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Abbreviations:
3q29del: 3q29 deletion syndrome; ADHD: attention deficit/hyperactivity disorder; ASD: autism spectrum disorder; BRIEF: Behavior Rating Inventory of Executive function; EF: executive function; eICV: estimated intracranial volume; GEC: global executive composite; ID: intellectual disability; MRI: magnetic resonance imaging; PFAC/MCM: posterior fossa arachnoid cysts and mega cisterna magna; ROC: receiver operating characteristic; SIPS: Structured Interview for Psychosis-Risk Syndromes; SZ: schizophrenia spectrum disorder; Vineland-3: Vineland Adaptive Behavior Scales, Third Edition, Comprehensive Parent/Caregiver Form

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Beyond IQ: executive function deficits and their relation to functional, clinical, and neuroimaging outcomes in 3q29 deletion syndrome

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Abstract

Background. 3q29 deletion syndrome (3q29del) is a rare (~1:30 000) genomic disorder associated with a wide array of neurodevelopmental and psychiatric phenotypes. Prior work by our team identified clinically significant executive function (EF) deficits in 47% of individuals with 3q29del; however, the nuances of EF in this population have not been described.

Methods. We used the Behavior Rating Inventory of Executive Function (BRIEF) to perform the first in-depth assessment of real-world EF in a cohort of 32 individuals with 3q29del (62.5% male, mean age = 14.5 ± 8.3 years). All participants were also evaluated with gold-standard neuropsychiatric and cognitive assessments. High-resolution structural magnetic resonance imaging was performed on a subset of participants ($n = 24$).

Results. We found global deficits in EF; individuals with 3q29del scored higher than the population mean on the BRIEF global executive composite (GEC) and all subscales. In total, 81.3% of study subjects ($n = 26$) scored in the clinical range on at least one BRIEF subscale. BRIEF GEC T scores were higher among 3q29del participants with a diagnosis of attention deficit/hyperactivity disorder (ADHD), and BRIEF GEC T scores were associated with schizophrenia spectrum symptoms as measured by the Structured Interview for Psychosis-Risk Syndromes. BRIEF GEC T scores were not associated with cognitive ability. The BRIEF-2 ADHD form accurately (sensitivity = 86.7%) classified individuals with 3q29del based on ADHD diagnosis status. BRIEF GEC T scores were correlated with cerebellar white matter and subregional cerebellar cortex volumes.

Conclusions. Together, these data expand our understanding of the phenotypic spectrum of 3q29del and identify EF as a core feature linked to both psychiatric and neuroanatomical features of the syndrome.

Introduction

3q29 deletion syndrome (3q29del) is a rare (1:30 000) (Kendall et al., 2017; Stefansson et al., 2014) genomic disorder caused by the 1.6 Mb recurrent, typically *de novo* 3q29 deletion (hg19, chr3:195725000–197350000) (Ballif et al., 2008; Glassford, Rosenfeld, Freedman, Zwick, & Mulle, 2016; Willatt et al., 2005). The clinical phenotype of 3q29del is heterogeneous, ranging from mild to moderate intellectual disability (ID) (Ballif et al., 2008; Cox & Butler, 2015; Glassford et al., 2016; Klaiman et al., 2022; Sanchez Russo et al., 2021; Willatt et al., 2005) to a 19-fold increased risk for autism spectrum disorder (ASD) (Itsara et al., 2009; Pollak et al., 2019; Sanders et al., 2015) and a greater than 40-fold increased risk for schizophrenia spectrum

disorders (SZ) (Kirov et al., 2012; Marshall et al., 2017; Mulle, 2015; Mulle et al., 2010; Szatkiewicz et al., 2014). Recent work by our team has uncovered additional phenotypes associated with 3q29del, including attention deficit/hyperactivity disorder (ADHD) and graphomotor weakness (Klaiman et al., 2022; Pollak et al., 2023b; Sanchez Russo et al., 2021). Further, 47% of study participants were found to have clinically significant executive function (EF) deficits (Klaiman et al., 2022; Sanchez Russo et al., 2021). However, our understanding of the nuances of these phenotypes, including EF, is still evolving.

EF refers to the constellation of higher-order cognitive processes that control and coordinate purposeful goal-directed behaviors (Baggetta & Alexander, 2016; Best & Miller, 2010; Miller & Wallis, 2009). It is generally agreed that EF is comprised of three core components: inhibitory control, working memory, and cognitive flexibility (Baggetta & Alexander, 2016; Best & Miller, 2010; Miller & Wallis, 2009). These foundational functions are moderately intercorrelated yet separable, they can be differentially affected in different patient populations, and they serve as the basis for more complex cognitive constructs, such as planning, problem solving, and abstract reasoning (Diamond, 2013; Miyake et al., 2000). EF allows an individual to integrate information about their goals with sensory input to guide actions in an adaptive and dynamic manner, in accordance with the demands of the present context. EF deficits can have an adverse impact on academic and occupational achievement, mood regulation, and social function (Baggetta & Alexander, 2016; Best & Miller, 2010; Miller & Wallis, 2009). Studies have identified EF deficits in individuals with ADHD (Biederman et al., 2004; Brown, 2009; Marije Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Martel, Nikolas, & Nigg, 2007) and SZ (Kraepelin, 1913; Lysaker et al., 2008; Orellana & Slachevsky, 2013; Pickup, 2008; Velligan & Bow-Thomas, 1999; Wobrock et al., 2009), as well as genomic disorders with phenotypic similarities to 3q29del, including 22q11.2 deletion syndrome (Albert, Abu-Ramadan, Kates, Fremont, & Antshel, 2018; Everaert et al., 2023; Gur et al., 2023; O'Hora et al., 2023). Notably, EF ability has been shown to associate with later-onset phenotypes in children with 22q11.2 deletion syndrome (Albert et al., 2018), highlighting the importance of understanding EF and its links to neurodevelopmental and psychiatric phenotypes, as well as its potential as an early treatment target with promising benefits for both childhood and adult outcomes.

The prefrontal cortex has canonically been associated with EF; however, it is now clear that these processes rely on distributed neural networks and emerging evidence points to a pivotal role for the cerebellum. Convergent evidence from neuropsychological testing, neuroimaging, humans with focal brain damage, and non-human animal studies have identified the cerebellum as a critical brain region for higher-order cognitive processing, including EF (Bellebaum & Daum, 2007; Deverett, Koay, Oostland, & Wang, 2018; Koziol, Budding, & Chidekel, 2012; Schmahmann, 2019; Schmahmann & Sherman, 1998). Notably, neuroimaging studies by our team have identified a particularly high frequency of structural anomalies in the posterior fossa of individuals with 3q29del, surpassing the combined occurrence of radiological anomalies found in all other brain regions; for example, more than 60% of 3q29del study participants have cerebellar hypoplasia and/or cystic or cyst-like malformations around the cerebellum, and both cerebellar cortex and white matter show significant volumetric differences compared to typically developing controls (Sanchez Russo et al., 2021; Sefik et al., 2024). These cerebellar abnormalities, coupled with the increased rate of EF deficits identified in individuals with 3q29del, highlight the importance of understanding this complex cognitive phenotype and its relationship with neurodevelopmental and psychiatric morbidity in 3q29del.

