosome 22 band q11, and has an estimated prevalence of 1:2.000–4.000 live births.[44] From a clinical perspective, 22q11DS is associated with high rates of psychiatric disorders, especially schizophrenia.[45] Indeed while in the general population the prevalence of psychotic symptoms and CHR state, assessed with semi-structured clinical interviews, has been recently estimated at 13.8% and 2.4%, respectively,[46] 22q11DS populations show

a prevalence of 38.8% for psychotic symptoms and 27% for CHR states.[47] Moreover, while in the general population the prevalence of schizophrenia spectrum disorder (SSD) is estimated at around 2%[48] in 22q11DS the prevalence of SSD is 30–40% by adulthood.[45] Furthermore, psychopathological path leading to FEP in 22q11DS is broadly comparable to that observed in other CHR samples,[49,50] and confirm that 22q11DS can serve as a good human model for studying environmental risk factors for psychosis.[43]

However, to date no studies have systematically investigated the role played by SLE and reactivity to stress on psychotic symptoms in 22q11DS, with only recent preliminary evidence of a possible impaired reactivity to stress in 22q11DS.[51]

Likewise at a neuroimaging level, no studies have systematically investigated PV in 22q11DS.

Hence, in this study we aimed to investigate (1) the level of exposure to SLE and the reactivity to them in a sample of participants with 22q11DS compared with healthy controls; (2) examine whether exposure to SLE in interaction with personal factors (ie, coping strategies) influence the expression of psychotic symptoms and schizotypal personality traits in the 22q11DS sample; (3) investigate the relationship between dysfunctional HPAA, as measured by PV, stress exposure and reactivity, and the psychiatric phenotype of 22q11DS.

We hypothesized that (1) both exposure to SLE and dysfunctional coping strategies would correlate with schizotypal personality traits in healthy controls and in patients with 22q11DS, as well as with psychotic symptoms in the 22q11DS group; (2) coping strategies would mediate the relationship between stress load and both schizotypal personality traits and psychotic symptoms. (3) PV would undergo aberrant development with age in 22q11DS recapitulating the dynamic patter of alteration described nonsyndromic psychosis.

Methods

Participants

The present study combines cross-sectional and longitudinal data acquired within the 22q11DS Swiss longitudinal study since 2002. This cohort has been the subject of previous publications and the global research strategy has already been published elsewhere.[45] Briefly, all participants were recruited through advertisements in patient association newsletters and through word of mouth. Controls were recruited among siblings of the patients and through the Geneva state school system. Written informed consent was obtained for all participants and their parents under the protocols approved by the Institutional Review Board of the Department of Psychiatry of the University of Geneva Medical School. The presence of a 22q11.2 microdeletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). A total of 59 participants diagnosed with a genetically confirmed 22q11DS and aged between 12 and 25 years (mean = 18.12 [SD = 4.05]; 57.6% females) were included in the present study. A total of 43 healthy controls (HCs) formed the control group (mean age = 17.55 [SD = 3.65]; 48.8% females). Both groups were matched for age ($t = -0.728$, $P = .468$) and gender distribution ($\chi^2 = 0.773$, $P = .379$).

Materials

Self-Reported Questionnaires

All participants completed the Coddington Life Event Scale (CLES;[52]) questionnaire to assess the presence and impact of important life events. For each item, the participant reported whether a specific event happened in 4 different time frames (0–3, 4–6, 7–9, and 10–12 months) and whether it was a single or a repeated episode. Subsequently, a stress load measure is computed based on the characteristics of the event (type, delay since the event, number of occurrence) experienced by the participant. For the present study, we computed the total stress load, the stress load for present events (0–6 months) and the stress load for past events (7–12 months).

