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The developmental trajectories of the behavioral phenotype and neuropsychiatric functioning in Cornelia de Lange and Rubinstein Taybi syndromes: A longitudinal study

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Abstract

Several changes in the behavioral phenotype arise with the growth of children affected by Cornelia de Lange Syndrome (CdLS) and Rubinstein-Taybi Syndrome (RSTS). However, previous research relied on a cross-sectional study design turning into age-related comparisons of different syndromic cohorts to explore age-dependent changes. We aim to outline the variating pathways of the neuropsychiatric functioning across the lifespan in CdLS and RSTS, through the setting up of a longitudinal study design. The sample included 14 patients with CdLS and 15 with RSTS. The assessments were carried out in two different timepoints. Our findings highlight that the cognitive profile of CdLS is subjected to a worsening trend with decreasing Intellectual Quotient (IQ) scores from T0 to T1, whereas RSTS shows a stable IQ over time. Patients affected by RSTS show greater improvements compared to CdLS in communication, daily living skills, social abilities, and motor skills across the lifespan. Both syndromes report an upward trend in behavioral and emotional difficulties even if CdLS exhibit a significant and major deterioration compared to individuals with RSTS. Being aware of the early dysfunctional patterns which might pave the way for later neuropsychiatric impairments is the first step for planning preventive interventions.

KEYWORDS
behavioral phenotype, CdLS, intellectual disability, longitudinal assessment, rehabilitation, RSTS

1 | INTRODUCTION

The diagnosis of a rare genetic condition demands life-long medical, multidisciplinary as well as social care, and it requires integrated interventions aimed at addressing different needs of the patient which are meant to evolve alongside the developmental stages. Despite the growing interest in the behavioral phenotype of individuals with rare genetic syndromes, studies evaluating developmental trajectories and

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behavioral characteristics across the lifespan and their implications for interventions are limited. Previous research (Cochran et al., 2015; Moss et al., 2017; Stevens et al., 2011) entirely relied on a cross-sectional study design turning into age-related comparisons of different individuals with syndromes to explore possible significant age-dependent changes in cognitive, behavioral, and mood aspects. However, to our knowledge, few studies (Cochran et al., 2015, 2019) have set up longitudinal assessments for the investigation of the changing pathways of the behavioral phenotypes, considering the whole developmental profile (Cochran et al., 2015; Fisher et al., 2016; Moss et al., 2017). It is methodologically relevant to follow the same cohort of patients because the lower skills observed in older individuals in cross-sectional studies might be better explained by cohort effects or recruitment biases rather than by a real decrease in skills expected with aging.

Therefore, we aim at overcoming previous methodological limitations laying out a longitudinal assessment of the behavioral phenotype in two rare genetic syndromes, namely Rubinstein-Taybi Syndrome (RSTS) and Cornelia de Lange Syndrome (CdLS), which share some overlapping symptoms, such as intellectual disability, communication impairments, and stereotypic behaviors, to provide indications for their best tailored management. The presence of these overlapping features allows us to compare the behavioral phenotype of the two syndromes and to detect any potential differences which might be related to the genotype, excluding the possible effect of other confounding variables.

Rubinstein-Taybi syndrome (RSTS) is a rare (1:125,000), plurimalformative disorder characterized by intellectual disability (ID), facial dysmorphic features, skeletal abnormalities, and epilepsy (Ajmone et al., 2018; Hennekam et al., 1992; Stevens et al., 1990). Pathogenic variants in the closely related *CREBBP* gene, located on chromosomal region 16p13.3, is responsible for up to 55% of cases, while the *EP300* gene on 22q13, for 8% of patients carrying the following syndrome (Fergelot et al., 2016; Negri et al., 2016; Spena et al., 2015). ID ranges from mild to profound (IQ range: 25–79; Van Gils et al., 2021), with a major incidence of moderate intellectual disabilities and few cases with typical intellectual functioning (IQ range: 36–102; Ajmone et al., 2018; Hennekam et al., 1992; Kumar et al., 2012). There is also evidence of a high proneness toward the onset of either internalizing or externalizing symptoms (Galera et al., 2009). The behavioral phenotype in early adulthood is characterized by mood disorders, repetitive and self-injurious behaviors, obsessive compulsive disorders, anxiety disorders, ADHD symptoms, language impairments, and an upward trend of autism-related traits (Crawford et al., 2017; Galéra et al., 2009; Stevens et al., 2011; Waite et al., 2015). However, few studies have described the development of these individuals' abilities across the lifespan with longitudinal follow-up assessments.

Previous cross-sectional studies comparing different age cohorts outlined that the behavioral phenotype of individuals affected by RSTS is characterized by anxiety symptoms, mood instabilities, and aggressive behaviors during adolescence (Yagihashi et al., 2012). It is possible to infer from studies conducted on adults that challenging behavioral problems represent a phenotypic hallmark of this specific phase of the lifespan (Galéra et al., 2009; Stevens et al., 1990, 2011; Yagihashi et al., 2012). In line with these premises, the study by Stevens et al. (2011) highlighted that those externalizing symptoms are expected to worsen with age and, in particular, Hennekam (2006, 2010) reported that short attention span, stubbornness, lack of persistence, impulsivity, and autism-related traits became increasingly apparent during early adulthood in RSTS, leading to hyperactive behaviors and occasional aggressiveness.

However, contrasting results emerged from the study by Giani et al. (2022) that highlighted similar changing pathways of psychopathology with the same proneness toward enhancement of anxiety problems in adolescents with CdLS and RSTS. Notably, anxiety was identified as a crucial phenotypic hallmark, independent of IQ but associated with autistic traits, that is expected to increase from infancy to adolescence in both neurogenetic conditions (Giani et al., 2022).

Behavioral characteristics of RSTS include insistence on sameness, adherence to routine, repetitive questions, and motor stereotypes (Waite et al., 2015) that might be explained by executive function deficits in set-shifting and working memory (Waite et al., 2016), whereas socio-communicative abilities appear to be less impaired compared to autistic children and CdLS (Ellis et al., 2021; Galéra et al., 2009). Specifically, the phenotypic profile illustrated by Ellis et al. (2021) shows a minor delay in early socio-cognitive skills in school-aged children with RSTS compared to those with CdLS which denotes higher abilities in understanding basic goal-directed actions than in performing tasks requiring joint attention skills.

Cornelia de Lange syndrome (CdLS) is a rare genetic disorder caused by pathogenic variants in genes involved in the cohesin complex (*NIPBL*, *SMC1A*, *SMC3*, *RAD21*, *HDAC8*, *ANKRD11*, *BRD4*) that result in peculiar facial dysmorphisms, limb malformations, postnatal growth retardation, intellectual disability and autism-related traits. It has an estimated prevalence rate ranging from 1 out of 10,000 to 1 out of 30,000 newborns (Kline et al., 2007). Classic (or typical) CdLS phenotypes are easily recognizable, but their clinical expression is widely variable. The recent International Consensus Statement has defined the whole CdLS phenotype as a spectrum and conceived a diagnostic score based on a combination of cardinal and suggestive features to clarify the definition of classic and non-classic CdLS (Kline et al., 2018).

There is mounting evidence that Intellectual Disability (ID), ranging from mild to profound, represents a cognitive hallmark of this syndrome even though a handful of CdLS cases performed within the normal IQ range (Ajmone et al., 2014). Adaptive behavior is impaired and communication abilities vary widely but, typically, both receptive and expressive language skills are highly compromised, with greater difficulties in expressive language abilities than in receptive ones (Ajmone et al., 2014; Goodban, 1993; Sarimski, 1997), concerning mostly verbal comprehension and explanation of concepts (Mulder et al., 2019).

A growing body of literature highlighted that CdLS behavioral phenotypes are not stable over individual developmental trajectories. CdLS patients are likely to show increased severity in social

impairments over time, especially social anxiety, social withdrawal, low mood, interest and pleasure, insistence on sameness, challenging behaviors, sleep disorders, and more severe autism spectrum disorder (ASD) symptomatology from 15 years old onward, but receptive language skills improve and adaptive behaviors experience broad stability reaching a plateau phase in adolescence and early adulthood (Ajmone et al., 2021; Basile et al., 2007; Cochran et al., 2019; Giani et al., 2021; Grados et al., 2017; Moss et al., 2017; Nelson et al., 2017; Srivastava et al., 2014). In addition, Groves et al. (2019) found that individuals with CdLS appear at risk for experiencing lower mood related to a decrease of interest and pleasure compared to Fragile X syndrome over the lifespan.