The present study is the first detailed description of EF abilities assessed in individuals with 3q29del. We define the profile of EF and we explore the relationship between EF and general cognitive ability, neurodevelopmental and psychiatric phenotypes, and cerebellar volume. This study is an important contribution to our evolving understanding of 3q29del; EF sits at the nexus of multiple neurodevelopmental and psychiatric phenotypes associated with 3q29del and may help to explain some of the underlying mechanisms contributing to the substantial psychiatric multimorbidity experienced by this population. The results from this study will help to guide future research to further explore EF in this population, as well as targeted interventions to improve EF abilities in individuals with 3q29del.

Methods

See online Supplementary information for detailed methods.

Study participants

Individuals with 3q29del were recruited from the online 3q29 registry (3q29deletion.org) for 2 days of in-person deep phenotyping, as previously described (Klaiman et al., 2022; Murphy et al., 2018; Sanchez Russo et al., 2021). Informed consent was provided by all participants over 18 years of age; for participants under 18 years of age, a parent or guardian provided informed consent and the study participant provided informed assent. In total, 32 individuals with 3q29del (62.5% male) were included in the present study. Study participants ranged in age from 4.85 to 39.12 years (mean = 14.5 ± 8.3 years). See Table 1 for a description of the study sample. This study was approved by Emory University's Institutional Review Board (IRB00064133) and Rutgers University's Institutional Review Board (PRO2021001360).

Measures

The measures used in this study were as previously described (Klaiman et al., 2022; Murphy et al., 2018; Sanchez Russo et al.,

Table 1. Demographic information for study participants with 3q29del ($n = 32$)

	Mean ± s.d.	Range
Age (years)	14.50 ± 8.26	4.85–39.12
Composite IQ	73.03 ± 14.18	40–99
	N	%
Sex		
Male	20	62.50
Female	12	37.50
Race		
White	29	90.63
More than one race	3	9.37
Ethnicity		
Hispanic/Latino	1	3.13
Not Hispanic/Latino	31	96.87

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2021). Briefly, EF was assessed using the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2), for participants 18 years of age and younger ($n = 26$) or the Behavior Rating Inventory of Executive Function for Adults (BRIEF-A) for participants over 18 years of age ($n = 6$) (Gioia, Isquith, Guy, & Kenworthy, 2015; Roth & Gioia, 2005). General cognitive ability was evaluated using the Differential Ability Scales, Second Edition (Elliott, Murray, & Pearson, 1990), for individuals under 18 years of age ($n = 24$) or the Wechsler Abbreviated Scale of Intelligence, Second Edition (Wechsler, 1999), for individuals 18 years of age and older ($n = 8$). Adaptive behavior was assessed using the Vineland Adaptive Behavior Scales, Third Edition, Comprehensive Parent/Caregiver Form (Vineland-3) (Sparrow, Cicchetti, & Saulnier, 2016). Psychosis symptoms were assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS) by trained personnel for individuals 8 years of age and older ($n = 23$) (Miller et al., 2003). Individual SIPS items are grouped within major symptom domains (positive, negative, and disorganization), and each item is rated on a scale from 0 (Absent) to 6 (Severe and Psychotic for positive symptoms, Extreme for others), with a rating of 3 (Moderate) indicating clinical significance. Item ratings were summed to produce a total score for each domain. Individuals exhibiting clinically significant attenuated positive symptoms (i.e. at least one positive symptom rated $\geqslant 3$) were considered to meet criteria for psychosis prodrome. Graphomotor abilities were assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI-6) (Beery & Beery, 2010). Clinically significant graphomotor weakness was defined as a standard score >2 S.D. below the expected mean. Diagnoses of neurodevelopmental and psychiatric phenotypes, including SZ and other psychotic disorders, were reached using gold-standard evaluations and clinician best estimate diagnosis (American Psychiatric Association & American Psychiatric Association, 2013). Our prior investigations of 3q29del have revealed only minor morbidity associated with somatic conditions; the majority of disability in this population is due to neurodevelopmental and psychiatric illness (Sanchez Russo et al., 2021). We have previously defined a set of neurodevelopmental and psychiatric conditions with increased prevalence in 3q29del (online Supplementary Table S1). Multimorbidity was therefore defined as the total number of these neurodevelopmental and psychiatric conditions, with a current diagnosis as established by our expert clinicians at the time of the study visit.

Neuroimaging

High-resolution structural magnetic resonance imaging (MRI) data were collected and processed as previously described (Sanchez Russo et al., 2021; Sefik et al., 2024).

Analysis

All analyses were performed in R version 4.0.4 (R Core Team, 2008). Due to the small sample size, most analyses were considered exploratory and unadjusted p values were reported. Statistical analysis was performed using simple linear models and one-sided, one-sample Student's t-tests implemented using the stats R package (R Core Team, 2008). p Values for simple linear models were calculated using robust standard errors via the sandwich and lmtest R packages (Hothorn et al., 2015; Zeileis, Lumley, Berger, Graham, & Zeileis, 2019). All models were adjusted for age and sex. For neuroimaging data, multiple linear regression models were constructed adjusting for age and sex; for models where there was a significant relationship with the absolute brain region volume, models were re-run adjusting for age, sex, and estimated total intracranial volume (eICV) to test for regional specificity beyond the influence of global variability in head size. Receiver operating characteristic (ROC) curves were constructed using the ROCit R package (Khan & Brandenburger, 2020). Data visualization was performed using the plotly R package (Sievert et al., 2017).

Results

Global EF deficits in 3q29del

Higher scores on the BRIEF indicate worse EF; a T score of 70 or higher indicates a clinically significant deficit. To account for developmentally appropriate changes in EF abilities over the lifespan (Anderson, 2002), BRIEF T scores are age-normed. On average, study participants with 3q29del scored nominally higher than the population mean T score of 50 on the Global Executive Composite (GEC) (mean = 67.8 ± 10.7, $p < 0.001$) and across all subscales (all $p < 0.001$, Fig. 1a, online Supplementary Table S3). There were no differences between males and females with 3q29del across all domains of the BRIEF (online Supplementary Fig. S1). In total, 15 study participants with 3q29del (46.9%) scored above the clinical threshold of 70 on the GEC, indicating clinically significant EF deficits. Of the nine subscales, study participants with 3q29del showed the most impairment on the Shift subscale (mean = 69.2 ± 12.5), and the least impairment on the Organization of Materials subscale (mean = 60.1 ± 11.6, Fig. 1a, online Supplementary Table S3). Study participants with 3q29del demonstrated a range of impairments across BRIEF subscales; six participants (18.8%) did not score above the clinical threshold on any subscales, while two participants (6.3%) scored above the clinical threshold on all nine subscales (Fig. 1b). A majority of study participants with 3q29del ($n = 22$, 68.8%) scored above the clinical threshold on two or more subscales and 81.3% of study participants with 3q29del ($n = 26$) scored above the clinical threshold on at least one subscale (Fig. 1b), further emphasizing the substantial burden of executive dysfunction in this population. Together, these data demonstrate significant adverse impacts to EF abilities in individuals with 3q29del.