To assess coping strategies, participants completed the Cognitive Emotion Regulation Questionnaire (CERQ;[53,54]) This scale assesses the use of functional (acceptance, positive refocusing, refocus on planning, positive reappraisal, putting into perspective) and dysfunctional (self-blame, rumination, catastrophizing, and blaming others) coping strategies to regulate emotions when confronted to negative events. Four items assess the frequency of use of each strategy (for a total of 36 items) on a 5-point Likert scale. The french version of the CERQ has been validated by d'Acremont et al[54] in a community sample of adolescents. The French version showed a very good reliability of the subscales, confirming that the French version is comparable to that of the original English questionnaire.

Finally, participants completed the Schizotypal Personality Questionnaire (SPQ[55]), a 74-item scale assessing the presence of schizotypal experiences. Specifically, 3 symptomatic dimensions can be extracted: cognitive-perceptual (eg, magical thinking, anomalous perceptual experiences), negative (eg, lack of close friends, constricted affect), and disorganized (eg, odd speech). This instrument has been validated in French[56] demonstrating high internal reliability (SPQ total: Cronbach's alpha = 0.91; SPQ nine subscales: Cronbach's alpha = 0.57–0.76) and confirming a 3-factor multidimensional structure.

Clinical Assessment

Participants with 22q11DS were assessed by a trained child psychiatrist using the Structured Interview for Psychosis-Risk Syndrome (SIPS;[57]) that covers 4 symptom domains: positive symptoms, negative symptoms, disorganized symptoms, and general symptoms. This instrument has already showed good reliability and predictability in patients with 22q11DS.[50]

Furthermore, the presence of any DSM-IV psychiatric disorder was assessed. For participants below 18 years, parents and participants completed the Diagnostic Interview for Children and Adolescents—Revised [DICA-IV[58]] and the psychotic disorders supplement of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version [K-SADS-PL[59]]. In adults, the Structured Clinical Interview for Axis I DSM-IV [SCID-I[60]] was administered.

Cognitive Assessment

Intellectual functioning in children and adolescents below 17 years was assessed using the Wechsler Intelligence Scale for Children—Third edition [WISC-III; [61]]. For the remaining participants, the Wechsler Adult Intelligence Scale—Third edition [WAIS-III; [62]] was used.

Neuroimaging Assessment of Pituitary Volume

T1-weighted structural magnetic resonance imaging (MRI) images were available in 94/102 individuals (56 22q11DS and 38 HC) and were acquired using a 3-dimensional volumetric pulse sequence with Siemens Trio (12 22q11DS and 7 HC) or Prisma (44 22q11DS and 31 HC) 3T scanners (sequence parameters: repetition time (TR) = 2500 ms, echo time (TE) = 3 ms, flip angle = 8°, acquisition matrix = 256 × 256, field of view = 22 cm, slice thickness = 1.1 mm, and 192 slices). Scanner type did not significantly differ across populations (P = .72) and was furthermore included as a covariate in all analyses.

The pituitary gland was manually traced with Mango Software (http://ric.uthscsa.edu/mango), by a single rater (MC) blind to diagnosis. We employed the same tracing method as previous studies, including the posterior-pituitary and excluding the pituitary stalk.[41,63] Specifically the anterior and posterior boundaries of the gland were identified on the midsagittal slice and the gland was then traced sequentially on coronal slices (supplementary figure 1). On a random subset of 10 cases intra-rater reliability was high (intraclass correlation coefficient = 0.915). Images were furthermore processed using Freesurfer Software (https://surfer.nmr.mgh.harvard.edu) to extract measures of total supra-tentorial brain volume (STV).

Statistical Analyses

All statistical analyses either performed using SPSS version 24 (IBM SPSS Statistics for Windows, Version 24.0., IBM Corp. Released 2013) or Matlab version 2015b (MATLAB and Statistics Toolbox Release 2015b, The MathWorks, Inc.). PV was corrected for age, gender, STV, and scanner type using linear regression. Group comparisons were assessed nonparametrically (Mann–Whitney U and Kruskal–Wallis tests). Correlations were measured with Spearman's rank correlation after controlling for the effects of age gender and IQ. Lastly, we employed Sobel test[64] to investigate significance of mediation effects between stress exposure, coping strategies, and clinical/subclinical outcome measures (SIPS and SPQ).

