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Longitudinal Development of Thalamocortical Functional Connectivity in 22q11.2 Deletion Syndrome

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ABSTRACT

BACKGROUND: The 22q11.2 deletion syndrome (22qDel) is a genetic copy number variant that strongly increases risk for schizophrenia and other neurodevelopmental disorders. Disrupted functional connectivity between the thalamus and the somatomotor/frontoparietal cortex has been implicated in cross-sectional studies of 22qDel, idiopathic schizophrenia, and youths at clinical high risk for psychosis. Here, we used a novel functional atlas approach to investigate longitudinal age-related changes in network-speci c thalamocortical functional connectivity (TCC) in participants with 22qDel and typically developing (TD) control participants.

METHODS: TCC was calculated for 9 functional networks derived from resting-state functional magnetic resonance imaging scans collected from 65 participants with 22qDel (63.1% female) and 69 demographically matched TD control participants (49.3% female) ages 6 to 23 years. Analyses included 86 longitudinal follow-up scans. Nonlinear age trajectories were characterized with generalized additive mixed models.

RESULTS: In participants with 22qDel, TCC in the frontoparietal network increased until approximately age 13, while somatomotor TCC and cingulo-opercular TCC decreased from age 6 to 23. In contrast, no signi cant relationships between TCC and age were found in TD control participants. Somatomotor connectivity was signi cantly higher in participants with 22qDel than in TD control participants in childhood, but lower in late adolescence. Frontoparietal TCC showed the opposite pattern.

CONCLUSIONS: 22qDel is associated with aberrant development of functional network connectivity between the thalamus and cortex. Younger individuals with 22qDel have lower frontoparietal connectivity and higher somatomotor connectivity than control individuals, but this phenotype may normalize or partially reverse by early adulthood. Altered maturation of this circuitry may underlie elevated neuropsychiatric disease risk in this syndrome.

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The 22q11.2 deletion syndrome (22qDel), also known as DiGeorge or velocardiofacial syndrome (OMIM 188400, 192430), is a genetic disorder that occurs in approximately 1 in 4000 live births (1). This syndrome is one of the greatest genetic risk factors for schizophrenia, with at least 1 in 10 individuals with 22qDel having a comorbid psychotic disorder and even higher rates after adolescence (2,3). Individuals with 22qDel also have high rates of autism and an increased incidence of intellectual disability, attentional de cits, and anxiety disorders (4–6). 22qDel is caused by a copy number variant (CNV) consisting of a hemizygous deletion of 1.5 to 2.6 Mb of genetic material (approximately 46 protein-coding genes) from chromosome 22q (7). This provides a genetics- rst framework for studying the biology underlying neurodevelopmental psychiatric disorders such as schizophrenia (8,9).

Functional neuroimaging studies of individuals with psychosis spectrum disorders have consistently identi ed alterations in the functional connectivity (FC) of the thalamus, speci cally, increased connectivity to somatomotor brain regions and decreased connectivity to frontoparietal associative regions compared with healthy control individuals (10–13). This marker is associated with conversion to psychosis in youths at clinical high risk (CHR) for the illness (14). In a cross-sectional study comparing participants (ages 7–26) with 22qDel with typically developing (TD) control participants, we observed a similar pattern of thalamic hyperconnectivity to the somatomotor network and hypoconnectivity to frontoparietal regions (15). This convergence of ndings in individuals with idiopathic schizophrenia, at CHR for psychosis, and with 22qDel may represent a shared phenotype relevant to psychosis risk. Interestingly, animal models of 22qDel implicate haploinsuf ciency of the *Dgcr8* gene (deleted in 22qDel) in elevation of thalamic dopamine D_2 receptors and age-related disruptions in thalamocortical synchrony (16,17) and may indicate an underlying neurobiological mechanism driving this dysfunction in 22qDel.

Thalamic dysconnectivity has additional cross-diagnostic relevance. Functional neuroimaging studies in autistic

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individuals have consistently observed altered thalamocortical functional connectivity (TCC) (18–21). Many of these ndings converge on increased connectivity within sensory networks. Furthermore, a broad convergence on disrupted thalamic connectivity has been identi ed in the functional connectomes from multiple idiopathic psychiatric conditions and neurodevelopmental CNVs (22,23).

