**Title**

Longitudinal development of thalamocortical functional connectivity in 22q11.2 deletion syndrome

**Short/Running Title**

Longitudinal thalamic FC in 22qDel

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**Keywords**

Copy Number Variant, Neurodevelopmental, Psychosis, Autism, Thalamus, fMRI

**Abstract**

*Background.* 22q11.2 Deletion Syndrome (22qDel) is a genetic Copy Number Variant (CNV) that strongly increases risk for schizophrenia and other neurodevelopmental disorders. Disrupted functional connectivity between the thalamus and somatomotor/frontoparietal cortex has been implicated in cross-sectional studies of 22qDel, idiopathic schizophrenia, and youth at clinical high risk (CHR) for psychosis. Here, we use a novel functional atlas approach to investigate longitudinal age-related changes in network-specific thalamocortical functional connectivity (TCC) in 22qDel and typically developing (TD) controls.

*Methods.* TCC was calculated for nine functional networks derived from resting-state functional magnetic resonance imaging (rs-fMRI) scans collected from n=65 22qDel participants (63.1% female) and n=69 demographically matched TD controls (49.3% female), ages 6 to 23 years. Analyses included 86 longitudinal follow-up scans. Non-linear age trajectories were characterized with general additive mixed models (GAMMs).

*Results.* In 22qDel, thalamocortical connectivity in the frontoparietal network increases until approximately age 13, while somatomotor and cingulo-opercular TCC decrease from age 6 to 23. No significant relationships between TCC and age were found in TD controls.

*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 controls, 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.

**Main Text**

**Introduction**

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). Individuals with 22qDel also have high rates of autism and an increased incidence of intellectual disability (ID), attentional deficits, and anxiety disorders (3–5). 22qDel is caused by a copy number variant (CNV), consisting of a hemizygous deletion of 1.5-2.6 Mb of genetic material (~46 protein-coding genes) from chromosome 22q (6). This provides a genetics-first framework for studying the biology underlying neurodevelopmental psychiatric disorders like schizophrenia (7,8).

Functional neuroimaging studies of psychosis spectrum disorders have consistently identified alterations in the functional connectivity (FC) of the thalamus, specifically, increased connectivity to somatomotor brain regions and decreased connectivity to frontoparietal associative regions compared to healthy controls (9–12). This marker is associated with conversion to psychosis in youth at clinical high risk (CHR) for the illness (13). In a cross-sectional study comparing individuals (ages 7-26) with 22qDel to typically developing (TD) controls, we observed a similar pattern of thalamic hyper-connectivity to the somatomotor network and hypo-connectivity to frontoparietal regions (14). This convergence of findings in idiopathic schizophrenia, CHR, and 22qDel may represent a shared phenotype relevant to psychosis risk. Interestingly, animal models of 22qDel implicate haploinsufficiency of the *Dgcr8* gene (deleted in 22qDel) in elevation of thalamic dopamine D2 receptors and disrupted thalamocortical synchrony (15,16) and may indicate an underlying neurobiological mechanism driving this dysfunction in 22qDel.

Thalamic dysconnectivity has additional cross-diagnostic relevance. Functional neuroimaging studies in autistic individuals have consistently observed altered thalamocortical FC (17–20). Many of these findings converge on increased connectivity within sensory networks. Furthermore, a broad convergence on disrupted thalamic connectivity has been identified in the functional connectomes from multiple idiopathic psychiatric conditions and neurodevelopmental CNVs (21,22).

The thalamus is a heterogeneous structure with dense reciprocal connections across the cortex (23). Structural and functional connectivity with the cortex across sensory and associative networks is thus a core organizational feature of the thalamus (24,25). Thalamocortical FC patterns specific to sensory and associative networks emerge early in development and have been identified in infancy (26). Recent studies of the relationship between age and thalamic FC have observed subtle developmental changes in sensory and associative network connectivity (27,28). 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 like schizophrenia (29). One prior study of 22qDel has shown altered development of thalamic nuclei volumes, along with cross-sectional disruptions in FC (30).