Results

Between-Group Comparisons

Schizotypal Traits and Exposure to SLE

Individuals with 22q11DS presented a significant increase in schizotypal negative traits compared with HCs, while no differences were observed for the positive and disorganized dimensions (table 1). The number of experienced SLE and stress load associated to these events for both groups are reported in table 1. Patients with 22q11DS reported an exposure to a lower number of SLEs (U = 876.50, P = .007) and were also exposed to a lower stress load compared with HCs during the previous year (U = 901.00, P = .013).

Use of Coping Strategies

Scores on the different CERQ dimensions in both groups are displayed in table 1.

Patients with 22q11DS reported a less frequent use of functional coping strategies compared with HCs (U = 636.50, P < .001). In particular, this was the case for acceptance (P < .001), refocus on planning (P < .001), positive reappraisal (P = .004), and putting into perspective (P < .001), but not positive refocusing (P = .737). The use of dysfunctional coping strategies was not significantly different between the 2 groups (U = 930.00, P = .077). When 22q11DS patients with intellectual disability (ie, FSIQ<70) were excluded from the group comparison, patients with 22q11DS still reported a less frequent use of functional (U = 387.50, P = .002) but not dysfunctional (U = 543.00, P = .159) strategies.

Association between SLE, Coping Strategies, and Schizotypy

We found a significant correlation between stress load and SPQ disorganized dimension for both populations (table 2). While this correlation was significant for both total (Rs = .377, P = .01) and present (0–6 months) stress load (Rs = .444, P = .003) in HCs, it was significant only for the past (7–12 months) stress load score (Rs = .256, P = .04) in patients with 22q11DS. Positive coping strategies did not significantly correlate with SPQ dimensions in either population. However, negative coping strategies strongly correlated with SPQ positive and disorganized dimensions in both groups and with SPQ negative dimension in 22q11DS.

Association between SLE, Coping Strategies and SIPS Subscales

Results are resumed in table 2. Total stress load was significantly correlated with SIPS positive and generalized

Table 1. Group Comparisons of Demographic Features and Variables of Interest

	Healthy Controls	22q11.2 Deletion Syndrome	*P*-value of Difference
Age	17.5 ± 3.6	18.1 ± 4	$t = -0.728$, $P = .468$
Gender (M/F)	25/34	22/21	$\chi^2 = 0.773$, $P = .379$
Full-scale IQ	114.2 ± 12.7	72.3 ± 13.5	$U = 20$, $P < .0001$
Mean years of parental secondary education	10.9 ± 2.7	10.3 ± 3.9	$U = 2121$, $P = .723$
No. of life events	5.6 ± 4.9	3.2 ± 3.4	$U = 876$, $P = .007$
Total stress load	191.8 ± 217.0	106.8 ± 130.9	$U = 901$, $P = .013$
Recent stress load (0–6 months)	139.9 ± 145.0	86.8 ± 113.1	$U = 938$, $P = .026$
Past stress load (7–12 months)	51.9 ± 116.3	20.0 ± 30.34	$U = 975$, $P = .039$
Functional coping strategies	65.5 ± 12.5	52.1 ± 17.4	$U = 363$, $P < .0001$
Dysfunctional coping strategies	32.1 ± 9.6	29.0 ± 10.6	$U = 930$, $P = .077$
SPQ positive dimension	5.3 ± 6.6	6.4 ± 6.3	$U = 1392$, $P = .4$
SPQ negative dimension	4.9 ± 4.1	9.0 ± 5.9	$U = 1806$, $P < .001$
SPQ disorganized dimension	3.9 ± 4.2	4.5 ± 3.9	$U = 1416$, $P = .31$
Corrected pituitary volume (mm^3)	689.1 ± 133.8	611.6 ± 118.1	$U = 706$, $P = .005$
Pituitary volume (mm^3) < 18	642.9 ± 99.8	641.0 ± 131.8	$U = 289$, $P = .91$
Pituitary volume (mm^3) > 18	746.9 ± 150.6	584.2 ± 98.2	$U = 80$, $P = .0001$