EF is orthogonal to cognitive ability in 3q29del

The 3q29 deletion is commonly associated with mild-to-moderate ID (Ballif et al., 2008; Cox & Butler, 2015; Glassford et al., 2016; Willatt et al., 2005); in the present study, the mean composite IQ in study participants with 3q29del was 73.03 ± 14.18, as previously reported (Klaiman et al., 2022; Sanchez Russo et al., 2021). However, there was substantial variability in IQ across study participants, ranging from moderate ID to normal cognitive ability (range = 40–99) (Klaiman et al., 2022; Sanchez Russo et al., 2021). We sought to determine whether variation in EF is correlated with variability in cognitive ability in our study participants. There was no relationship between BRIEF GEC T scores and composite ($r^2 = -0.01$, $p = 0.4$), non-verbal ($r^2 = 0.04$, $p = 0.15$), or verbal IQ ($r^2 = -0.03$, $p = 0.9$; Fig. 2a–c). Together, these data demonstrate that EF is orthogonal to cognitive ability in individuals with 3q29del, and that poor performance on the BRIEF is not an artifact of diminished cognitive ability in our study population.

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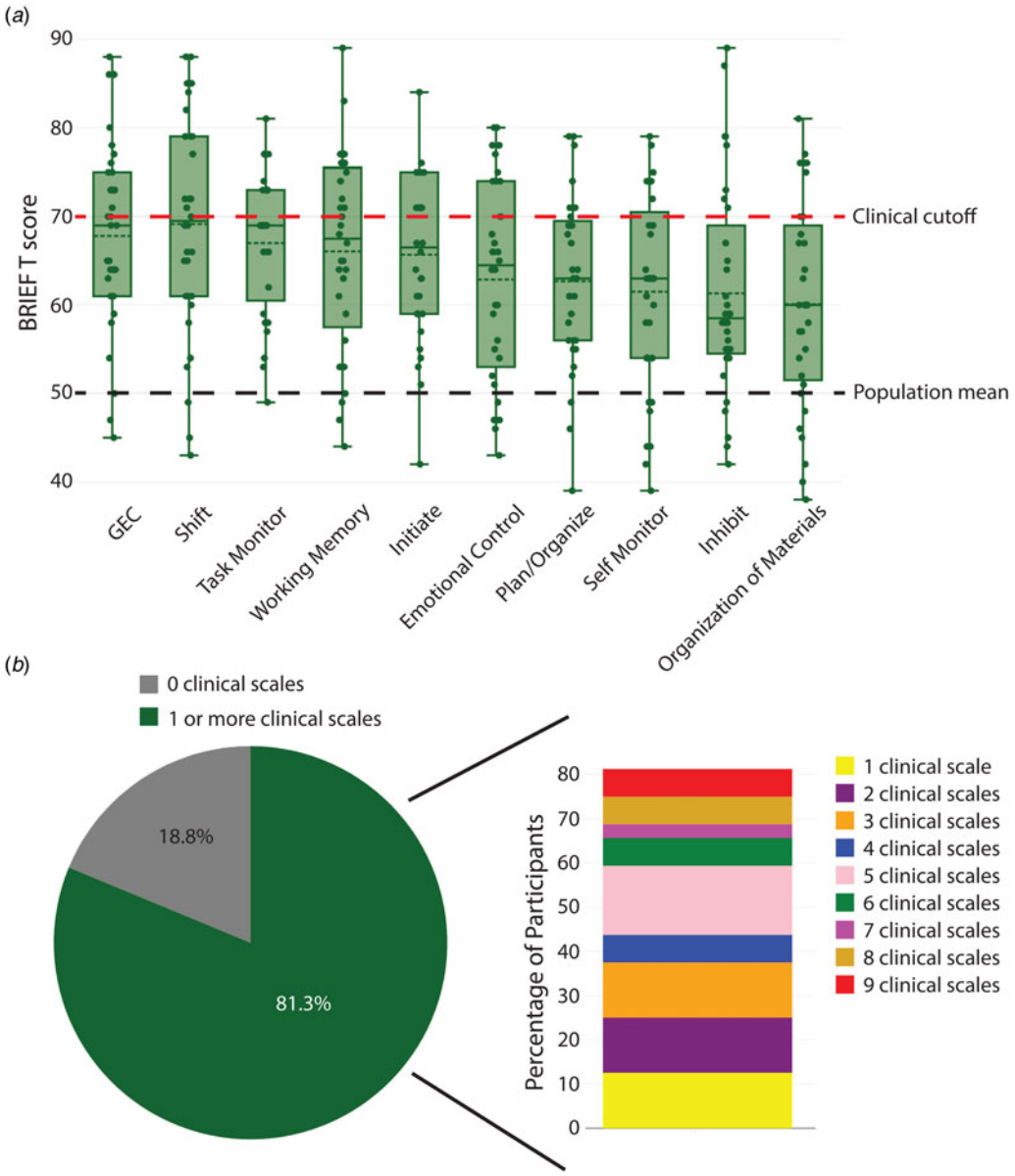

Figure 1. (a) Distribution of *T* scores on the BRIEF GEC and BRIEF subscales for study participants with 3q29del ($n = 32$). The black dashed line indicates the population mean; the red dashed line indicates the clinical cutoff. Subscales are ordered left to right by decreasing mean severity. (b) Pie chart showing the proportion of study participants with 3q29del ($n = 32$) scoring in the clinical range (*T* scores $\geqslant 70$) on one or more BRIEF scales, expanded to show the proportion of participants scoring in the clinical range on 1 to 9 BRIEF scales. 3q29del, 3q29 deletion syndrome; BRIEF, Behavior Rating Inventory of Executive Function; GEC, global executive composite.