The thalamus is a heterogeneous structure with dense reciprocal connections across the cortex (24). Structural and functional connectivity with the cortex across sensory and associative networks is thus a core organizational feature of the thalamus (25,26). TCC patterns speci c to sensory and associative networks emerge early in development and have been identi ed in infancy (27). Recent studies of the relationship between age and thalamic FC have observed subtle developmental changes in sensory and associative network connectivity (28,29). Adolescence represents an important developmental window during which interactions between the thalamus and cortex have been hypothesized to shape prefrontal development, which may be disrupted in disorders such as schizophrenia (30). One prior study of 22qDel has shown altered development of thalamic nuclei volumes, along with cross-sectional disruptions in FC (31).

In this longitudinal resting-state functional magnetic resonance imaging (fMRI) study, we mapped age-related changes in TCC in participants with 22qDel and demographically matched TD control participants from childhood to early adulthood. To our knowledge, this is the rst analysis of age-related changes in thalamic FC in 22qDel and one of the rst longitudinal analyses of TCC in any population. Here, we used a novel functional atlas approach to compute network-speci c TCC and generate nonlinear mixed models of the relationship between age and TCC to test the prediction that development of frontoparietal and somatomotor TCC would be altered in 22qDel. By examining the developmental trajectory of TCC in 22qDel, this study aimed to shed light on the neurobiological mechanisms underlying the increased risk of psychosis and other neurodevelopmental disorders in this population.

METHODS AND MATERIALS

Participants

The total longitudinal sample consisted of 220 scans from 135 participants (6–23 years of age; 65 participants with 22qDel baseline; 69 TD control participants baseline) (Figure 1) recruited from an ongoing longitudinal study at the University of California, Los Angeles (UCLA). Participants with 22qDel and TD control participants were statistically matched based on baseline age, sex, dominant hand, and fMRI movement [percent frames flagged based on displacement/intensity thresholds recommended by Power *et al* (32)], as well as mean number of longitudinal visits and interval between visits using appropriate tests (analysis of variance or χ^2 test) (Table 1). See Supplemental Methods for details on inclusion and exclusion criteria and clinical assessment procedures. After study procedures were fully explained, adult participants provided written consent, while participants younger than 18 years provided written assent with the written consent of their parent or guardian. The UCLA Institutional Review Board approved all study procedures and informed consent documents.

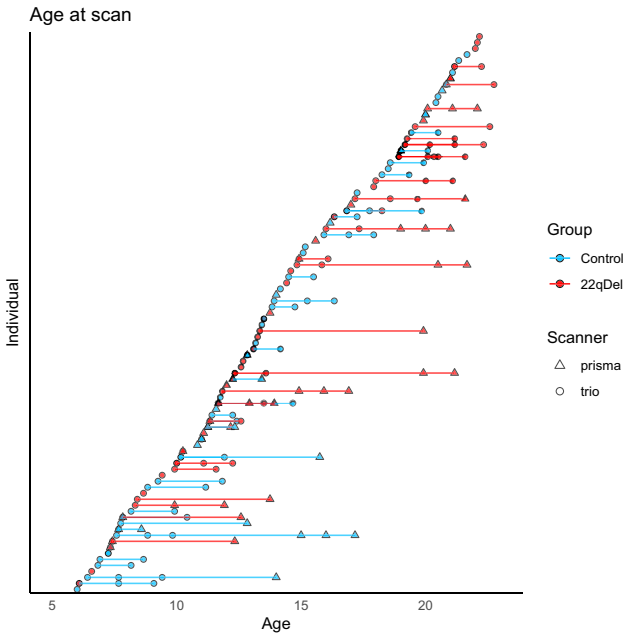

Figure 1. Participant age distribution. Typically developing control participants (blue) and participants with 22q11.2 deletion syndrome (red), with lines connecting follow-up visits from the same individual. Scanner type (Siemens Trio or Prisma) is indicated by circle or triangle, respectively. PATIENT-DEL, patients with 22q11.2 deletion syndrome.