Table 2. Spearmann Correlations between Stress Load, Coping Strategies, PV, SPQ, and SIPS

	CLES Total Stress Load	CLES Present Stress Load	CLES Past Stress Load	CERQ Positive Coping	CERQ Negative Coping	PV
Controls						
SPQ positive	0.199; $P = .19$	0.286; $P = .06$	−0.055; $P = .72$	0.212; $P = .17$	0.423**; $P = .005$	0.022
SPQ negative	−0.033; $P = .83$	0.099; $P = .52$	−0.075; $P = .63$	0.009; $P = .95$	0.257; $P = .09$	0.112
SPQ disorganized	0.377*; $P = .01$	0.444**; $P = .003$	0.117; $P = .45$	0.256; $P = .10$	0.423**; $P = .005$	−0.009
CERQ positive coping	0.295; $P = .057$	0.284; $P = .06$	0.093; $P = .55$			
CERQ negative coping	0.285; $P = .06$	0.262; $P = .09$	0.09; $P = .55$			
Patients with 22q11DS						
SPQ positive	0.221; $P = .09$	0.221; $P = .09$	0.206; $P = .11$	0.026; $P = .84$	0.511**; $P = .0001$	−0.079
SPQ negative	0.154; $P = .24$	0.110; $P = .40$	0.235; $P = .07$	−0.065; $P = .63$	0.388**; $P = .003$	−0.044
SPQ disorganized	0.150; $P = .25$	0.098; $P = .45$	0.256*; $P = .04$	−0.058; $P = .66$	0.429**; $P = .001$	−0.046
SIPS positive	0.329*; $P = .01$	0.297*; $P = .02$	0.336**; $P = .009$	0.189; $P = .16$	0.416**; $P = .001$	−0.241
SIPS negative	0.005; $P = .96$	0.02; $P = .87$	0.11; $P = .36$	−0.076; $P = .57$	0.388**; $P = .003$	−0.104
SIPS disorganized	0.203; $P = .12$	0.212; $P = .10$	0.280*; $P = .03$	0.082; $P = .55$	0.523***; $P = .00003$	−0.158
SIPS generalized	0.274*; $P = .03$	0.258*; $P = .04$	0.407**; $P = .001$	0.064; $P = .63$	0.356**; $P = .007$	−0.311*
CERQ positive coping	0.162; $P = .231$	0.175; $P = .20$	0.052; $P = .66$			
CERQ negative coping	0.185; $P = .17$	0.136; $P = .30$	0.414**; $P = .0017$			

*$P < .05$; **$P < .01$; ***$P < .001$.

subscales and was significant for both present and past stress load. Moreover, past stress load was also significantly correlated with SIPS disorganized subscale.

Functional coping strategies were not significantly correlated with any of the SIPS subscales. However, dysfunctional coping strongly correlated with all of the SIPS subscales.

PV Alterations in Relationship to Stress and Psychiatric Phenotype

Results are resumed in table 1 and displayed in figure 1. Corrected PV was significantly reduced in patients with 22q11DS compared with HCs ($U = 706$, $P = .005$). This effect was driven by a significant age by group interaction ($P = .006$) with controls displaying a significant