However, controversial results exist with regard to the evolution of adaptive skills in this target population. If, on one hand, no changes have been reported in adaptation to daily challenges at 2-year follow-up (Nelson et al., 2014), on the other hand, a downward trend of adaptive skills has emerged at 2.5-year follow-up (Cochran et al., 2015).

These findings underline the need for additional longitudinal research on the clinical modification of the behavioral phenotype in CdLS, and new ones involving individuals with RSTS.

In light of these theoretical premises, our crucial aim is to understand the natural history of these neurogenetic conditions, their clinical developmental evolution, and behavioral features to guide appropriate targeted clinical interventions and management for patients and their families. We decided to compare CdLS with RSTS as, being similar according to the ID level, it allows us to deal with the ubiquitous control group problem in behavioral phenotype research.

Based on findings of pioneristics cross-sectional studies, we hypothesize that CdLS individuals are more likely to exhibit a worse behavioral phenotype, mainly characterized by internalizing symptoms, than RSTS individuals who are expected to be more prone to develop externalizing symptoms as soon as they grow up. Furthermore, we envisage an enhancement of autism-related traits in both syndromes.

TABLE 1 Sample characteristics

Syndrome/age (years)	Gender	T0	T1
CdLS ($n = 14$)	8 males, 6 females	4.14 ± 2.60	7.79 ± 3.56
RSTS ($n = 15$)	8 males, 7 females	6.00 ± 4.23	9.40 ± 4.69

Abbreviations: CdLS, Cornelia de Lange syndrome; RSTS, Rubinstein-Taybi syndrome.

2 | METHODS

2.1 | Editorial policies and ethical considerations

Written Informed Consent was obtained from parents/legal tutors, following a full explanation of the procedures undertaken. This study was performed in accordance with the Declaration of Helsinki (1964) and was approved on May 6, 2021 by the local Ethics Committee of the Fondazione IRCCS (anonymized for blind revision) (ID: 130231, parere: 745_2021).

2.2 | Participants

The sample was composed of 29 patients affected by CdLS and RSTS (as described in Table 1) who were recruited through referral to our outpatient clinic for first neuropsychiatric and/or follow-up assessments, as well as through the (anonymized for blind peer review) CdLS Association and the (anonymized for blind peer review) RSTS Association. All patients have received a clinical and molecular diagnosis of RSTS or CdLS. Their final inclusion in the study relied on the attainment of written informed consent, following a full explanation of the procedures undertaken. All patients were Caucasian from different Italian regions. All individuals affected by CdLS carried *NIPBL pathogenic variants* whereas all individuals affected by RSTS carried *CREBP pathogenic variants*. The absence of a spectrum of pathogenic variants in both syndromes was not intentionally determined by the application of specific inclusion criteria. The small sample size did not allow to catch the whole spectrum of pathogenic variants involved in the etiopathogenesis, including the rarest ones (Figure 1).

No dropouts were detected in the longitudinal assessment as 100% (14 CdLS and 15 RSTS) of participants enrolled in the study at T0 responded to the follow-up call at T1.

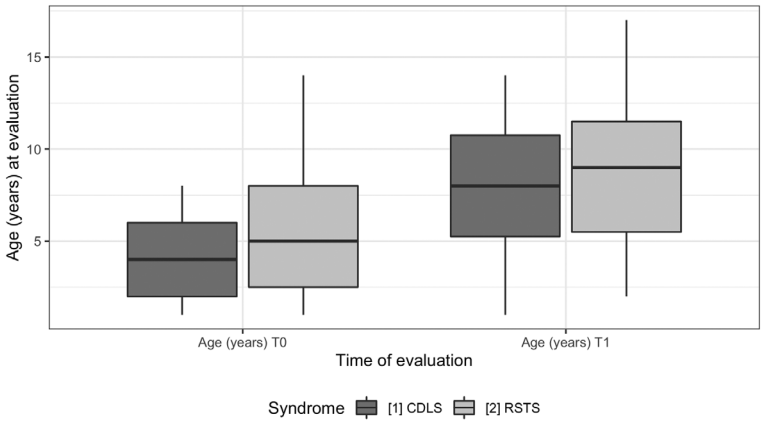

FIGURE 1 Sample characteristics

All patients were assessed at the Child and Adolescent Neuropsychiatric Service, Fondazione IRCCS (anonymized for blind revision). The assessment protocol was administered to all subjects during outpatient visits or during a brief hospitalization.

2.3 | Measures

2.3.1 | Cognitive and developmental assessment

A cognitive assessment was carried out administering Leiter International Performance Scales Revised (Leiter-R) to children affected by CdLS and RSTS aged over 2 years, whereas a developmental assessment was performed administering Griffith Mental Developmental Scales to children aged under 8 years whose behavioral impairment was so severe as to not allow a cognitive assessment with Leiter-R.

The Griffiths Mental Developmental Scales (Griffiths, 1986) provides a General Quotient of Development (GQ) for children aged between 0 and 8 years. The GQ is composed of six sub-quotients, one for each area investigated (locomotor, personal-social, language, eye and hand coordination, performance, and practical reasoning).

The Leiter International Performance Scales Revised (Roid & Miller, 1997) is a non-verbal cognitive test designed to be administered from 2 to 20 years. It shapes up to be the most suitable tool for assessing the Intellectual Quotient (IQ) of individuals with severe attention deficits and linguistic impairments. Although GQ and IQ do not perfectly correspond, we considered both as indices of the children's development. Both tests yielded a standardized quotient with $M = 100$ and $SD = 15$. The use of a combined IQ/GQ index is well-known and validated if participants are at significantly different developmental stages with respect to the level of functioning (e.g., Van Schooneveld & Braun, 2013). In addition, the Griffiths GQ appeared to be a good predictor of later IQ (e.g., Bowen et al., 1996).

2.3.2 | Adaptive behavior and communication assessment

The Vineland Adaptive Behavior Scale (VABS: Balboni & Pedrabissi, 2003) is a semi-structured interview turned to primary caregivers that provides a global score indicating the level of individual adaptive functioning (Adaptive Behavior Composite score) and four different scores concerning abilities in the following specific domains: Communication, Daily Living skills, Socialization, and Motor skills. Raw scores were adopted to catch the overall adaptive profile of patients. The expressive and receptive linguistic abilities were assessed directly administering the Communication domain of the VABS.

2.3.3 | Behavioral and emotional assessment

The Child Behavior Checklist (CBCL: Achenbach et al., 2001) is a parent-report questionnaire composed of 100 items rated on a 3-point Likert scale with scores ranging from 0 (not true) to 2 (very true or often true) that reflect the caregiver viewpoint of the child behavioral and emotional difficulties in the last 6 months. It yields 8 syndromic subscales: withdrawn behavior, somatic complaints, anxiety/depressed behavior, opposite behavior, aggressive behavior, social problems, thought problems, and attention problems. Rated items can also be clustered in three broad classifications of symptoms: internalizing (consisting of anxious/depressed, withdrawn, emotionally reactive, somatic complaints) and externalizing (consisting of attention problems, aggressive behavior, rule-breaking) and total problems. Although it has been used less often among children with intellectual disability, the factorial validity of the CBCL has been evaluated by Borthwick-Duffy et al. (1997), who examined the CBCL scores of 67 children and adolescents with ID. The Cronbach's α for the CBCL Total Problem scale was high, ranging from 0.83 to 0.91 (Frigerio et al., 2004).

The Childhood Autism Rating Scale (CARS: Schopler et al., 1988) is a behavioral observation rating scale used as a screening tool for ASD in clinical and research settings. This scale investigates the presence of behavioral, cognitive, and communicative characteristics associated with autism and provides a total score ranging from 15 to 60. The cut-off score is set at 30. For the purpose of the present study, the cross-sectional comparisons between syndromes and longitudinal analyses were carried out considering the CARS total score obtained by the subject.

Studies on children reported a sensitivity of 0.98 for CARS scores equal or above the autism cut-off of 30 (Eaves & Milner, 1993) used to detect the presence of autistic symptoms eligible for diagnosis. Several studies revealed high internal consistency among CARS items, with acceptable Cronbach's alpha coefficient ≥0.90 (Magyar & Pandolfi, 2007; Schopler et al., 1988). Moreover, CARS cut-off scores turned out to be adequate to accurately differentiate ASD from pervasive developmental disorders for toddlers and preschool aged children in clinical settings (Schopler et al., 2010). These results suggest that the CARS is a valid and reliable instrument for evaluating the presence and severity of symptoms of autism spectrum disorders.