EF is correlated with psychosis spectrum symptoms

The 3q29 deletion is the largest known genetic risk factor for SZ (Mulle, 2015; Mulle et al., 2010; Singh et al., 2022); EF deficits have a well-established association with SZ (Kraepelin, 1913; Lysaker et al., 2008; Orellana & Slachevsky, 2013; Pickup, 2008; Velligan & Bow-Thomas, 1999; Wobrock et al., 2009). We sought to define the relationship between EF and psychosis spectrum symptoms in our study population. We found nominally significant positive correlations between the BRIEF GEC and positive and disorganization symptoms endorsed on the SIPS (Fig. 2d–f), indicating that individuals with 3q29del and poorer EF experience more severe psychosis spectrum symptoms on average. The strongest correlation was between the BRIEF GEC and the SIPS disorganization symptom dimension ($r^2 = 0.18$, $p = 0.02$; Fig. 2f). There was a weak relationship between the BRIEF GEC and the SIPS positive symptom dimension ($r^2 = 0.06$, $p = 0.03$; Fig. 2d). There was no relationship between the BRIEF GEC and the SIPS negative symptom dimension ($r^2 = -0.008$, $p = 0.4$; Fig. 2e). These data show that EF deficits are nominally significantly associated with the severity of two major dimensions of psychosis spectrum symptoms in individuals with 3q29del.

Psychiatric and neurodevelopmental multimorbidity is associated with EF deficits

Individuals with 3q29del are at increased liability for a wide range of neurodevelopmental and psychiatric phenotypes, including

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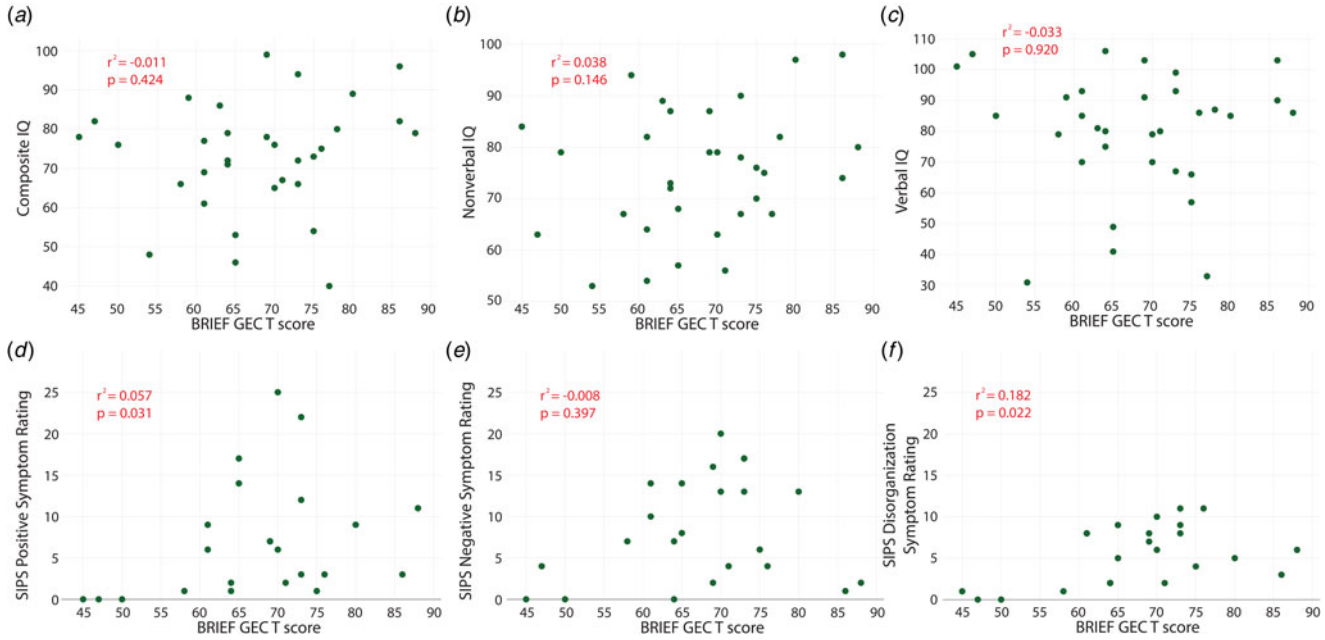

Figure 2. (a) Correlation between BRIEF GEC *T* scores and composite IQ for study participants with 3q29del ($n = 32$). (b) Correlation between BRIEF GEC *T* scores and non-verbal IQ for study participants with 3q29del ($n = 32$). (c) Correlation between BRIEF GEC *T* scores and verbal IQ for study participants with 3q29del ($n = 32$). (d) Correlation between BRIEF GEC *T* scores and SIPS Positive Symptom Ratings for study participants with 3q29del ($n = 23$). (e) Correlation between BRIEF GEC *T* scores and SIPS Negative Symptom Ratings for study participants with 3q29del ($n = 23$). (f) Correlation between BRIEF GEC *T* scores and SIPS Disorganization Symptom Ratings for study participants with 3q29del ($n = 23$). 3q29del, 3q29 deletion syndrome; BRIEF, Behavior Rating Inventory of Executive Function; GEC, global executive composite; SIPS, Structured Interview for Psychosis-Risk Syndromes.

ASD, anxiety disorder, ADHD, and SZ (Ballif et al., 2008; Cox & Butler, 2015; Glassford et al., 2016; Itsara et al., 2009; Kirov et al., 2012; Klaiman et al., 2022; Marshall et al., 2017; Mulle, 2015; Mulle et al., 2010; Pollak et al., 2019; Sanchez Russo et al., 2021; Sanders et al., 2015; Szatkiewicz et al., 2014; Willatt et al., 2005). In the general population, ADHD and SZ are both associated with poorer EF (Biederman et al., 2004; Brown, 2009; Kraepelin, 1913; Lysaker et al., 2008; Marije Boonstra et al., 2005; Martel et al., 2007; Orellana & Slachevsky, 2013; Pickup, 2008; Velligan & Bow-Thomas, 1999; Wobrock et al., 2009). To determine whether any individual neurodevelopmental or psychiatric diagnosis was associated with EF in our study population, we compared the BRIEF GEC *T* scores for individuals with 3q29del with and without ASD, SZ prodrome/psychosis, ADHD, anxiety disorders, graphomotor weakness, ID, and enuresis (Fig. 3a). We found that individuals with 3q29del and a diagnosis of ADHD have nominally significantly worse EF relative to individuals with 3q29del without ADHD (ADHD mean = 72.8 ± 8.06, no ADHD mean = 59.5 ± 9.4, $p = 3.08 \times 10^{-8}$; Fig. 3a); there were no other relationships. These data demonstrate that the relationship between EF and ADHD phenotypes is present in individuals with 3q29del.