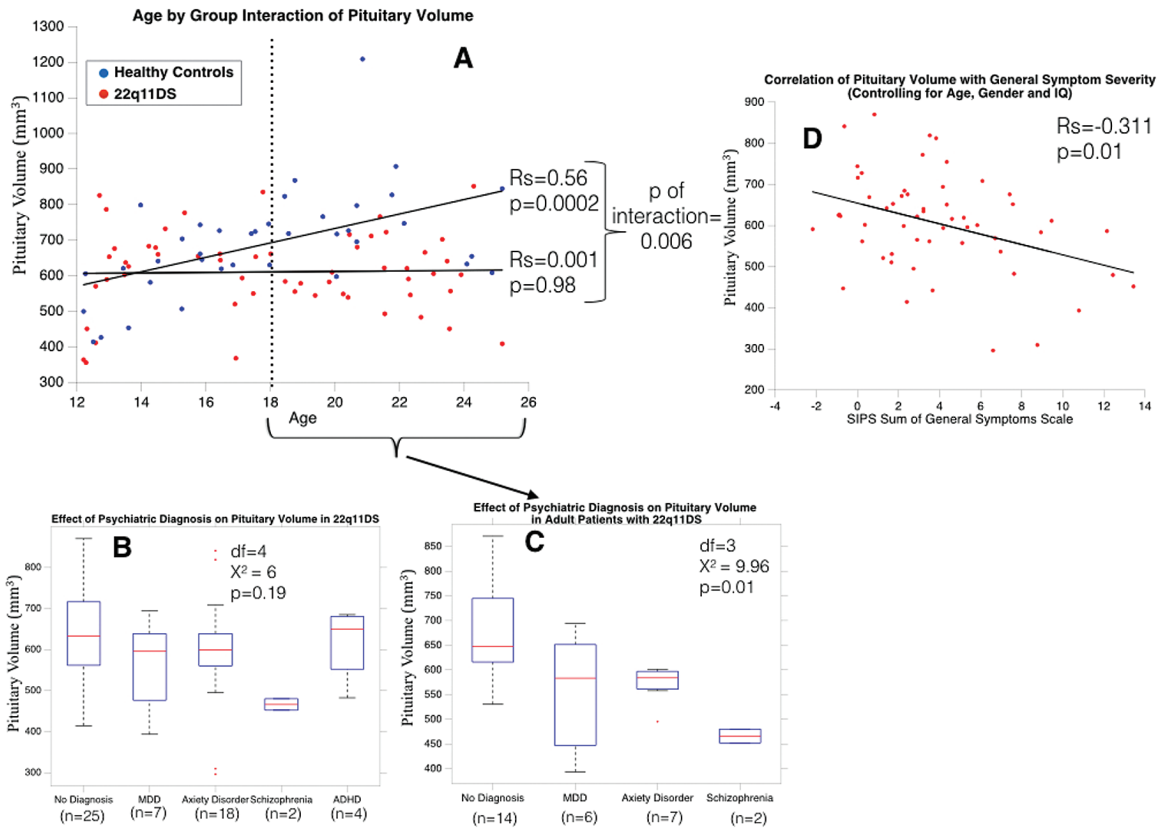

Fig. 1. (A) Correlation of age and pituitary volume in Healthy Controls and 22q11DS and age by group interaction. (B) Effect of psychiatric diagnosis on pituitary volume in 22q11DS. (C) Effect of psychiatric diagnosis on pituitary volume in adult patients (older than 18 years of age) with 22q11DS. (D) Correlation of pituitary volume and SIPS general symptoms subscale in 22q11DS, controlling for age, gender and IQ.

increase of PV with age (Rs = 0.56, P = .0002) that was not observed in 22q11DS (Rs = 0.001, P = .98). Given the observed evidence for altered development of PV with age, we asked whether the overall reductions of PV in 22q11DS might be selectively driven by adult patients. Indeed, before the age of 18 (21 HCs vs 27 22q11DS), PV did not significantly differ between groups (U = 289, P = .91), while it was strongly reduced in 22q11DS after the age of 18 (17HCs vs 29 22q11DS, U = 80, P = 0.0001).