2.4 | Procedures

Neuropsychiatric phenotype of CdLS and RSTS patients was assessed at T0 and T1. The T1 timepoint was carried out 40.96 ± 20.37 months later than the baseline (T0). In particular, the average time CdLS individuals were followed up at T1 was: 43.14 ± 25.87 months, whereas RSTS individuals were followed up at T1 39.07 ± 13.05 months later than T0 using a specific protocol aimed at providing clinical data concerning IQ/GQ, communicative skills, behavioral and emotional aspects, and adaptive behaviors based on direct and indirect evaluations. A cognitive assessment was carried out administering Leiter-R to children affected by CdLS and RSTS aged over 2 years, whereas a developmental assessment was performed administering Griffith Mental Developmental Scales to children aged under 8 years whose behavioral impairment was so severe as to not allow a cognitive

assessment with Leiter-R. Examiners were not blind to the syndrome diagnosis of the participants but they were blind to T0 assessment scores at T1. All the direct instruments were scored at the end of the examination of CdLS and RSTS patients for reducing memory recall biases.

2.5 | Data analysis

Descriptive statistics were conducted on demographic variables (e.g., age) to delineate the characteristics of CdLS and RSTS individuals. T-tests for independent samples were run to exclude age differences at T0 between CdLS and RSTS and differences between the two syndromes in the amount of time from assessment at T0 to T1. Robust multiple mixed 2 × 2 ANOVA (Syndrome: 2 levels; Time-points of assessment: 2 levels) were performed on the participants' linguistic and adaptive characteristics to outline both between-group differences and temporal evolution of phenotypes from T0 to T1. Huber M-estimators (Huber, 2011) were used as a measure of central tendency, and in case of statistical significance, post-hoc comparisons were performed as follows: (i) test statistic for two-sample trimmed mean proposed by Yuen (1974) for between syndrome comparison at each timepoint; and (ii) the generalized approach as explained by Mair and Wilcox (2018). Both tests use the robust version of Cohen's *d* (Cohen, 2013) as proposed by Algina et al. (2005). Multiple mixed 2 × 2 ANOVA (Syndrome: 2 levels; Time-points of assessment: 2 levels) were performed on the participants' behavioral, emotional, cognitive, and autistic characteristics.

G-power analyses show that a sample size of 28 subjects is enough to obtain a power of 0.80 and a significance level of 0.05 with 2 × 2 conditions in a linear model with a large effect size ($f^2 = 0.39$) according to Cohen (1988).

Statistical analyses were performed using R 4.1.0 and R Studio 1.4.1717.

3 | RESULTS

3.1 | Sample characteristics: Time span between assessment at T0 and T1

Firstly, a T-test for independent samples was performed to exclude significant age differences at T0 between the two syndromes (CdLS: 4.14 ± 2.60 years; RSTS: 6.00 ± 4.23 years). The results confirmed the absence of relevant age differences between CdLS and RSTS at baseline ($t_{[27]} = -1.452$, $p = 0.158$, $d = -0.54$).

Secondly, a T-test for independent samples was carried out to exclude differences between CdLS and RSTS in the amount of time from assessment at T0 to T1 (CdLS: 3.71 ± 2.16 years; RSTS: 3.40 ± 1.12 years). The results showed that there are no significant differences and that these two timespans are comparable ($t_{[27]} = 0.496$, $p = 0.632$, $d = 0.177$).

3.2 | Developmental and cognitive assessment

To describe the sample's cognitive level, we considered GQ values for patients under 8 years with behavior disorders that did not allow a cognitive assessment with Leiter-R.

Mixed 2 × 2 ANOVA showed a significant effect of time (T0 vs. T1, $F_{[1,27]} = 6.92$, $p < 0.05$, $\eta_p^2 = 0.20$) and a significant interaction effect between time and syndrome ($F_{[1,27]} = 6.63$, $p < 0.05$, $\eta_p^2 = 0.20$), with CdLS showing a significant difference over time ($p < 0.05$).

3.3 | Adaptive behavior and communication assessment

Adaptive behavior was assessed for all children and age-equivalent scores were used to perform mixed 2 × 2 ANOVAs.

In the Composite score, main effect of syndrome ($F_{[1,11.745]} = 6.334$, $p = 0.027$) and time ($F_{[1,10.039]} = 38.742$, $p < 0.001$) and their interaction resulted significant ($F_{[1,10.039]} = 14.701$, $p = 0.003$). Pairwise comparisons between group levels showed significant difference only at T1 ($t_{[14.296]} = 2.938$, $p = 0.011$, $d = 0.643$), while each group showed significant difference in both syndromes between T0 and T1 (CdLS: $t_{(7)} = -2.772$, $p = 0.028$, $d = 0.272$; RSTS: $t_{(9)} = -5.574$, $p < 0.001$, $d = 0.54$).

In the Communication domain, main effect of syndrome ($F_{[1,7.986]} = 8.086$, $p = 0.022$) and time ($F_{[1,8.814]} = 15.819$, $p = 0.003$) and their interaction resulted significant ($F_{[1,8.814]} = 11.419$, $p = 0.008$). Pairwise comparisons between group levels showed a significant difference only at T1 ($t_{[10.552]} = 3.169$, $p = 0.009$, $d = 0.652$), while only RSTS showed significant difference between T0 and T1 ($t_{(9)} = -3.913$, $p = 0.004$, $d = 0.435$).

In the Daily Living Skills domain, main effect of syndrome ($F_{[1,8.911]} = 5.794$, $p = 0.04$) and time ($F_{[1,8.746]} = 9.248$, $p = 0.014$) resulted significant as well as their interaction ($F_{[1,8.746]} = 7.514$, $p = 0.023$). Pairwise comparisons between group levels showed significant difference only at T1 ($t_{[10.267]} = 2.665$, $p = 0.023$, $d = 0.704$), while only RSTS showed significant difference between T0 and T1 ($t_{(9)} = -3.069$, $p = 0.013$, $d = 0.507$).

In the Socialization domain, main effect of syndrome ($F_{[1,10.159]} = 8.815$, $p = 0.014$) and time ($F_{[1,11.408]} = 13.473$, $p = 0.003$) resulted significant as their interaction ($F_{[1,11.408]} = 7.229$, $p = 0.02$). Pairwise comparisons between group levels showed significant difference only at T1 ($t_{[13.339]} = 3.044$, $p = 0.009$, $d = 0.587$), while only RSTS showed significant difference between T0 and T1 ($t_{(9)} = -3.7$, $p = 0.005$, $d = 0.506$).

In the Motor Skills domain, the main effect of syndrome was not significant ($F_{[1,13.396]} = 2.634$, $p = 0.128$) as the interaction between time and syndrome ($F_{[1,13.791]} = 2.11$, $p = 0.169$), whereas the main effect of time was significant ($F_{[1,13.791]} = 13.236$, $p = 0.003$). No differences were found at T0 and T1 between syndromes but RSTS significantly improved between T0 and T1 ($t_{(9)} = -3.844$, $p = 0.004$, $d = 0.557$).

Expressive and receptive abilities were assessed using VABS. In the Expressive subscale, the main effect of syndrome ($F_{[1,6.216]} = 2.069$, $p = 0.199$) and time ($F_{[1,6.714]} = 2.61$, $p = 0.152$) did not result resulted significant as the while interaction ($F_{[1,6.714]} = 1.737$, $p = 0.231$).

In the Receptive subscale none of the main effects of syndrome ($F_{[1,10.724]} = 1.812$, $p = 0.206$) and time ($F_{[1,7.023]} = 1.506$, $p = 0.259$) resulted significant as their interaction ($F_{[1,7.023]} = 1.442$, $p = 0.269$). However, the improvement in receptive linguistic abilities was smaller in CdLS patients than in RSTS (Figure 2, Table 2).