Prior work by our team has identified neurodevelopmental and psychiatric multimorbidity as a hallmark feature of 3q29del (Pollak et al., 2023a; Sanchez Russo et al., 2021); we found that increasing degrees of multimorbidity, rather than individual neurodevelopmental or psychiatric diagnoses, is significantly associated with poorer adaptive function in this population (Pollak et al., 2023a). We sought to determine whether there is a similar relationship between EF and multimorbidity in our study population. We found that BRIEF GEC *T* scores are correlated with multimorbidity, where increasing multimorbidity is nominally significantly associated with poorer EF ($p = 0.04$; Fig. 3b). Together, these data emphasize the central nature of neurodevelopmental and psychiatric multimorbidity to the 3q29del phenotype, and show that multimorbidity, rather than individual neurodevelopmental or psychiatric diagnoses, has a stronger relationship with EF in individuals with 3q29del.

BRIEF-2 is an accurate screener for ADHD in individuals with 3q29del

Screening tools are valuable instruments that can be used to prioritize individuals for diagnostic evaluations or to identify subpopulations for future studies. In the case of 3q29del, identifying effective screening tools for specific neurodevelopmental or psychiatric phenotypes will help to ensure that the highest-risk individuals will receive critical diagnostic evaluations as early as possible, while simultaneously reducing the burden of multidisorder diagnostic batteries on caregivers and the healthcare system. Our team has identified ADHD as one of the most common psychiatric diagnoses in individuals with 3q29del, with 63% of individuals with 3q29del qualifying for a diagnosis of ADHD in a recent study (Sanchez Russo et al., 2021). ADHD is intimately linked to EF (Biederman et al., 2004; Brown, 2009; Marije Boonstra et al., 2005; Martel et al., 2007); here, we sought to determine whether the BRIEF-2 ADHD form is an accurate screening tool for ADHD in children with 3q29del ($n = 26$). We found that the BRIEF-2 ADHD form had a sensitivity rate of 86.7%, indicating that 13.3% of individuals with ADHD did *not* screen positive on the ADHD form ($n = 2$), and a specificity rate of 60.0%, indicating that 40.0% of individuals that screened positive did not have an ADHD diagnosis ($n = 4$) (Fig. 3c). The BRIEF-2 ADHD form is a more sensitive screener for ADHD in

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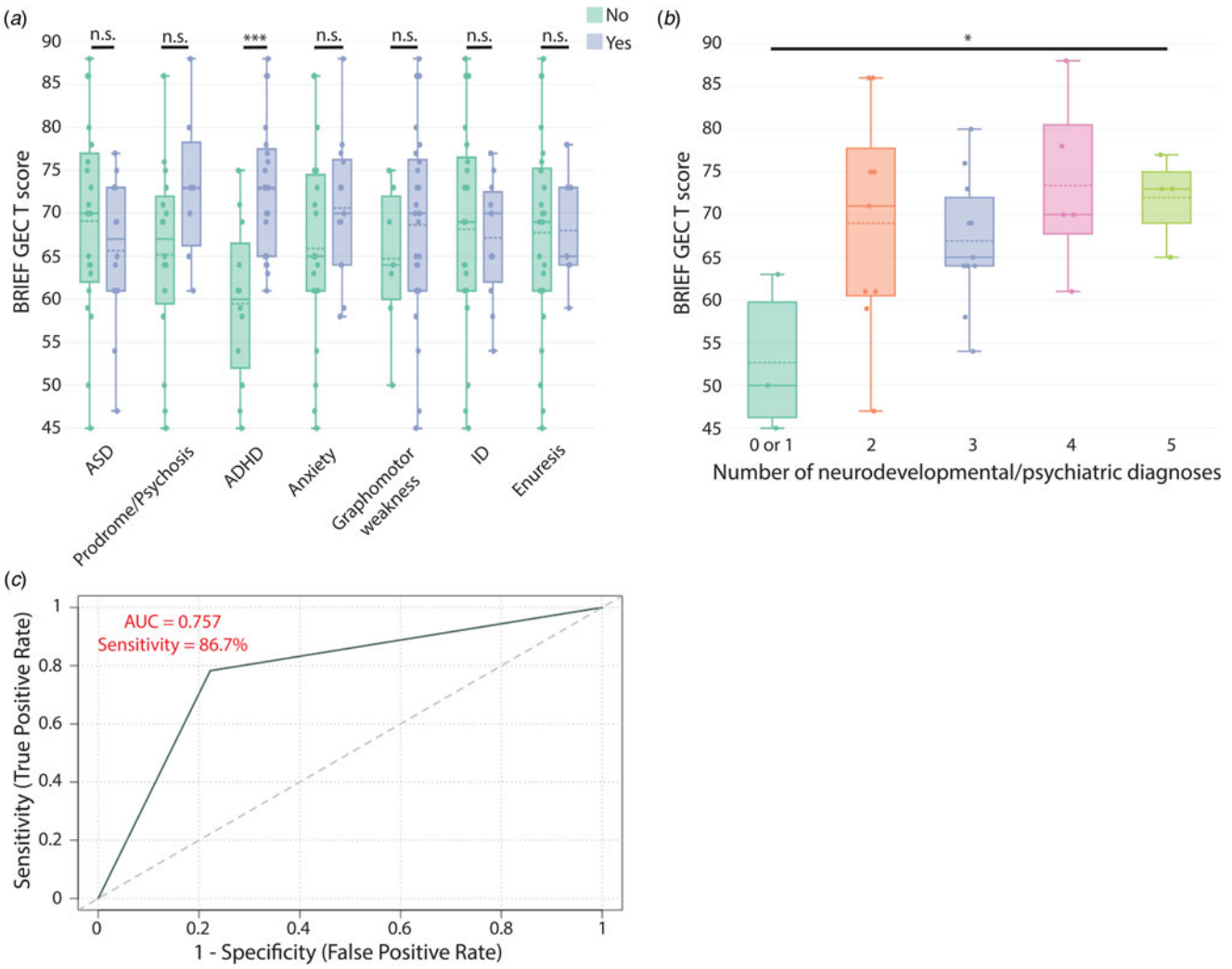

Figure 3. (a) Distribution of BRIEF GEC *T* scores for study participants with 3q29del ($n = 32$) with and without specific neurodevelopmental or psychiatric diagnoses. (b) Distribution of BRIEF GEC *T* scores for study participants with 3q29del ($n = 32$) with an increasing number of multimorbid neurodevelopmental and psychiatric diagnoses. (c) Receiver operating characteristic curve showing the ability of the BRIEF-2 ADHD form to correctly classify study participants with 3q29del ($n = 26$) with and without a diagnosis of ADHD. 3q29del, 3q29 deletion syndrome; BRIEF, Behavior Rating Inventory of Executive Function; GEC, global executive composite; ADHD, attention-deficit/hyperactivity disorder.

individuals with 3q29del than the Achenbach Child Behavior Checklist DSM-keyed Attention-deficit/hyperactivity problems scale (Pollak, Mortillo, Murphy, & Mulle, 2024), which had a sensitivity of 72.2% and a specificity of 81.8%. Together, these data show that the BRIEF-2 ADHD form can be a useful screening tool for ADHD in children with 3q29del.