Moreover, PV displayed a significant negative correlation with SIPS general symptom scale (Rs = .311, P = .01), while PV did not significantly correlate with measures of stress load or coping strategies. Kruskal–Wallis test conducted on the entire 22q11DS sample did not reveal any significant effect of psychiatric diagnosis (df = 4, χ^2 = 6, P = .19). However, when considering only patients older than 18 years, we observed a significant effect of diagnosis with volumetric reductions affecting 22q11DS individuals with anxiety disorders (N = 7), major depressive disorder (N = 6) and SSD (N = 2) compared with 22q11DS individuals without psychiatric diagnosis (N = 14) (df = 3, χ^2 = 9.9, P = .01).

Mediation Analysis between Stress Load, Coping Strategies, Schizotypal Traits and SIPS Subscales

Results are displayed in figure 2. In HCs, coping strategies did not significantly correlate with measures of stress load. On the other hand, past stress load strongly correlated with dysfunctional coping strategies in patients with 22q11DS (Rs = .387, P = .004). We therefore performed a mediation analysis to test whether coping strategies mediated the relationship between stress load and outcome measures (SPQ dimensions and SIPS subscales) in 22q11DS.

Dysfunctional coping significantly mediated the relationship between past stress load and SPQ positive (T = 2.1, SE = 0.08, P = .03) and disorganized (T = 2.2, SE = 0.05, P = .02) dimensions, as well as with SIPS positive (T = 2.3, SE = 0.06, P = .02), negative (T = 2.0, SE = 0.05, P = 0.04), disorganized (T = 2.3, SE = 0.04, P = 0.01), and generalized (T = 2.1, SE = 0.04, P = .03) subscales.

We also performed a stepwise linear regression in 22q11DS group for 2 main variables of interest (SPQ positive dimension and SIPS positive subscale).

We found that CERQ negative coping and gender significantly predicted the severitiy of schizotypal positive dimension, while CERQ negative coping and IQ

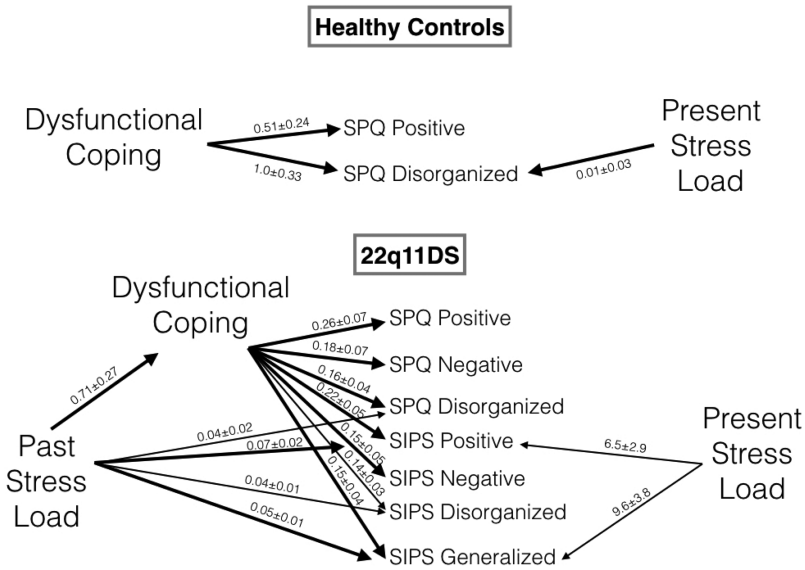

Fig. 2. Regression coefficients and mediation analysis between variables of interest. Arrows indicate significant Spearman Correlations at $p<0.01$ (thick arrows) or $p<0.05$ (thin arrows).

significantly predicted SIPS positive subscale. The results are displayed in supplementary tables 1 and 2.

Discussion

In our sample, we observed that 22q11DS individuals are less exposed to SLE compared with controls. In both groups, stress load and dysfunctional coping strategies correlated with schizotypal personality traits, while they also correlated with psychotic symptoms in patients with 22q11DS. In addition, dysfunctional coping mediated the relationship between past stress load and the psychiatric phenotype in 22q11DS.