Neuroimaging Acquisition and Processing

Resting-state fMRI and high-resolution structural images were collected on 2 scanners (Siemens MAGNETOM Trio and Siemens MAGNETOM Prisma; Siemens Healthineers) at the UCLA Center for Cognitive Neuroscience and processed with the Quantitative Neuroimaging Environment & Toolbox (33), which adapts the Human Connectome Project preprocessing pipelines (34) for broader use. Additional processing of the fMRI time series included bandpass ltering; motion scrubbing for frames exceeding either a framewise displacement or signal change threshold (32); spatial smoothing; and regression of mean signal from ventricles, deep white matter, and mean gray matter (35). Scans with >50% frames flagged for motion were excluded. For a detailed description of preprocessing methods, see Supplemental Methods and previous work in a subset of these data (15).

For each scan, TCC was computed based on the correlation in fMRI signal between the thalamic and cortical components of 9 networks (frontoparietal, somatomotor, cingulo-opercular, default mode, dorsal attention, auditory, posterior multimodal, primary visual, and secondary visual) de ned by the Cole-Anticevic Brain-wide Network Partition, a recently developed whole-brain functional atlas (36) (Figure 2). Data from the 2 scanners were harmonized using the longitudinal ComBat package in R (37), a linear mixed effects adaptation of the ComBat approach that uses empirical Bayes methods to estimate and remove site/batch effects with increased robustness to outliers in small samples compared with general linear model methods (38) (Supplemental Methods).

Table 1. Baseline Demographics

	TD Control Participants	Participants With 22qDel	*p* Value
Sample Size, *n*	69	65	
Age, Years, Mean (SD)	13.44 (4.76)	14.39 (4.56)	.242
Sex, Female, *n* (%)	34 (49.3%)	41 (63.1%)	.151
Handedness, Right, *n* (%)	31 (44.9%)	34 (52.3%)	.561
fMRI % Movement, Mean (SD)	6.86 (9.93)	9.84 (13.12)	.139
Siemens Trio MAGNETOM Scanner, *n* (%)	50 (73%)	48 (74%)	.857
WASI-II Full Scale IQ, Mean (SD)	112.15 (20.53)	79.00 (12.70)	.001
SIPS Positive Total, Mean (SD)	1.18 (2.16)	5.44 (5.61)	.001
Psychosis Risk Symptoms, *n* (%)	4 (5.8%)	20 (30.8%)	.001
Psychotic Disorder, *n* (%)	0 (0.0%)	5 (7.7%)	.058
ADHD, *n* (%)	5 (7.2%)	30 (46.2%)	.001
Autism, *n* (%)	0 (0.0%)	36 (55.4%)	.001
Antipsychotic Medication, *n* (%)	0 (0.0%)	5 (7.7%)	.004
Visit Count, Mean (SD)	1.57 (0.85)	1.72 (0.96)	.314
Days Between Visits, Mean (SD)	653.21 (425.56)	787.04 (549.92)	.296

Participants with 22q11.2 deletion syndrome (22qDel) and typically developing (TD) control participants with *p* values for between-group comparisons (based on analysis of variance for continuous variables and χ^2 for categorical variables). All χ^2 tests had 1 *df*, except handedness, which included an ambidextrous group, giving 2 *df*. Baseline cohorts were statistically matched based on age, sex, dominant hand, and functional magnetic resonance (fMRI) % movement (percentage of frames removed per subject for exceeding displacement and/or signal change thresholds) as well as mean number of longitudinal visits and interval between visits and proportion of the cohort acquired on each of 2 scanner types (Siemens MAGNETOM Trio or Siemens MAGNETOM Prisma). Cognition was measured with Wechsler Abbreviated Scale of Intelligence–Second Edition (WASI-II). Prodromal (psychosis-risk) symptoms were assessed with Structured Interview for Psychosis-Risk Syndromes (SIPS). Psychosis risk symptoms were operationalized here as having any score of 3 or greater (i.e., prodromal range) on any SIPS positive symptom item. Psychotic disorder diagnosis was based on Structured Clinical Interview for DSM/SCID-5 and included schizophrenia, schizoaffective disorder, brief psychotic disorder, and psychotic disorder not otherwise specified.