3.4 | Behavioral and emotional assessment

Mixed 2 × 2 ANOVAs showed no main effect of syndrome (Int: $F_{(1,21)} = 0.504$, $p = 0.480$, $\eta_p^2 = 0.010$; Ext: $F_{(1,21)} = 1.614$, $p = 0.218$, $\eta_p^2 = 0.050$) and time (Int: $F_{(1,21)} = 0.603$, $p = 0.446$, $\eta_p^2 = 0.040$; Ext: $F_{(1,21)} = 2.402$, $p = 0.136$, $\eta_p^2 = 0.129$) as well as interaction effect (Int: $F_{(1,21)} = 0.119$, $p = 0.734$, $\eta_p^2 = 0.002$; Ext: $F_{(1,21)} = 0.501$, $p = 0.487$, $\eta_p^2 = 0.007$) either in Internalizing or Externalizing symptoms; whereas there was a significant main effect of time ($F_{[1,22]} = 5.92$, $p = 0.039$, $\eta_p^2 = 0.21$) in the Total problems score.

According to CARS data, the main effect of syndrome was not significant ($F_{[1,26]} = 0.550$, $p = 0.465$, $\eta_p^2 = 0.021$), as well as the main effect of time ($F_{[1,26]} = 1.027$, $p = 0.320$, $\eta_p^2 = 0.015$) and their interaction ($F_{[1,26]} = 4.032$, $p = 0.055$, $\eta_p^2 = 0.087$) (Figure 3, Table 3).

4 | DISCUSSION

The present study has contributed to outlining the variating pathways of neuropsychiatric functioning and behavioral phenotypes from childhood to adolescence in CdLS and RSTS by setting up a longitudinal study design and matching both direct and indirect evaluations for guiding interventions' planning. The innovative aspect of our study deals with the methodology adopted, which has allowed us to overcome the limits and cohort effects encountered in the previous cross-sectional studies. Moreover, to our knowledge, this is also the first study that has explored the age-dependent behavioral and emotional difficulties in such an early stage of life in both syndromes.

Overall, our findings highlighted that children affected by CdLS are subjected to a worse developmental trajectory, with decreasing scores or only slighter improvements, in all the investigated areas concerning the cognitive, linguistic, adaptive, behavioral and emotional development compared to those with RSTS.

In particular, two different developmental trajectories across syndromes emerged.

The cognitive profile of CdLS is subjected to a worsening trend with decreasing IQ/GQ scores from T0 to T1; whereas RSTS shows a stable IQ/GQ over time.

It is worth mentioning that CdLS and RSTS cognitive level at T0 is comparable. Therefore, we might acknowledge that the IQ is not an influential variable able to explain a relevant quote of variance of the behavioral phenotype changes. In contrast, individuals with CdLS show a downward trend in cognitive abilities at T1. In this case, it could not be possible to exclude a potential influence of the IQ on the achievement of the developmental milestones. However, divergent results emerged from the study by Giani et al. (2022) that outlined how changes in behavioral phenotypes across the lifespan are independent of IQ but associated with autistic traits. In our case, no relevant differences in autistic traits emerged between the two timepoints of assessment in CdLS individuals. Therefore, changing pathways in behavioral phenotypes might be considered independent of both IQ and ASD-related symptoms. Significant differences between syndromes emerged also in the analyses of the adaptive skills in various life's domains. Notably, communication abilities improve more over time in RSTS than in CdLS, whereas socialization abilities increase longitudinally both in CdLS and in RSTS, even if less in individuals with CdLS. A relevant improvement of global adaptive behaviors has been detected in both syndromes, with a higher growth of adaptive functioning in RSTS than in CdLS from T0 to T1. This result offers a divergent perspective from the previous studies (Basile et al., 2007; Kline et al., 2018; Olioso et al., 2009) that reported a decrease of adaptive behaviors with age in individuals with CdLS. Similarly, Cochran et al. (2019) demonstrated a significant decline in standard scores in all areas of adaptive behavior alongside stability of age equivalent scores in a 7-years follow-up, suggesting adaptive behaviors are likely to be plateaued. Concerning RSTS, our study has contributed to filling the existing research gap in the literature, providing missing information about adaptive skills and behaviors and their evolution over time in this target population.

Communication skills increase longitudinally only in RSTS, as expressive abilities in CdLS do not show signs of increase or decrease from early infancy to late adolescence.

Our findings about expressive and receptive linguistic abilities differ from the pioneering ones reported by Hennekeam et al. (1992), which assumed a loss of speech as soon as RSTS grew up, as in our case both communication abilities improved, even though with a significant increasing trend of receptive language than expressive ones, that remains a weakness point.

There is also evidence that impairments in social interactions and anxiety, a distinctive hallmark of the CdLS behavioral phenotype, may worsen language skills which, in turn, impact adaptive abilities. Conversely, the greater gap in expressive abilities observed in CdLS across the lifespan is meant to generate frustration that often negatively affects behavioral and social outcomes.

Additionally, a recent review provided evidence that social impairments in CdLS individuals are characterized by heightened levels of social anxiety which are mediated by both the nature of the social demand and the familiarity of the examiner they interact with (Giani et al., 2021). Considering the age-related increase of external demands and the major information children are exposed to, it is crucial to focus on the ability to comprehend changes and heighten predictability to reduce social anxiety. These findings guide us to consider the communicative aspect as one of these patients' intervention priorities. Early Augmentative and Alternative Communication

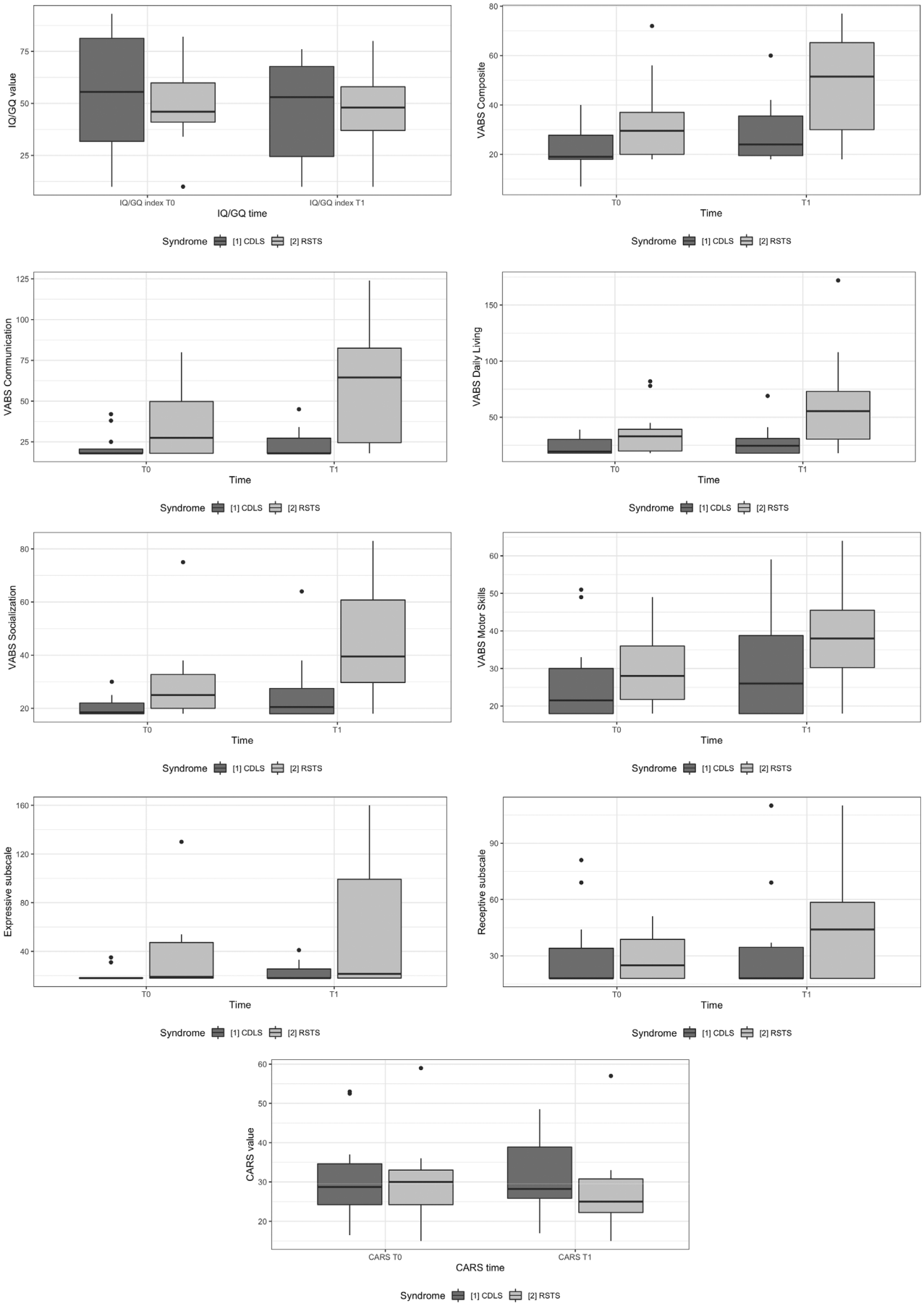

FIGURE 2 Results of the developmental, adaptive and autism assessment at T0 and T1 in both syndromes