We furthermore report reduced PV during adulthood in 22q11DS that was correlated with general psychopathology.

Level of Exposure to Stressful Events and Coping Abilities

A possible explanation for the overall reduced exposure to SLE in 22q11DS is that the CLES scale includes mostly environmental stressors, to which individuals with 22q11DS are usually less exposed for at least 2 reasons. Firstly, families of affected individuals often engage in overprotective behavior regarding environmental exposure, due to concerns of increasing risk of psychiatric disorders.[65] Secondly, impaired social cognition, poor social functioning, and consequent social withdrawal are characteristic of the 22q11DS phenotype,[66,67] all of which potentially reducing the likelihood of being exposed to SLE. This interpretation is in line with current evidence reporting reduced exposure to alcohol and drug use in 22q11DS.[51]

Patients with 22q11DS also presented reduced functional coping strategies compared with controls, in line with findings in nondeleted population at CHR.[5] However interestingly, functional coping strategies were not significantly correlated with the SIPS or SPQ subscales in any of the 2 groups. While the protective role of functional coping strategies has been consistently reported particularly in the field of mood disorders,[68] results in the psychosis spectrum are nonconclusive with one study reporting a positive[69] and another negative correlations[70] with the severity of psychotic symptoms.

Alterations of Pituitary Volume in 22q11DS

This is the first study to systematically investigate alterations of PV in 22q11DS. We observed a significant reduction of PV in 22q11DS that was selectively present in adults and that was correlated to the psychiatric phenotype.

The emergence of PV reductions during adulthood suggests that PV alterations cannot be accounted for by disturbances during early development, but presumably arise from altered maturation during adolescence, as captured by the observed age by group interaction.

Several studies have investigated PV in the field of psychosis. Two meta-analysis conducted on this topic highlighted a dynamic pattern of alteration following disease progression. Indeed, while PV was increased in CHR and FEP, it regressed and tended to PV reductions in the chronic phase of schizophrenia.[71,72]

To account for these dynamic alterations, it was proposed that chronically elevated levels of cortisol may ultimately lead to inhibitory effects on pituitary corticotrophs, with a corresponding reduction of PV and extinction of HPAA activation.[37,41,63] Such HPAA extinction can be captured by reduced HPA responsiveness (ie, blunted CAR) that indeed characterizes mostly chronic disease stages.[34]

In this perspective, our finding that PV reductions selectively emerge after 18 years of age could potentially be due to the chronic elevation of cortisol concentrations during adolescence, leading to a reduction of PV by adulthood. However, as PV was not increased during adolescence this hypothesis remains speculative. Future longitudinal biochemical investigations are required to disentangle how altered development of the HPA is linked to psychopathology in 22q11DS. It should also be emphasized that altered PV was not significantly correlated to the intensity of positive negative or disorganized symptoms of psychosis but appeared to affect more general psychopathology. While this finding was unexpected, it is in line with previous literature implicating HPA axis alterations in a broad range of psychiatric conditions.[73–76]

Effect of Stress Exposure on Schizotypal Personality Traits and Psychiatric Symptoms

Individuals with 22q11DS presented a significant increase in schizotypal negative traits compared with HCs, while no differences were observed for the positive and disorganized dimensions. The lack of significant difference in positive and disorganized dimensions could appear surprising, given the increased susceptibility to psychotic symptoms in this population. However as discussed by Fonseca-Pedrero, we believe that self-report questionnaires tend to underestimate schizotypal traits in 22q11DS due to a combination of reduced ideational richness and a high prevalence of suspiciousness.[77]

We observed significant correlations between SLE and the disorganized dimension of schizotypy in both groups, with a stronger correlation observed in HCs. Broadly, this finding is in line with previous evidence in the general population.[24,78] The observation of overall weaker correlations in 22q11DS could suggest that schizotypal personality in 22q11DS is more related to genetic predisposition, while environmental factors play a less relevant role.[77]

On the other hand, we found significant correlations between the total stress load and the SIPS positive and general subscales, again in line with previous evidence in the general population. To the best of our knowledge, this is the first time that the association between stress and psychosis is investigated in 22q11DS.