ADHD, attention-deficit/hyperactivity disorder.

Modeling Age Trajectories

Nonlinear relationships between age and TCC in the 22qDel and TD cohorts were assessed with generalized additive mixed models (GAMMs) as in Jalbrzikowski *et al* (39). Similar to linear mixed effects models, GAMMs can account for repeated within-subject measures with random effects. Nonlinear curves are estimated with basis functions, with overfitting prevented by penalization of polynomials and restricted estimation of maximum likelihood (40–42). We examined the effects of age on TCC separately in the 22qDel and TD cohorts because GAMMs allow the shape of the relationship between the smoothed predictor and dependent variable to differ between groups. For each network, a GAMM was fitted predicting TCC from the smoothed effect of age and group, controlling for sex and scanner type, with a random intercept for participant identifier. Test statistics were computed for the effect of age in each group, and *p* values were corrected for multiple comparisons with false discovery rate (43). Secondary analyses were performed to assess the impact of outliers, scanner type, movement, medication status, cardiac defect diagnosis, and global signal regression (GSR). Additionally, a secondary TCC analysis was performed using anatomically defined regions of interest segmented by FreeSurfer (44,45), as in Huang *et al* (28) (Supplemental Methods). As an exploratory analysis, IQ (measured with the Wechsler Abbreviated Scale of Intelligence–Second Edition) and positive psychosis symptoms [measured with the Structured Interview for Psychosis Risk Syndromes (46)] were tested for associations with frontoparietal and somatomotor TCC (Supplemental Methods).

RESULTS

Nonlinear Age Trajectories

For all 9 networks in TD control participants, there were no significant relationships between TCC and age after multiple comparison correction (Table 2). In contrast, in participants with 22qDel, 3 networks (frontoparietal, somatomotor, and cingulo-opercular) exhibited a significant effect of age on TCC after false discovery rate correction. Analysis of the 95% CIs of the first derivatives of the TCC age curves identified age ranges in which significant change occurred (Table 2). Specifically, frontoparietal connectivity in participants with 22qDel increased between ages 7.5 and 12.8 years, relative to TD control participants, while somatomotor and cingulo-opercular TCC decreased between ages 6 and 22.7 years. Based on the 95% CI for the group difference in age curves (Table 2), frontoparietal connectivity in participants with 22qDel was significantly lower than in TD control participants in childhood, from ages 6 to 9.6, but higher in late adolescence, from ages 16.8 to 19 years. Somatomotor TCC was higher in participants with 22qDel than in TD control participants before age 14.5 years, but became lower in participants with 22qDel compared with TD control participants after age 14.8 years. Cingulo-opercular TCC showed a similar pattern of age-related decrease in both groups and thus did not significantly differ between groups at any age. See Figure 3 for a visualization of frontoparietal and somatomotor age effects. Visualizations of all 9 networks are presented in Figure S1.

Secondary Analyses

Various iterations of the final model were tested to confirm robustness to potential confounds (Supplemental Methods). Test statistics and probabilities are reported in Supplemental Results. Conclusions from the models were not altered by inclusion of movement, medication status (antipsychotic, yes/no), or history of congenital cardiac diagnosis. Results were also robust to 90% Winsorization (i.e., restricting outliers to the 5th and 95th percentiles) before testing GAMMs and to the exclusion of 1 scanner (i.e., using only Trio data, excluding Prisma). Secondary analysis split by age groups revealed no differences in prepubertal and postpubertal subgroups in terms of which cortical networks are preferentially connected to thalamic networks of interest (Supplemental Results).

An additional analysis using anatomically defined regions of interest broadly corroborated the findings from our primary analysis using a functionally defined atlas. However, the