TABLE 2 Results of the developmental, adaptive and autism assessment at T0 and T1 in both syndromes

Measure	Syndrome	T0	T1	Pairwise comparisons between time points
Griffiths or leiter				
GQ/IQ	CdLS	56.57 ± 28.61	45.93 ± 25.15	$p < 0.05$
	RSTS	49.25 ± 17.47	49.13 ± 17.86	$p = 0.96$
VABS				
Composite[a]	CdLS	21.885 (15.051–28.719)	27.033 (20.023–34.042)	$p = 0.028$
	RSTS	30.324 (22.860–37.788)	48.929 (37.817–60.040)	$p < 0.001$
Communication[a]	CdLS	18.000 (NA)	18.000 (NA)	$p = 0.41$
	RSTS	32.076 (21.464–42.687)	58.063 (37.726–78.399)	$p = 0.004$
Daily Living[a]	CdLS	20.708 (17.889–23.527)	25.792 (20.041–31.544)	$p = 0.668$
	RSTS	32.654 (23.326–41.982)	56.810 (37.146–76.474)	$p = 0.013$
Socialization[a]	CdLS	18.855 (17.892–19.818)	21.551 (18.474–24.628)	$p = 0.369$
	RSTS	26.843 (22.116–31.570)	44.608 (32.690–56.525)	$p = 0.005$
Motor Skills[a]	CdLS	23.215 (18.695–27.736)	28.429 (19.420–37.437)	$p = 0.188$
	RSTS	29.535 (23.757–35.313)	38.833 (31.865–45.802)	$p = 0.004$
Expressive subscale[a]	CdLS	18.000 (NA)	18.000 (NA)	$p > 0.05$
	RSTS	19.710 (17.836–21.584)	23.985 (17.245–30.725)	$p > 0.05$
Receptive subscale[a]	CdLS	18.000 (NA)	18.000 (NA)	$p > 0.05$
	RSTS	28.320 (19.263–37.376)	46.669 (24.365–68.974)	$p > 0.05$
CARS				
Total score	CdLS	30.82 ± 10.94	31.75 ± 9.14	$p = 0.49$
	RSTS	29.63 ± 10.36	27.47 ± 9.59	$p = 0.15$

Abbreviations: CARS, childhood autism rating scale; CdLS, Cornelia de Lange syndrome; GQ, general quotient; IQ, intellectual quotient; RSTS, Rubinstein-Taybi syndrome; VABS, vineland adaptive behavior scale.
[a]For VABS scales and subscales we used Huber M-estimators as a measure of central tendency and values of lower and upper confidence interval as a measure of variance.

(AAC) interventions and speech therapy are therefore of paramount importance from the outset to prevent the onset and deterioration of challenging behaviors and produce favorable developmental outcomes (Kline et al., 2018).

Concerning behavioral aspects, our study shows that both syndromes report a worsening trend in CBCL assessment even if CdLS exhibit a significant and major deterioration compared to individuals with RSTS.

In line with previous findings, our study has confirmed the social proneness of individuals affected by RSTS who are often described as friendly, more easily engaged in social contacts, and with fewer social impairments (Galèra et al., 2009; Moss et al., 2017; Yagihashi et al., 2012), but it has also highlighted a slight increase of social abilities in individuals with CdLS who are known in the literature to be more compromised in interpersonal relationships and situations (Grados et al., 2017; Kline et al., 2018; Mulder et al., 2016; Richards et al., 2009; Srivastava et al., 2014) with symptoms resembling ASD.

However, our study indicates that both syndromes show comparable levels of ASD-related traits that are meant to persist and to remain stable over time undergoing only slight fluctuations not statistically relevant. The absence of an improvement of ASD symptomatology in parallel with chronological age is not consistent with previous findings (Basile et al., 2007; Cochran et al., 2019; Kline et al., 2007; Olioso et al., 2009, 2011). It is also worth noting that ASD symptoms in CdLS differ from those observed in idiopathic autism. CdLS show significantly less repetitive behaviors, lower sensory reactivity, more eye contact, and intentional communicative gestures than ASD (Moss, Howlin, Magiati & Oliver, 2012), and social impairments are characterized by social anxiety, selective mutism, and extreme shyness (Collis et al., 2006; Goodban, 1993; Richards et al., 2009). The divergent results could be due to the different methodology applied and study design.

Lastly, our work has outlined two different trajectories with a specific behavioral phenotype independent of the ID with a more favorable trend of improvements in individuals with RSTS than with CdLS.

There is mounting evidence that these variating pathways of behavioral phenotypes and neuropsychiatric functioning in CdLS and RSTS might be explained by biological dysregulated processes, accounting for a quote of age-related changes across the lifespan. A widely accepted theory for CdLS is the oxidative stress hypothesis which could provide a further contribution to the genome instability detected in the CdLS spectrum and the premature aging signs encountered in patients affected by CdLS. In general, any abnormal

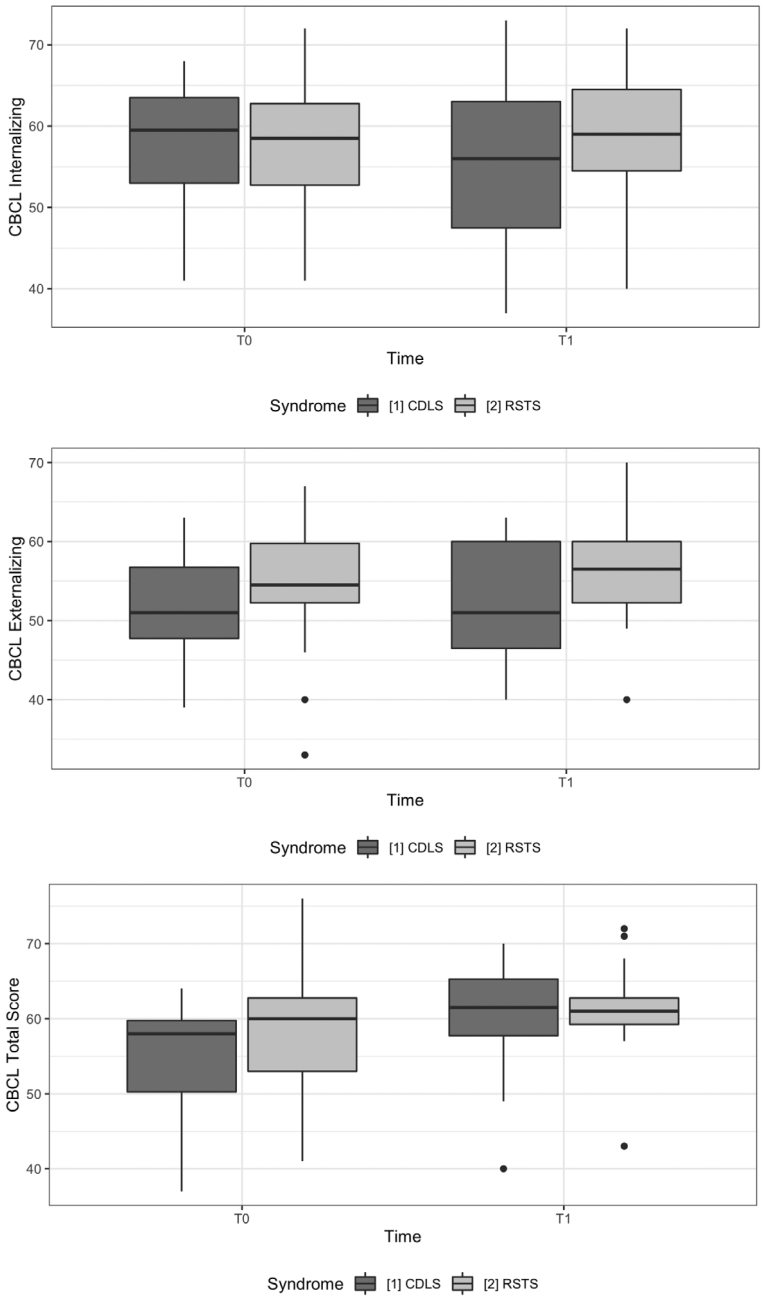

FIGURE 3 Results of the psychopathological assessment at T0 and T1 in both syndromes