Such evidence suggests that particular clinical attention should be directed toward the assessment and management of exposure to stress in 22q11DS, as is the case in nondeleted CHR patients.[79] This is particularly the case when considering the overall reduced exposure to SLE in 22q11DS, that points to heightened stress vulnerability in this population.

Indeed, reducing exposure to SLE may ultimately help lower the risk of developing psychosis in individuals with 22q11DS. In line with this argument, previous studies have shown significant effectiveness of trauma-focused treatments in nondeleted CHR patients.[80]

Effect of Coping Strategies on Schizotypal Personality Traits and Psychiatric Symptoms

Dysfunctional coping strategies strongly correlated with positive and disorganized schizotypal personality traits in both groups, while correlations with negative symptom dimension were significant only in patients with 22q11DS. While to date no such investigations have been conducted in 22q11DS, the reported correlations between schizotypal personality traits and dysfunctional coping strategies are in accordance with previous studies conducted in the general population.[25–27]

Moreover, dysfunctional coping strategies strongly correlated with SIPS positive, negative, disorganized, and generalized subscales in the 22q11DS group. This is in line with a growing body of literature pointing to the importance of coping strategies in the development of psychotic symptoms[27,69,70,81] and psychopathology in general.[68,82]

Mediating Effects of Coping Strategies

In accordance with our hypothesis, dysfunctional coping mediated the relationship between stress load and both schizotypal personality and psychotic symptoms in 22q11DS. The crucial mediating role played by dysfunctional coping strategies in the path toward psychosis has been recently reported in 2 independent cohorts of nonsyndromic individuals.[26,69] This parallelism suggests that although 22q11DS dramatically increases the genetic risk for psychosis, the underlying pathways leading to disease onset are largely shared with the general population and are critically influenced by environmental factors. This consideration further validates 22q11DS as a valuable model for the study of psychosis. More broadly, significant mediation effects were also observed for measures of general psychopathology such as anxiety, which are known to increase risk of future psychotic onset in 22q11DS.[45,83]

Taken together, such evidence strongly suggests the potential benefits of therapeutic intervention aimed at improving coping strategies in 22q11DS. Indeed, coping-oriented interventions have demonstrated to be effective in nondeleted psychotic patients.[84] Moreover, coping strategies significantly mediated effects of stress load not only on psychotic but also on negative symptoms that represents a major predictor of functional outcome in 22q11DS and that are largely nonresponsive to current treatment strategies.[75]

Limitations

Limitations of the article include the relatively small sample size that prevented a more detailed analysis of interactions between variables. This limitation should be considered in light of the low prevalence of the syndrome. A second limitation of this study is that the cross-sectional design precluded the analysis of the prediction of outcome, thus

allowing only inferential speculation as regards the direction of causality and the magnitude of risk. A third limitation is the lack of biochemical measures of HPAA function.

Conclusions and Implications for Clinical Management

While individuals with 22q11DS often face several serious medical issues since birth, patients and families indicate that the risk of psychosis is their greatest source of concerns, mostly due to the notion that this risk is genetic determined and therefore unavoidable.[65] From a clinical perspective, the key finding of the present study is that, even though genetic loading dramatically increases risk for psychosis in 22q11DS, environmental factors such as SLE and coping strategies, still play a crucial role.

Our findings suggest a strong rational for applying environmental and coping oriented treatment interventions currently proposed in nondeleted CHR populations to patients with 22q11DS. More specifically, targeting negative coping strategies would appear particularly promising given the observed mediating effect between stress load and psychopathology. Indeed simple psychoeducation intervention aimed at developing safer behavior and at reducing stress exposure might prove insufficient, since overall stress load was already reduced in the 22q11DS population.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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