EF ability is associated with cerebellar volumetric changes

While the prefrontal cortex has long been considered the locus of EF, emerging evidence highlights the cerebellum's contribution to higher-order cognition (Bellebaum & Daum, 2007; Koziol et al., 2012; Schmahmann, 2019; Schmahmann & Sherman, 1998). Work by our team has identified significant cerebellar abnormalities associated with 3q29del; for example, over 60% of 3q29del individuals show cerebellar hypoplasia (Sanchez Russo et al., 2021; Sefik et al., 2024). We sought to determine whether cerebellar anomalies are associated with EF abilities in individuals with 3q29del. There was no relationship between BRIEF GEC *T* scores and total cerebellar volume ($r^2 = -0.05$, $p = 0.82$; Fig. 4b). There was a nominally significant relationship between BRIEF GEC *T* scores and cerebellar white matter volume, where worse EF is associated with *increased* cerebellar white matter volume ($r^2 = 0.35$, $p = 8.11 \times 10^{-4}$; Fig. 4c); this relationship persisted after adjusting for eICV ($r^2 = 0.35$, $p = 7.72 \times 10^{-4}$). There was a nominally significant relationship between BRIEF GEC *T* scores and cerebellar cortical volume, where worse EF is associated with *decreased* cerebellar cortical volume ($r^2 = 0.05$, $p = 0.04$; Fig. 4d); however, this relationship did not persist after adjusting for eICV ($r^2 = 0.02$, $p = 0.1$). In a prior study our team identified an increased prevalence of posterior fossa arachnoid cysts and mega cisterna magna (PFAC/MCM) in individuals with 3q29del (Sanchez Russo et al., 2021; Sefik et al., 2024); however, BRIEF GEC *T* scores were not significantly different between individuals with 3q29del with and without PFAC/MCM (PFAC/MCM mean = 66.23 ± 9.19, no PFAC/MCM mean = 67.09 ± 11.77, $p = 0.65$; online Supplementary Fig. S2A).

To further explore the putative relationship between EF and cerebellar cortical volume in study subjects with 3q29del, we analyzed the relationship between BRIEF GEC *T* scores and cerebellar

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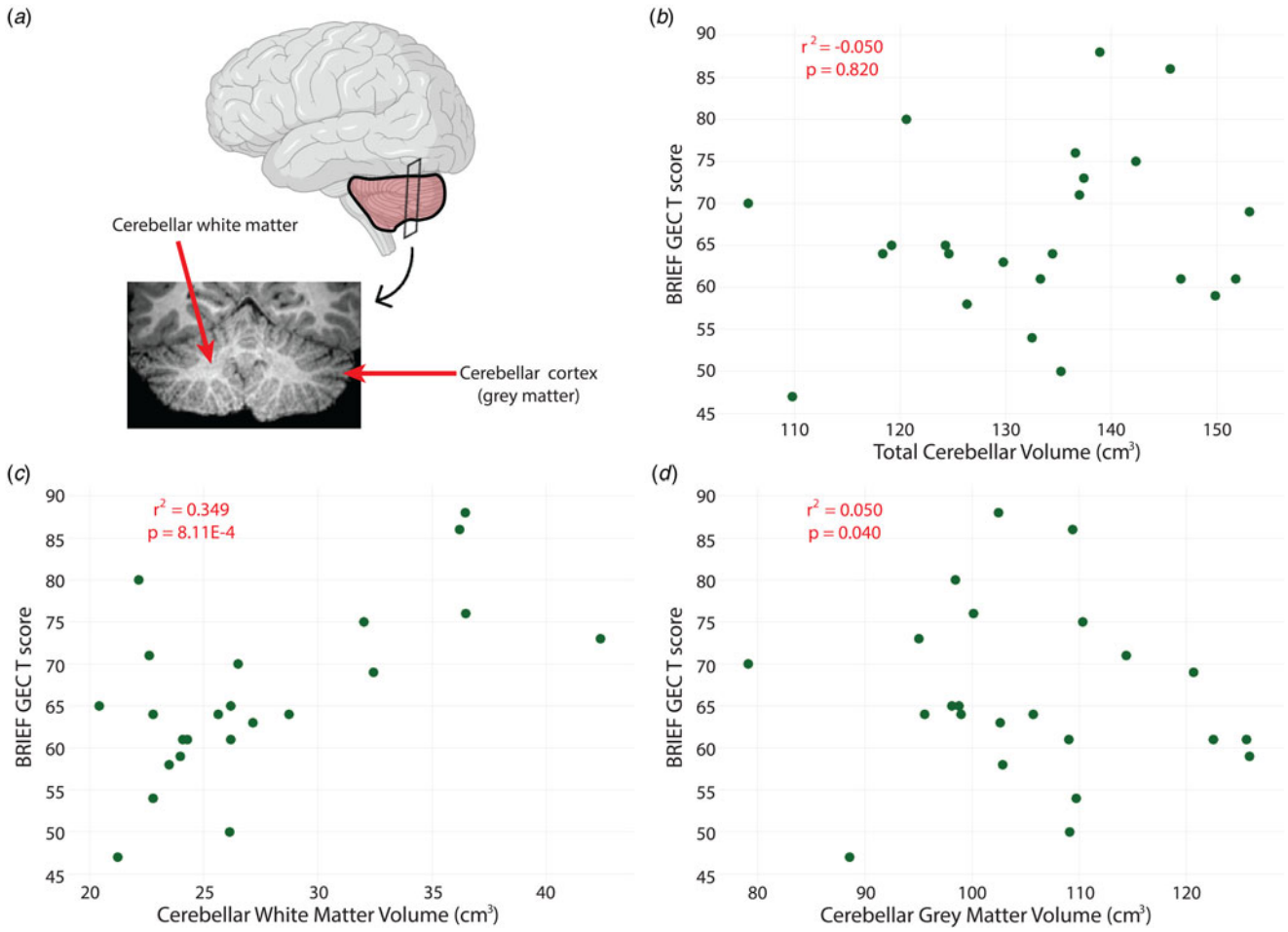

Figure 4. (a) Diagram illustrating the cerebellum with a representative coronal image from a *T*1-weighted MRI showing cerebellar white matter and cerebellar cortex. (b) Correlation between BRIEF GEC *T* scores and total cerebellar volume for study participants with 3q29del ($n = 23$). (c) Correlation between BRIEF GEC *T* scores and cerebellar white matter volume for study participants with 3q29del ($n = 23$). (d) Correlation between BRIEF GEC *T* scores and cerebellar cortical (grey matter) volume for study participants with 3q29del ($n = 23$). 3q29del, 3q29 deletion syndrome; BRIEF, Behavior Rating Inventory of Executive Function; GEC, global executive composite.