increase in oxidative stress-promoting substances, often called pro-oxidants, is mitigated by an antioxidant response. However, when this balance is altered, oxidative and nitrosative stress is initiated as a result of the overproduction of reactive oxygen species (ROS) and insufficiency of the antioxidant defense mechanisms (Salim, 2014). Excessive ROS may have detrimental effects and can disturb the maintenance of normal adenine and pyridine nucleotide status, which, in turn, can affect the viability of DNA, trigger mutations and modify gene expression (Kohen & Nyska, 2002). The brain, with its extensive capacity to consume large amounts of oxygen and production of free radicals, is considered highly vulnerable to oxidative damage. Therefore, it is not surprising that oxidative stress is implicated in several neurodegenerative and psychiatric disorders, like anxiety, depression, bipolar disorder and schizophrenia (Halliwell, 2006; Ng et al., 2008; Reynolds et al., 2007; Salim, 2014). The phenotypic markers in CdLS, including growth delay, short stature, delayed puberty and cognitive decline/intellectual disability are well explained by mutant cohesin that may contribute to DNA damage, as a result of reduced DNA repair capability induced by oxidative stress promoting genome instability, apoptosis and cell growth arrest (Chamorro et al., 2016; Gorrini et al., 2013; Sarogni et al., 2020). Similarly, impairments in the KREB cycle have been associated with memory deficits (Josselyn & Nguyen, 2005). However, no evidence about the link between those neurobiological impairments and age-related changes in the behavioral phenotype of RSTS exists as it is still in its infancy.

TABLE 3 Results of the psychopathological assessment at T0 and T1 in both syndromes

CBCL		
Internalizing symptoms		
CdLS	57.08 ± 9.59	55.82 ± 11.50
RSTS	57.57 ± 8.79	58.93 ± 8.17
Externalizing symptoms		
CdLS	51.42 ± 7.61	52.55 ± 8.80
RSTS	54.14 ± 9.39	56.29 ± 7.41
Total score		
CdLS	54.00 ± 9.33	59.50 ± 8.99
RSTS	58.29 ± 9.00	61.21 ± 6.96

Abbreviations: CBCL, child behavior checklist; CdLS, Cornelia de Lange syndrome; RSTS, Rubinstein-Taybi syndrome.

There are several strengths of this study that are worthy of mention. Firstly, the current study is the first one that has set up a longitudinal research design to follow the changing pathways of the CdLS and RSTS behavioral phenotypes, using an assessment protocol composed of direct and indirect evaluations. Moreover, specific indications for interventions have been discussed to provide personalized healthcare for patients. As a future direction, this study could be a starting point for a consensus statement about rehabilitative guidelines for these two genetic conditions.

Notwithstanding the innovative aspects of this study, some limitations must be acknowledged. Patients with CdLS and RSTS were compared without considering the wide genetic heterogeneity involved in the etiopathogenesis of the syndrome that turns into different severity degrees of behavioral phenotypes as well as the great variability of age among the two syndrome groups which might account for the differences in the increases/decreases of particular skills at specific developmental timepoints. Furthermore, previous interventions were not put under experimental control as potential confounding variables able to account for part of the outcomes observed in the longitudinal assessment. It is worth mentioning that in our country, the care pathway for individuals with complex disabilities is characterized by an early and timely intervention that is meant to change according to age and various specific needs. Future studies should also covariate this variable to distinguish improvements and/or worsening of abilities due to the developmental trajectories of the syndrome or to interventions.

5 | CONCLUSION

In summary, knowing the natural history of the behavioral phenotype and his longitudinal trajectory across the lifespan has allowed us to define more tailored intervention programs based on the strengths and weaknesses encountered as distinctive of the different developmental stages of CdLS and RSTS patients. In particular, Early Augmentative and Alternative Communication (AAC) interventions are highly recommended to obtain favorable outcomes in developmental milestones and to reduce the risk of behavioral disorders. Our findings highlighted that children affected by CdLS are subjected to a worse developmental trajectory, with decreasing scores or only slighter improvements, in all the investigated areas concerning the cognitive, linguistic, adaptive, behavioral and emotional development compared to those with RSTS.

Being aware of the early dysfunctional patterns which might pave the way for later neuropsychiatric impairments is the first step for preventive interventions. Every developmental stage has its milestones expected to be reached to ensure proper individual maturation and different therapeutic windows, which might be taken into account because the timing of interventions is an essential element for outcomes maximization. Moreover, different syndromes have different aspects of being monitored and dealt with. Priorities change and evolve alongside the increasing demands expected with age and should always be established and discussed with the family in the treatment plan, in line with the theoretical assumptions of the Family Centred Care (FCC) model.

AUTHOR CONTRIBUTIONS

P.A. and L.G. are both first authors of the present manuscript as they equally contributed to its drafting and revisions. BA, GM, FD, FM, CR, PV provided substantial contributions to the conception and design of the work, provided substantial contributions to the analysis and interpretation of data, and revised the work critically for important intellectual content. SS, AS, DM, and AC provided final approval of the version to be published. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

Achenbach, T. M., Dumenci, L., & Rescorla, L. A. (2001). *Ratings of relations between DSM-IV diagnostic categories and items of the CBCL/6–18, TRF, and YSR*. University of Vermont.

Ajmone, P. F., Allegri, B., Cereda, A., Michelini, G., Dall'Ara, F., Mariani, M., Rigamonti, C., Selicorni, A., Vizziello, P., & Costantino, M. A. (2021). Neuropsychiatric functioning in CDLS: A detailed phenotype and genotype correlation. *Journal of Autism and Developmental Disorders*, *52*, 4763–4773. https://doi.org/10.1007/s10803-021-05343-8

Ajmone, P. F., Avignone, S., Gervasini, C., Giacobbe, A., Monti, F., Costantino, A., Esposito, S., Marchisio, P., Triulzi, F., & Milani, D. (2018). Rubinstein–Taybi syndrome: New neuroradiological and neuropsychiatric insights from a multidisciplinary approach. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *177*(4), 406–415. https://doi.org/10.1002/ajmg.b.32628

Ajmone, P. F., Rigamonti, C., Dall'Ara, F., Monti, F., Vizziello, P., Milani, D., Cereda, A., Selicorni, A., & Costantino, A. (2014). Communication, cognitive development and behavior in children with Cornelia de Lange syndrome (CdLS): Preliminary results. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *165*(3), 223–229. https://doi.org/10.1002/ajmg.b.32224

Algina, J., Keselman, H., & Penfield, R. D. (2005). An alternative to Cohen's standardized mean difference effect size: A robust parameter and confidence interval in the two independent groups case. *Psychological Methods*, *10*(3), 317–328. https://doi.org/10.1037/1082-989X.10.3.317

Balboni, G., & Pedrabissi, L. (2003). *Adattamento italiano della Vineland Adaptive Behavior Scales (VABS)*. O.S. Organizzazioni Speciali.

Basile, E., Villa, L., Selicorni, A., & Molteni, M. (2007). The behavioural phenotype of Cornelia de Lange syndrome: A study of 56 individuals. *Journal of Intellectual Disability Research*, *51*(9), 671–681. https://doi.org/10.1111/j.1365-2788.2007.00977.x

Borthwick-Duffy, S. A., Lane, K. L., & Widaman, K. F. (1997). Measuring problem behaviors in children with mental retardation: Dimensions and predictors. *Research in Developmental Disabilities*, *18*(6), 415–433, ISSN 0891–4222. https://doi.org/10.1016/S0891-4222(97)00020-6

Bowen, J. R., Gibson, F. L., Leslie, G., Arnold, J. D., Ma, P. J., & Starte, D. R. (1996). Predictive value of the Griffiths assessment in extremely low birthweight infants. *Journal of Paediatrics and Child Health*, *32*(1), 25–30. https://doi.org/10.1111/j.1440-1754.1996.tb01536.x

Chamorro, Á., Dirnagl, U., Urra, X., & Planas, A. M. (2016). Neuroprotection in acute stroke: Targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *The Lancet Neurology*, *15*(8), 869–881. https://doi.org/10.1016/S1474-4422(16)00114-9

Cochran, L., Moss, J., Nelson, L., & Oliver, C. (2015). Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, fragile X, and cri du chat syndromes: Results from a 2.5-year follow-up. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *169*(2), 188–197. https://doi.org/10.1002/ajmg.c.31438

Cochran, L., Welham, A., Oliver, C., Arshad, A., & Moss, J. F. (2019). Age-related behavioural change in Cornelia de Lange and cri du chat syndromes: A seven-year follow-up study. *Journal of Autism and Developmental Disorders*, *49*(6), 2476–2487. https://doi.org/10.1007/s10803-019-03966-6

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Erlbaum.