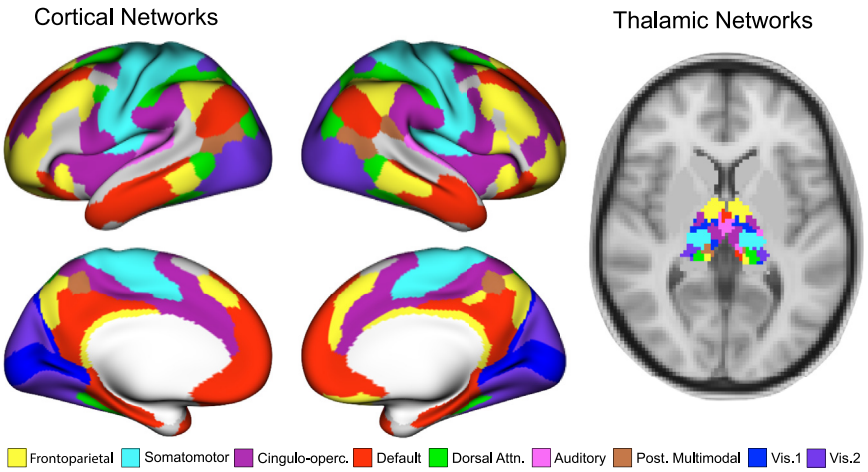

Figure 2. Cortical and thalamic regions for functional connectivity analysis. (Left panel) Nine cortical functional networks from the Cole-Anticevic brain-wide network partition (36). (Right panel) The same functional networks in the thalamus. Network thalamocortical functional connectivity was computed between the mean functional magnetic resonance imaging time series in corresponding cortical and thalamic regions. Attn., attention; Cingulo-operc., cingulo-opercular; Vis.1, primary visual; Vis.2, secondary visual.

functional atlas analysis was more sensitive to group differences and frontoparietal effects (Supplemental Results). Using anatomically de ned regions, the only signi cant age effect was a negative relationship with motor region TCC in participants with 22qDel. Frontal and parietal regions were analyzed separately in this case, and while the effect was not signi cant in either group, the age curves qualitatively resembled the frontoparietal effect from the functional atlas analysis.

IQ was found to be positively related to frontoparietal network TCC in TD control participants (= 0.004, p = .0174) and trended toward signi cance in participants with 22qDel (= 0.005, p = .058) (Supplemental Results). No relationship was found between IQ and somatomotor connectivity or

Table 2. Effects of Age on Thalamocortical Functional Connectivity

Group	Network	F (df)	p Value	FDR q	Signi cant Change[a]	Signi cant Difference[b]
22qDel	Frontoparietal	5.89 (2.2)	.002	.0177	7.5–12.8	6–9.6 | 16.8–19
	Somatomotor	9.84 (1.0)	.002	.0177	6–22.7	6–14.5 | 14.8–22.8
	Cingulo-opercular	7.53 (1.0)	.007	.0399	6–22.7	–
	Auditory	5.47 (1.0)	.020	.0915	6–21.4	–
	Default	2.53 (3.9)	.031	.0998	20.7–21.5	12.3–15
	Dorsal attention	2.43 (1.6)	.066	.1690	–	–
	Posterior multimodal	0.01 (1.0)	.930	.9520	–	–
	Primary visual	1.79 (1.0)	.180	.3290	–	–
	Secondary visual	1.39 (1.0)	.240	.3910	–	–
TD	Frontoparietal	1.03 (1.0)	.310	.4320	–	6–9.6 | 16.8–19
	Somatomotor	0.00 (1.0)	.950	.9520	–	6–14.5 | 14.8–22.8
	Cingulo-opercular	4.60 (1.0)	.033	.0998	6–22.7	–
	Auditory	2.57 (1.0)	.110	.2200	–	–
	Default	0.43 (1.0)	.680	.7630	–	12.3–15
	Dorsal attention	3.04 (1.0)	.083	.1870	–	–
	Posterior multimodal	0.28 (1.0)	.600	.7160	–	–
	Primary visual	1.19 (1.8)	.310	.4320	–	–
	Secondary visual	0.63 (1.0)	.430	.5520	–	–

Generalized additive mixed model predicting thalamocortical functional connectivity (TCC) from age, diagnosis, sex, and scanner, with a random intercept for repeated measures within subjects. For each network, a separate TCC age curve was modeled for 22q11.2 deletion syndrome (22qDel) and typically developing (TD) control groups. F values and p values are reported for each age effect as well as false discovery rate (FDR)–corrected q values (calculated from the set of 18 p values).

[a]Signi cant change denotes age ranges with signi cant change in TCC, determined where zero was not included in the 95% CI for the rst derivative of the TCC vs. age model.