cortex subregional volumes (online Supplementary Fig. S2B–R). There were no significant relationships between BRIEF GEC *T* scores and any subregions of the anterior lobe of the cerebellar cortex (online Supplementary Fig. S2C and D). Within the vermis, posterior lobe, and flocculonodular lobe of the cerebellar cortex, specific subregions were nominally significantly associated with BRIEF GEC *T* scores. In general, increased volume of the subregion was associated with worse EF. The following regions showed nominally significant relationships with BRIEF GEC *T* scores that persisted after adjusting for eICV: left cerebellar hemisphere lobule VI volume (unadjusted $r^2 = 0.072$, $p = 0.037$; adjusted $r^2 = 0.13$, $p = 0.04$; online Supplementary Fig. S2F); right cerebellar hemisphere lobule VIII volume (unadjusted $r^2 = 0.13$, $p = 0.04$; adjusted $r^2 = 0.15$, $p = 0.04$; online Supplementary Fig. S2N); and left cerebellar hemisphere lobule IX volume (unadjusted $r^2 = 0.12$, $p = 0.03$; adjusted $r^2 = 0.15$, $p = 0.03$; online Supplementary Fig. S2O). There were two regions that had a nominally significant relationship with BRIEF GEC *T* scores that did not persist after adjusting for eICV: cerebellar vermis VI–VII volume (unadjusted $r^2 = 0.12$, $p = 0.05$; adjusted $r^2 = 0.15$, $p = 0.06$; online Supplementary Fig. S2E); and right cerebellar hemisphere lobule X volume (unadjusted $r^2 = 0.17$, $p = 0.05$; adjusted $r^2 = 0.19$, $p = 0.06$; online Supplementary Fig. S2R). Together, these data demonstrate a relationship between EF and cerebellar white matter volume in individuals with 3q29del and reveal subregion-specific relationships between EF and cerebellar cortical volume localized mostly to the posterior lobe of the cerebellar cortex, consistent with the presence of a functional topography within the cerebellum (Stoodley & Schmahmann, 2010; Stoodley, Desmond, Guell, & Schmahmann, 2020).

Discussion

The present study is the first detailed description of EF abilities in individuals with 3q29del. We identified global deficits in EF, with elevated mean scores on the BRIEF GEC as well as across all nine BRIEF subscales. The Shift subscale, a measure of cognitive flexibility, showed the highest mean impairment in 3q29del. Individuals with 3q29del and a diagnosis of ADHD had substantially poorer EF relative to individuals with 3q29del without ADHD; poorer EF was also associated with more severe SZ spectrum symptoms as measured by the SIPS. Additionally, the BRIEF-2 ADHD form accurately discriminated between

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individuals with 3q29del with and without a diagnosis of ADHD, highlighting its potential role as a time-efficient screening tool in this population. Neurodevelopmental and psychiatric multimorbidity was associated with EF, with an increasing number of diagnoses corresponding to poorer EF. Furthermore, BRIEF GEC scores showed no correlation with cognitive ability, indicating that mechanisms underlying cognitive ability and everyday EF may be orthogonal in 3q29del, while both factors contribute to adaptive behavior as reported previously (Pollak et al., 2023a). Finally, EF was correlated with volumetric measures of the cerebellum, potentially identifying neuroanatomical changes contributing to EF deficits in this population.

While this is the first description of EF in 3q29del, deficits in EF in this population are not without precedent. Genomic disorders with phenotypic similarities to 3q29del, including 22q11.2 deletion syndrome (Albert et al., 2018; Everaert et al., 2023; Gur et al., 2023; O'Hora et al., 2023), have documented evidence of significant EF deficits. There is a large body of literature surrounding EF abilities in 22q11.2 deletion syndrome specifically; EF deficits in this population have been identified across the lifespan, from preschool-aged children to adults (Albert et al., 2018; Everaert et al., 2023; Gur et al., 2023; O'Hora et al., 2023). Worsening EF is associated with psychosis spectrum symptoms in children with 22q11.2 deletion syndrome (Gur et al., 2023), and measures of childhood EF can predict young adult outcomes in this population, including symptoms of psychosis (Albert et al., 2018). These data are similar to our findings in the present study of individuals with 3q29del and suggest that EF may be a core feature central to understanding the wide neurodevelopmental and psychiatric phenotypic spectrum associated with the 3q29 deletion, including the substantial risk for conversion to psychosis.

In addition to the links between EF and genomic disorders phenotypically similar to 3q29del, EF deficits have also been long associated with idiopathic SZ and ADHD. Indeed, concepts related to EF have been associated with the SZ phenotype since the early 20th century (Kraepelin, 1913); EF deficits are the most common cognitive phenotype in individuals with SZ (Orellana & Slachevsky, 2013; Velligan & Bow-Thomas, 1999; Wobrock et al., 2009). EF deficits are also a core feature of ADHD (Brown, 2009; Silverstein et al., 2020) and are present across the lifespan (Biederman et al., 2004; Marije Boonstra et al., 2005; Martel et al., 2007). Previous research indicates that behavioral scales like the BRIEF can more accurately predict ADHD status and assess different components of EF than performance-based measures (Mahone & Hoffman, 2007; Tan, Delgaty, Steward, & Bunner, 2018; Toplak, Bucciarelli, Jain, & Tannock, 2008). It is important to recognize that both the BRIEF and the diagnostic assessment of ADHD rely on caregiver reports of everyday behaviors, which may lead to overlapping evaluations that could inflate their correlation. However, while there is an intersection between the constructs assessed by the BRIEF and ADHD diagnosis, EF weaknesses are neither necessary nor sufficient to reach a DSM-5 diagnosis in the clinic. Additional performance-based assessments or reports from other sources will be used in the future to provide further evaluation of the relationship between EF difficulties and clinical diagnoses in larger cohorts. We identified a relationship between EF and diagnoses of ADHD, as well as SZ spectrum symptom severity, in our study sample of individuals with 3q29del. EF was nominally significantly associated with both Positive and Disorganized SZ spectrum symptom severity. Some items included in the Disorganized domain of the SIPS are similar to features assessed by the BRIEF, including Trouble with Focus and Attention, and this similarity may be contributing to the nominal association between the BRIEF and the SIPS Disorganized symptom domain. Other Disorganized symptom domain items like Odd Behavior or Appearance and Bizarre Thinking are less entangled with the BRIEF. All items were rated based on their presence and severity and without regard to other comorbidities. Notably, the distinct features measured by the BRIEF and the SIPS Positive symptom domain indicate that the nominal association between the BRIEF and SZ spectrum symptom severity in individuals with 3q29del is not merely due to confounding. The concordance between our findings and results from studies of idiopathic cases of SZ and ADHD suggest that understanding EF deficits in the context of the 3q29 deletion may provide generalizable insights to the study of SZ and ADHD at large.