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. Routledge.

Collis, L., Oliver, C., & Moss, J. (2006). Low mood and social anxiety in Cornelia de Lange syndrome. *Journal of Intellectual Disability Research*, *50*, 792.

Crawford, H., Waite, J., & Oliver, C. (2017). Diverse profiles of anxiety related disorders in fragile X, Cornelia de Lange and Rubinstein-Taybi syndromes. *Journal of Autism and Developmental Disorders*, *47*(12), 3728–3740. https://doi.org/10.1007/s10803-016-3015-y

Eaves, R. C., & Milner, B. (1993). The criterion-related validity of the childhood autism rating scale and the autism behavior checklist. *Journal of Abnormal Child Psychology*, *21*, 481–491. https://doi.org/10.1007/BF00916315

Ellis, K., Moss, J., Stefanidou, C., Oliver, C., & Apperly, I. (2021). The development of early social cognitive skills in neurogenetic syndromes associated with autism: Cornelia de Lange, fragile X and Rubinstein-Taybi syndromes. *Orphanet Journal of Rare Diseases*, *16*(1), 488. https://doi.org/10.1186/s13023-021-02117-4

Fergelot, P., Van Belzen, M., Van Gils, J., Afenjar, A., Armour, C. M., Arveiler, B., Beets, L., Burglen, L., Busa, T., Collet, M., Deforges, J., de Vries, B. B. A., Garrido, E. D., Dorison, N., Dupont, J., Francannet, C., Garciá-Minaúr, S., Gab, E., & Hennekam, R. C. (2016). Phenotype and genotype in 52 patients with Rubinstein–Taybi syndrome caused by EP300 mutations. *American Journal of Medical Genetics Part A*, *170*(12), 3069–3082. https://doi.org/10.1002/ajmg.a.37940

Fisher, M. H., Lense, M. D., & Dykens, E. M. (2016). Longitudinal trajectories of intellectual and adaptive functioning in adolescents and adults with Williams syndrome. *Journal of Intellectual Disability Research*, *60*(10), 920–932. https://doi.org/10.1111/jir.12303

Frigerio, A., Cattaneo, C., Cataldo, M., Schiatti, A., Molteni, M., & Battaglia, M. (2004). Behavioral and emotional problems among Italian children and adolescents aged 4 to 18 years as reported by parents and teachers. *European Journal of Psychological Assessment*, *20*(2), 124–133. https://doi.org/10.1027/1015-5759.20.2.124

Galéra, C., Taupiac, E., Fraisse, S., Naudion, S., Toussaint, E., Rooryck-Thambo, C., Delrue, M.-A., Arveiler, B., Lacombe, D., & Bouvard, M. P. (2009). Socio-behavioral characteristics of children with Rubinstein-Taybi syndrome. *Journal of Autism and Developmental Disorders*, *39*(9), 1252–1260. https://doi.org/10.1007/s10803-009-0733-4

Giani, L., Michelini, G., Ajmone, P. F., Scaini, S., Selicorni, A., Vizziello, P., & Costantino, A. (2022). Age-related hallmarks of psychopathology in Cornelia de Lange and Rubinstein-Taybi syndromes. *Research in Developmental Disabilities*, *126*, 104235. https://doi.org/10.1016/j.ridd.2022.104235

Giani, L., Michelini, G., Nobile, M., Ajmone, P., Vizziello, P., & Scaini, S. (2021). Behavioral markers of social anxiety in Cornelia de Lange syndrome: A brief systematic review. *Journal of Affective Disorders*, *299*, 636–643. https://doi.org/10.1016/j.jad.2021.12.099

Goodban, M. T. (1993). Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia de Lange syndrome. *American Journal of Medical Genetics*, *47*(7), 1059–1063. https://doi.org/10.1002/ajmg.1320470725

Gorrini, C., Harris, I. S., & Mak, T. W. (2013). Modulation of oxidative stress as an anticancer strategy. *Nature Reviews Drug Discovery*, *12*(12), 931–947. https://doi.org/10.1038/nrd4002

Grados, M., Alvi, H., & Srivastava, S. (2017). Behavioral and psychiatric manifestations in Cornelia de Lange syndrome (CdLS). *Current Opinion in Psychiatry*, *30*(2), 92–96. https://doi.org/10.1097/YCO.0000000000000311

Griffiths, R. (1986). *The abilities of babies: A study in mental measurement*. The Test Agency Ltd.

Groves, L., Moss, J., Crawford, H., Nelson, L., Stinton, C., Singla, G., & Oliver, C. (2019). Lifespan trajectory of affect in Cornelia de Lange syndrome: Towards a neurobiological hypothesis. *Journal of Neurodevelopmental Disorders*, *11*(1), 6. https://doi.org/10.1186/s11689-019-9269-x

Halliwell, B. (2006). Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiology*, *141*(2), 312–322. https://doi.org/10.1104/pp.106.077073

Hennekam, R. C. (2006). Rubinstein–Taybi syndrome. *European Journal of Human Genetics*, *14*(9), 981–985. https://doi.org/10.1038/sj.ejhg.5201594

Hennekam, R. C. (2010). Rubinstein-Taybi syndrome. In S. B. Cassidy & J. E. Allanson (Eds.), *Management of genetic syndromes* (3rd ed., pp. 705–716). John Wiley & Sons.

Hennekam, R. C., Baselier, A. C., Beyaert, E., Bos, A., Blok, J. B., Jansma, H. B., Thorbecke-Nilsen, V. V., & Veerman, H. (1992). Psychological and speech studies in Rubinstein-Taybi syndrome. *American Journal on Mental Retardation*, *96*(6), 645–660.

Huber, P. J. (2011). *Robust statistics* (pp. 1248–1251). Springer. https://doi.org/10.1007/978-3-642-04898-2_594

Josselyn, S. A., & Nguyen, P. V. (2005). CREB, synapses and memory disorders: Past progress and future challenges. *Current Drug Targets. CNS and Neurological Disorders*, *4*(5), 481–497. https://doi.org/10.2174/156800705774322058

Kline, A. D., Krantz, I. D., Sommer, A., Kliewer, M., Jackson, L. G., FitzPatrick, D. R., Levin, A. V., & Selicorni, A. (2007). Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. *American Journal of Medical Genetics Part A*, *143*(12), 1287–1296. https://doi.org/10.1002/ajmg.a.31757

Kline, A. D., Moss, J. F., Selicorni, A., Bisgaard, A. M., Deardorff, M. A., Gillett, P. M., Ishman, S. L., Kerr, L. M., Levin, A. V., Mulder, P. A., Ramos, F. J., Wierzba, J., Ajmone, P. F., Axtell, D., Blagowidow, N., Cereda, A., Costantino, A., Cormier-Daire, V., FitzPatrick, D., … Hennekam, R. C. (2018). Diagnosis and management of Cornelia de Lange syndrome: First international consensus statement. *Nature Reviews Genetics*, *19*(10), 649–666. https://doi.org/10.1038/s41576-018-0031-0

Kohen, R., & Nyska, A. (2002). Invited review: Oxidation of biological systems: Oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. *Toxicologic Pathology*, *30*(6), 620–650. https://doi.org/10.1080/01926230290166724

Kumar, S., Suthar, R., Panigrahi, I., & Marwaha, R. K. (2012). Rubinstein-Taybi syndrome: Clinical profile of 11 patients and review of literature. *Indian Journal of Human Genetics*, *18*(2), 161–166. https://doi.org/10.4103/0971-6866.100751

Magyar, C. I., & Pandolfi, V. (2007). Factor structure evaluation of the childhood autism rating scale. *Journal of Autism and Developmental Disorders*, *37*, 1787–1794. https://doi.org/10.1007/s10803-006-0313-9

Mair, P., & Wilcox, R. (2018). Robust statistical methods using WRS2. The Wrs2 package.