[b]Signi cant difference denotes age ranges with signi cant group differences in TCC based on the 95% CI. If multiple discontinuous periods of signi cant difference were found for a network, they are separated by "|".

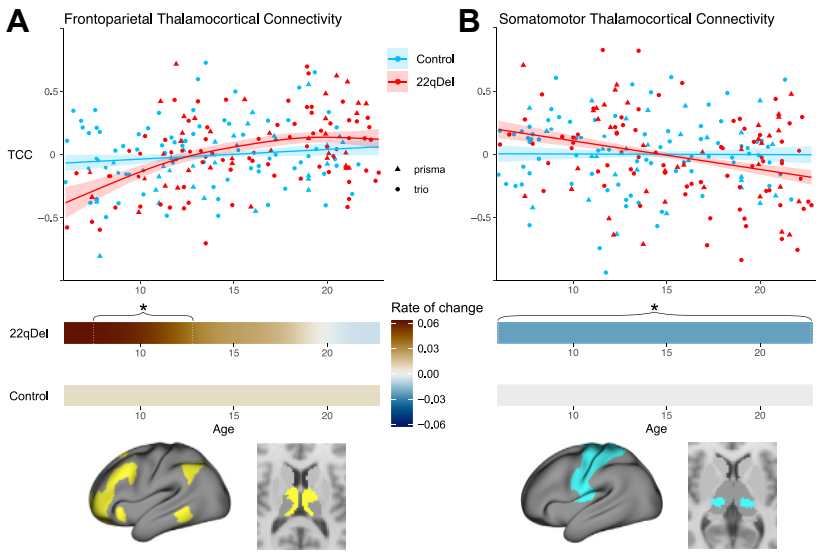

Figure 3. Age trajectories of frontoparietal and somatomotor thalamocortical functional connectivity (TCC). TCC vs. age curves in participants with 22q11.2 deletion syndrome (22qDel) and typically developing control participants. **A)** (Upper panel) Smoothed age curves and partial residuals for frontoparietal TCC from the generalized additive mixed model predicting TCC from age, diagnosis, sex, and scanner, with a random intercept for repeated measures within subjects. The partial residual plots reflect the relationship between age and TCC, given the other covariates in the model. (Middle panel) First derivatives of the TCC vs. age curve in participants with 22qDel and control participants, with intervals of signi cant change determined where the 95% CI for the rst derivative did not include zero (marked with brackets and asterisk). There was no change in frontoparietal TCC across the age range for control participants, but 22qDel TCC increased across ages 7.5–12.8 years. (Lower panel) Cortical and thalamic regions used for TCC measure. **B)** Same as panel **A)** for the generalized additive mixed model predicting somatomotor TCC, showing no change across the age range in control participants, but a negative slope across the full age range for 22qDel.

between Structured Interview for Psychosis positive symptoms and somatomotor or frontoparietal connectivity. The observed relationship between frontoparietal TCC and IQ did not survive stringent multiple comparison correction across all behavioral relationships tested.

Effects of Global Signal Regression

Analyses were repeated with fMRI inputs that had not been subjected to GSR as a denoising step. Without inclusion of GSR, the pattern for somatomotor and cingulo-opercular TCC was similar, but was reduced to a trend level after multiple comparison correction (Table S6; Figure S2). The smoothed age effect on TCC no longer met multiple correction–adjusted = 0.05 for any network in participants with 22qDel or TD control participants. Despite the inclusion of motion scrubbing and nuisance regression of motion parameters, quality control FC analysis showed that inclusion of GSR additionally reduced the relationship between motion and whole-brain FC in this sample, suggesting that GSR improved the data with respect to motion (Figure S3).

DISCUSSION

Altered FC between the thalamus and brain regions involved in somatomotor and frontoparietal networks has been implicated in cross-sectional studies of individuals with schizophrenia, individuals at CHR for psychosis, and individuals with 22qDel (12,14,15). However, little is known about how thalamic connectivity develops with age in genetic high-risk conditions such as 22qDel. This is the rst study to investigate developmental trajectories of thalamic FC in in this population. We used a powerful and flexible GAMM approach to map linear and nonlinear age-related changes in network-level TCC, assessed via resting-state fMRI in an accelerated longitudinal cohort of individuals with 22qDel and matched TD control participants ages 6 to 23 years. This novel GAMM approach has recently been applied for the rst time to case-control neuroimaging investigations and has identi ed altered developmental trajectories of structural MRI phenotypes associated with 22q11.2 CNVs (39).