Cognitive ability, specifically composite IQ, has canonically been used as a proxy for an individual's level of everyday functioning. The results of the present study, notably the astonishingly high rate of clinically significant EF deficits alongside the lack of a relationship between cognitive ability and EF, suggest that IQ alone may not be a sufficient measure to understand real-world function for individuals with 3q29del. Traditional cognitive testing may overlook impairments in crucial aspects of higher-order cognitive functioning that are relevant to everyday behaviors in this population. This finding is aligned with prior reports that have shown that certain EFs, including cognitive flexibility, are either uncorrelated with or are relatively weakly related to IQ (Ardila, Pineda, & Rosselli, 2000; Friedman et al., 2006), suggesting that traditional intelligence tests are insufficient in gauging the full spectrum of fundamental executive control abilities essential for various behaviors. This is of particular concern for individuals with 3q29del who have IQ scores well within the normal range alongside compromised EF; IQ scores in the normal range may create a perception of academic ability that is not accurate, given the co-occurring EF deficits. Together, these data suggest that individuals with 3q29del should be clinically evaluated using measures of both cognitive ability and EF as a standard of care. Furthermore, plans for treatment, management, and educational and occupational support should explicitly address and support EF deficits.

We identified a nominally significant relationship between cerebellar volumetric measures and EF in the present study. There is emerging evidence linking the cerebellum to a range of cognitive processes, including EF (Bellebaum & Daum, 2007; Koziol et al., 2012; Schmahmann, 2019; Schmahmann & Sherman, 1998). Changes in cerebellar structure and function have been identified in children with ADHD (Bechtel et al., 2009; Tomasi & Volkow, 2012), suggesting that cerebellar anomalies may contribute to the pathogenesis of ADHD. The cerebellum is also thought to have a role in SZ, due to its role in cognitive processes and the increased incidence of cerebellar anomalies in individuals with SZ (Andreasen & Pierson, 2008; Picard, Amado, Mouchet-Mages, Olié, & Krebs, 2008; Yeganeh-Doost, Gruber, Falkai, & Schmitt, 2011). Consistent with the findings of the present study, increased cerebellar white matter volume has been reported in idiopathic SZ, possibly indicating abnormal cerebellar connectivity (Lee et al., 2007). Our findings suggest that this is another point of convergence between 3q29del and idiopathic SZ; further exploration of cerebellar connectivity and EF in 3q29del may shed light on the neuroanatomical underpinnings of these complex phenotypes. In an exploratory analysis, we also identified nominally significant relationships between EF and

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cerebellar cortical subregional volumes, where increased subregional volume was associated with poorer EF. Future studies are required to replicate these exciting preliminary findings and may yield additional insight into altered cerebellar connectivity in 3q29del.

The genes affected by the 3q29 deletion may provide some insight into the mechanisms contributing to EF deficits in this population. The multi-domain scaffolding protein DLG1 and the serine/threonine kinase PAK2, encoded by two genes in the 3q29 interval, are important in synapse maintenance, cytoskeletal dynamics, long-term potentiation, and synaptic transmission (Howard, Elias, Elias, Swat, & Nicoll, 2010; Kreis & Barnier, 2009; Nakagawa et al., 2004; Wang et al., 2018). Another 3q29 interval gene, UBXN7, participates in the ubiquitin–proteasome system, which is increasingly recognized as a crucial regulator of synaptic development and learning-dependent synaptic plasticity (Patrick, Omar, Werner, Mitra, & Jarome, 2023). UBXN7 is the only gene in the interval that is implicated as a 'hub gene', with a large number of predicted connections to other genes expressed in human cortex (Sefik, Purcell, Walker, Bassell, & Mulle, 2021). Studies have demonstrated the importance of synaptic strength, synaptic remodeling, and brain connectivity for the development of EF abilities (Fiske & Holmboe, 2019), and members of the *DLG* gene family are intimately associated with the development of complex cognitive processes, including EF (Nithianantharajah et al., 2013). Studies have linked variation in SZ risk genes to specific, predictable changes in EF based on gene expression and functional connectivity measures (Eisenberg & Berman, 2010). Together, these data suggest that synaptic dysfunction, potentially mediated by DLG1, PAK2, and UBXN7, may contribute to the EF deficits in individuals with 3q29del. Other interval genes may also play a role in these deficits through various mechanisms yet to be fully understood.

EF deficits can have a major impact on day-to-day function, but there are techniques and interventions that can improve an individual's EF abilities. Targeted interventions to improve EF can be applied across the lifespan; studies have shown efficacy in improving EF in children as young as 3–4 years of age (Dowsett & Livesey, 2000; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005; Tang, Yang, Leve, & Harold, 2012) through adulthood (Franklin & Franklin, 2012; Goudreau & Knight, 2018; Kramer, Larish, & Strayer, 1995; Parker & Boutelle, 2009). Specific interventions have also been designed for clinical populations, such as the Unstuck and On Target Program for children on the autism spectrum (Kenworthy et al., 2014) and training programs for children and adults with ADHD (Klingberg et al., 2005; White & Shah, 2006). Together, these studies emphasize the malleable nature of EF, and suggest that individuals with 3q29del would benefit from targeted EF interventions from an early age.

While the present study is the first detailed description of EF in individuals with 3q29del, it is not without limitations. The average age of our study subjects is young (mean = 14.50 ± 8.26 years); as such, a majority of individuals have not reached the age at onset for SZ and psychotic disorders. Longitudinal follow up of study participants is needed to determine if EF abilities predict later-onset phenotypes. Additionally, the small sample size of the present study rendered our analyses exploratory, and we were likely underpowered for some comparisons, particularly in the neuroimaging analysis. Ongoing work by our team includes EF measurements in a larger sample of individuals with 3q29del; we will aim to replicate the results of the present study in that cohort. Finally, we were unable to assess the relative effect of race and ethnicity on EF in the current study, as our sample was overwhelmingly white and non-Hispanic. Current and future recruitment efforts will aim to include more underrepresented minorities so that future studies ideally have a more representative study sample.

The present study is the first to describe details of EF in individuals with 3q29del. We identified global deficits in EF, which were consistent between males and females. We found that EF was not correlated with IQ, but was associated with SZ spectrum symptom severity, ADHD diagnosis, and neuropsychiatric and neurodevelopmental multimorbidity; the BRIEF-2 ADHD form accurately discriminated between individuals with 3q29del with and without ADHD. This study, coupled with previous work by our team, emphasizes the central nature of EF to the 3q29del phenotype beyond general intellectual ability, and highlights the need for EF evaluation and interventions for all individuals with 3q29del. The malleable nature of EF means that early intervention in this population will likely yield substantial gains in abilities and improvements in long-term outcomes and ability to function independently.

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

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