Moss, J., Howlin, P., Magiati, I., & Oliver, C. (2012). Characteristics of autism spectrum disorder in Cornelia de Lange syndrome. *Journal of Child Psychology and Psychiatry*, *53*(8), 883–891. https://doi.org/10.1111/j.1469-7610.2012.02540.x

Moss, J., Penhallow, J., Ansari, M., Barton, S., Bourn, D., FitzPatrick, D. R., Goodship, J., Hammond, P., Roberts, C., Welham, A., & Oliver, C. (2017). Genotype–phenotype correlations in Cornelia de Lange syndrome: Behavioral characteristics and changes with age. *American Journal of Medical Genetics Part A*, *173*(6), 1566–1574. https://doi.org/10.1002/ajmg.a.38228

Mulder, P. A., Huisman, S. A., Hennekam, R. C., Oliver, C., Van Balkom, I. D., & Piening, S. (2016). Behaviour in Cornelia de Lange syndrome: A systematic review. *Developmental Medicine and Child Neurology*, *59*(4), 361–366. https://doi.org/10.1111/dmcn.13361

Mulder, P. A., Huisman, S., Landlust, A. M., Moss, J., SMC1A Consortium, Piening, S., Hennekam, R. C., & van Balkom, I. D. (2019). Development, behaviour and autism in individuals with SMC1A variants. *Journal of Child Psychology and Psychiatry*, *60*(3), 305–313. https://doi.org/10.1111/jcpp.12979

Negri, G., Magini, P., Milani, D., Colapietro, P., Rusconi, D., Scarano, E., Bonati, M. T., Priolo, M., Crippa, M., Mazzanti, L., Wischmeijer, A., Tamburrino, F., Pippucci, T., Finelli, P., Larizza, L., & Gervasini, C. (2016). From whole gene deletion to point mutations of EP300-positive Rubinstein–Taybi patients: New insights into the mutational spectrum and peculiar clinical hallmarks. *Human Mutation*, *37*(2), 175–183. https://doi.org/10.1002/humu.22922

Nelson, L., Crawford, H., Reid, D., Moss, J., & Oliver, C. (2017). An experimental study of executive function and social impairment in Cornelia de Lange syndrome. *Journal of Neurodevelopmental Disorders*, *9*(1), 1–15. https://doi.org/10.1186/s11689-017-9213-x

Nelson, L., Moss, J., & Oliver, C. (2014). A longitudinal follow-up study of affect in children and adults with Cornelia de Lange syndrome. *American Journal on Intellectual and Developmental Disabilities*, *119*(3), 235–252. https://doi.org/10.1352/1944-7558-119.3.235

Ng, F., Berk, M., Dean, O., & Bush, A. I. (2008). Oxidative stress in psychiatric disorders: Evidence base and therapeutic implications. *The International Journal of Neuropsychopharmacology*, *11*(6), 851–876. https://doi.org/10.1017/S1461145707008401

Olioso, G., Passarini, A., Atzeri, F., Milani, D., Cereda, A., Cerutti, M., Maitz, S., Menni, F., & Selicorni, A. (2009). Clinical problems and everyday abilities of a group of Italian adolescents and young adults with Cornelia de Lange syndrome. *American Journal of Medical Genetics Part A*, *149*(11), 2532–2537. https://doi.org/10.1002/ajmg.a.33075

Oliver, C., Berg, K., Moss, J., Arron, K., & Burbidge, C. (2011). Delineation of behavioral phenotypes in genetic syndromes: Characteristics of autism spectrum disorder, affect and hyperactivity. *Journal of Autism and Developmental Disorders*, *41*(8), 1019–1032. https://doi.org/10.1007/s10803-010-1125-5

Reynolds, A., Laurie, C., Mosley, R. L., & Gendelman, H. E. (2007). Oxidative stress and the pathogenesis of neurodegenerative disorders. *International Review of Neurobiology*, *82*, 297–325. https://doi.org/10.1016/S0074-7742(07)82016-2

Richards, C., Moss, J., O'Farrell, L., Kaur, G., & Oliver, C. (2009). Social anxiety in Cornelia de Lange syndrome. *Journal of Autism and Developmental Disorders*, *39*(8), 1155–1162. https://doi.org/10.1007/s10803-009-0730-7

Roid, G. H., & Miller, L. J. (1997). *Leiter international performance scale-revised (Leiter-R)*. Stoelting.

Salim, S. (2014). Oxidative stress and psychological disorders. *Current Neuropharmacology*, *12*(2), 140–147.

Sarimski, K. (1997). Communication, social-emotional development and parenting stress in Cornelia-de-Lange syndrome. *Journal of Intellectual Disability Research*, *41*(1), 70–75. https://doi.org/10.1111/j.1365-2788.1997.tb00678.x

Sarogni, P., Pallotta, M. M., & Musio, A. (2020). Cornelia de Lange syndrome: From molecular diagnosis to therapeutic approach. *Journal of Medical Genetics*, *57*(5), 289–295. https://doi.org/10.1136/jmedgenet-2019-106277

Schopler, E., Reichler, R. J., & Renner, B. R. (1988). *The childhood autism rating scale (CARS)*. Western Psychological Services.

Schopler, E., Wellman, G. J., & Love, S. R. (2010). *Childhood autism rating scale* (2nd ed.). Western Psychological Services.

Spena, S., Milani, D., Rusconi, D., Negri, G., Colapietro, P., Elcioglu, N., Bedeschi, F., Pilotta, A., Spaccini, L., Ficcadenti, A., Magnani, C., Scarano, G., Selicorni, A., Larizza, L., & Gervasini, C. (2015). Insights into genotype–phenotype correlations from CREBBP point mutation screening in a cohort of 46 Rubinstein–Taybi syndrome patients. *Clinical Genetics*, *88*(5), 431–440. https://doi.org/10.1111/cge.12537

Srivastava, S., Landy-Schmitt, C., Clark, B., Kline, A. D., Specht, M., & Grados, M. A. (2014). Autism traits in children and adolescents with Cornelia de Lange syndrome. *American Journal of Medical Genetics Part A*, *164*(6), 1400–1410. https://doi.org/10.1002/ajmg.a.36573

Stevens, C. A., Carey, J. C., & Blackburn, B. L. (1990). Rubinstein-Taybi syndrome: A natural history study. *American Journal of Medical Genetics*, *37*(6), 30–37. https://doi.org/10.1002/ajmg.1320370605

Stevens, C. A., Pouncey, J., & Knowles, D. (2011). Adults with Rubinstein–Taybi syndrome. *American Journal of Medical Genetics Part A*, *155*(7), 1680–1684. https://doi.org/10.1002/ajmg.a.34058

Van Gils, J., Magdinier, F., Fergelot, P., & Lacombe, D. (2021). Rubinstein-Taybi syndrome: A model of epigenetic disorder. *Genes*, *12*(7), 968. https://doi.org/10.3390/genes12070968

Van Schooneveld, M. M. J., & Braun, K. P. J. (2013). Cognitive outcome after epilepsy surgery in children. *Brain and Development*, *35*(8), 721–729. https://doi.org/10.1016/j.braindev.2013.01.011

Waite, J., Beck, S. R., Heald, M., Powis, L., & Oliver, C. (2016). Dissociation of cross-sectional trajectories for verbal and visuo-spatial working memory development in Rubinstein-Taybi syndrome. *Journal of Autism and Developmental Disorders*, *46*(6), 2064–2071. https://doi.org/10.1007/s10803-016-2736-2

Waite, J., Moss, J., Beck, S. R., Richards, C., Nelson, L., Arron, K., Burbidge, C., Berg, K., & Oliver, C. (2015). Repetitive behavior in Rubinstein–Taybi syndrome: Parallels with autism Spectrum phenomenology. *Journal of Autism and Developmental Disorders*, *45*(5), 1238–1253. https://doi.org/10.1007/s10803-014-2283-7

Yagihashi, T., Kosaki, K., Okamoto, N., Mizuno, S., Kurosawa, K., Takahashi, T., Sato, Y., & Kosaki, R. (2012). Age-dependent change in behavioral features in Rubinstein-Taybi syndrome. *Congenital Anomalies*, *52*(2), 82–86. https://doi.org/10.1111/j.1741-4520.2012.00356.x

Yuen, K. K. (1974). The two-sample trimmed t for unequal population variances. *Biometrika*, *61*(1), 165–170. https://doi.org/10.1093/biomet/61.1.165

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