We found that participants with 22qDel exhibited signi cant age-related increases in frontoparietal TCC and decreases in somatomotor TCC. Frontoparietal connectivity increased steeply during childhood, and the rate of change slowed during adolescence, whereas somatomotor connectivity decreased consistently through the age range. TCC was generally stable across the studied age range in TD control participants. TCC in the cingulo-opercular network was also found to signi cantly decrease across the age range in the 22qDel group, while the TD group trended toward signi cance in the same direction.

Development of TCC in 22qDel and TD Youth

These results expand on our prior ndings from a cross-sectional analysis in a smaller subset of this dataset where, controlling for age, whole-thalamus FC in participants with 22qDel relative to control participants was found to be significantly increased to somatomotor regions and decreased to regions involved in the frontoparietal network (15). Our new longitudinal analysis suggests that the younger participants with 22qDel were likely driving the previously observed nding of somatomotor hyperconnectivity and frontoparietal hypoconnectivity and that this phenotype may normalize or even reverse to an abnormal extent during adolescence. Here, the bidirectional pattern of somatomotor and frontoparietal thalamocortical disruptions in 22qDel can be seen to extend to developmental trajectories. In 22qDel, frontoparietal TCC increases signi cantly with age, particularly before age 13 years, while somatomotor TCC decreases across the age range, intersecting with the typical development curve in early/mid adolescence (Table 2; Figure 3). Notably, GAMMs were analyzed across all 9 networks represented in the thalamus, in a data-driven approach, the results of which support our initial

hypothesis of preferential disruptions in somatomotor and frontoparietal TCC.

Only a small number of fMRI studies have investigated typical development of thalamic FC in childhood and adolescence. A recent study in 107 TD participants found a linear decrease in salience network (cingulo-opercular) thalamic connectivity across ages 5 to 25 years (29). Another recent study of TCC in a large community sample (Philadelphia Neurodevelopmental Cohort), which included 1100 total scans, including TD youth and individuals with psychosis spectrum symptoms and other psychopathology, found a negative linear association between age and somatosensory thalamic connectivity, but no age by psychiatric group interactions (28). In contrast to the previous 2 described studies, an analysis of thalamic connectivity in 52 TD individuals, which treated age as a categorical variable (child, adolescent, adult) found greater thalamic-frontal FC in adults compared with children (47). In the context of this literature, our results can be seen to generally replicate the nding of normative age-related decreases in salience network connectivity (29) in both 22qDel and TD participants (for whom the effect of age on cingulo-opercular TCC trended toward signi cance and the 95% CI of the rst derivative did not include zero) (Table 2). It is still not clear how much age-related change is to be expected in typical development of somatomotor and frontoparietal thalamocortical networks (28,47). Our nding of signi cant age effects in these networks for youth with 22qDel, but not TD youth, could be explained by either a pathological developmental mechanism in 22qDel or a compensatory exaggeration of typical developmental pathways. Future research in 22qDel mouse models can shed light on genetic and cellular mechanisms underlying age-related FC disruptions, which may in turn suggest potential interventions for such aberrant maturational patterns.

Exploratory analysis of brain-behavior relationships revealed that increased frontoparietal TCC was associated with higher Full Scale IQ in TD control participants, with a similar relationship trending toward signi cance in the 22qDel cohort (Supplemental Results). Future studies in larger cohorts should characterize this relationship in more detail. Structured Interview for Psychosis positive symptom severity was not found to be associated with frontoparietal or somatomotor TCC in participants with 22qDel. Notably, in our baseline sample, 30.8% of participants with 22qDel had subthreshold positive symptoms in the prodromal range, but only 7.7% had overt psychosis (Table 1).

Strengths Limitations and Future Directions

This study has several key strengths that support the reliability of our ndings. The sample size of 112 scans from 65 patients with 22qDel is large for this population or populations with similar rare disorders (48). We took advantage of an accelerated longitudinal recruitment design to map cohort-level FC-age trajectories across a key developmental window, whereas prior studies of TCC development have relied on cross-sectional samples (28,29,47). Our GAMM analyses leveraged this longitudinal design, with the additional bene t of being able to capture developmental trajectories whose shapes differ between cohorts (40). Potential confounds were addressed through multiple complementary approaches. To minimize the impact of scanner type, we used the longitudinal ComBat algorithm, which was speci cally adapted for longitudinal neuroimaging data and represents the state of the art in batch correction methods (37). Our secondary analyses showed that our primary results were robust to outliers via Winsorization; to scanner effects via exclusion of data collected on 1 of 2 scanners; and to inclusion of movement parameters, antipsychotic medication status, and congenital cardiac defect diagnosis as covariates of no interest in the nal model. Together, these results support a robust nding in a unique clinical population that allows for genetics- rst study of phenotypes relevant to neurodevelopmental disorders.

However, certain limitations of this study must be noted. First, this dataset is not well suited for analyses of within-subject change, which might be more informative for analyses of symptom relationships over time. An additional limitation is that the GAMM results differed if fMRI inputs were used that had not been subject to GSR as a preprocessing step (Table S6). Without GSR, no age effects remained signi cant after multiple comparison correction, although 22qDel somatomotor and cingulo-opercular connectivity trended in the same direction. Quality control FC analysis, developed by Power *et al* (49) to quantify the effect of participant movement on FC, indicated that, despite motion scrubbing and regression of motion parameters, GSR additionally reduced the relationship between movement (framewise displacement) and FC. To reduce the impact of motion on FC results in our neurodevelopmental sample, and for consistency with our prior work and other similar studies in the eld (15,29), we thus present our primary results with GSR included. Another limitation is that the data were acquired on 2 different Siemens scanners, and the data from the Prisma scanner (approximately 25% of the full sample) used a Human Connectome Project–style sequence with a multiband factor of 8, which can increase subcortical noise compared with single-band acquisitions (50). Band-pass temporal ltering, which we applied during preprocessing, can help mitigate this noise (50). Importantly, scanner type was controlled for through longitudinal ComBat, inclusion of a scanner covariate in the nal model, and a secondary analysis using only data from the same Trio scanner, which corroborated our ndings of altered development of somatomotor and frontoparietal TCC in 22qDel (Table S1). An additional consideration is diagnostic heterogeneity within the 22qDel sample (46% met criteria for attention-de cit/hyperactivity disorder, and 55% met criteria for autism) (Table 1).

Future research directions include mapping TCC development in other clinical populations, including autistic individuals, youth at CHR for psychosis, and individuals with other neuropsychiatric CNVs, to determine unique versus shared maturational patterns of this circuitry. Characterizing changes across the life span, including early through late adulthood, in these populations will also be valuable. While our sample is large in the context of rare genetic disorders, even larger studies of 22qDel will be important for more precise characterization of developmental trajectories and brain-behavior relationships. International multisite studies such as the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) CNV working group are currently making progress

toward this goal (48). Other methods for assessing TCC-related phenotypes, such as electroencephalography and sleep spindle detection, will also be highly informative in 22qDel and related conditions (51). Additionally, the high construct validity of 22qDel animal models will allow for testing molecular and cell/circuit level hypotheses about development in 22qDel.

Conclusions

This study is the first to our knowledge to characterize longitudinal age-related changes in TCC in children and adolescents with 22qDel. Using a novel functional atlas approach to investigate network-specific TCC, we found that children with 22qDel exhibit altered maturation of these functional networks, involving a pattern of increased TCC in the somatomotor network, concomitant with decreased connectivity in the frontoparietal network relative to TD control participants. This pattern normalizes by early/mid adolescence and potentially reverses by late adolescence. TD control participants do not show the same age-related changes in frontoparietal and somatomotor connectivity. Future research in animal and in vitro models can shed light on biological mechanisms underlying the observed alterations in FC development in 22qDel.

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ARTICLE INFORMATION

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