In this longitudinal resting-state functional magnetic resonance imaging (rs-fMRI) study, we map age-related changes in thalamocortical FC in 22qDel and demographically matched TD control subjects, from childhood to early adulthood. To our knowledge, this is the first analysis of age-related changes in thalamic FC in 22qDel, and one of the first longitudinal analyses of thalamocortical FC in any population. Here, we use a novel functional atlas approach to compute network-specific thalamocortical functional connectivity (TCC) and generate non-linear mixed models of the relationship between age and TCC to test the prediction that development of frontoparietal and somatomotor TCC is altered in 22qDel. By examining the developmental trajectory of TCC in 22qDel, this study aims to shed light on the neurobiological mechanisms underlying the increased risk of psychosis and other neurodevelopmental disorders in this population.

**Methods**   
*Participants* The total longitudinal sample consisted of 220 scans from 135 participants (6–23 years of age; 65 22qDel baseline; 69 TD controls baseline; see **Figure 1**), recruited from an ongoing longitudinal study at the University of California, Los Angeles (UCLA). 22qDel and TD participants were statistically matched based on baseline age, sex, dominant hand, fMRI movement (percent frames flagged based on displacement/intensity thresholds recommended by Power et al. 2012 (31)), as well as mean number of longitudinal visits and interval between visits, using appropriate tests (ANOVA or chi-squared; see **Table 1**). See **Supplemental Methods** for details on inclusion/exclusion criteria and clinical assessment procedures. After study procedures were fully explained, adult participants provided written consent, while participants under the age of 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.

*Neuroimaging acquisition and processing*

Rs-fMRI and high-resolution structural images were collected on two scanners (Siemens Trio and Siemens Prisma) at the UCLA Center for Cognitive Neuroscience, and processed with the Quantitative Neuroimaging Environment & Toolbox (QuNex) (32), which adapts the Human Connectome Project (HCP) preprocessing pipelines (33) for broader use. Additional processing of the fMRI time series included bandpass filtering, motion scrubbing for frames exceeding either a framewise displacement or signal change threshold (31), spatial smoothing, and regression of mean signal from ventricles, deep white matter, and mean gray matter (34). 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 (14).

For each scan, TCC was computed based on the correlation in fMRI signal between the thalamic and cortical components of nine networks (frontoparietal, somatomotor, cingulo-opercular, default mode, dorsal attention, auditory, posterior multimodal, primary visual, and secondary visual) defined by the Cole-Anticevic Brain-wide Network Partition, a recently developed whole-brain functional atlas (35) (see **Figure 2**). Data from the two scanners were harmonized using the longitudinal ComBat (longComBat) package in R (36), a linear mixed effects adaptation of the ComBat approach which 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 (37) (see **Supplemental Methods**).

*Modeling age trajectories*

Non-linear relationships between age and TCC in 22qDel and TD cohorts were assessed with general additive mixed models (GAMMs) as in Jalbrzikowski et al., 2022 (38). Like linear mixed effects models, GAMMs can account for repeated within-subject measures with random effects. Non-linear curves are estimated with basis functions, with overfitting prevented by penalization of polynomials and restricted estimation of maximum likelihood (39–41). We examined the effects of age on TCC separately in 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 subject ID. Test statistics were computed for the effect of age in each group, and *p*-values were corrected for multiple comparisons with False Discovery Rate (42). Secondary analyses were performed to assess the impact of outliers, scanner type, movement, medication status, cardiac diagnosis, and global signal regression (GSR; see **Supplemental Methods**).

**Results**

*Non-linear age trajectories*

For all nine networks in TD controls, there were no significant relationships between TCC and age after multiple comparison correction (see **Table 2**). In contrast, in 22qDel three networks (frontoparietal, somatomotor, and cingulo-opercular) exhibited a significant effect of age on TCC after FDR correction. Analysis of the 95% confidence intervals (CI) of the first derivatives of the TCC age curves identified age ranges in which significant change occurred (see **Table 2**). Specifically, frontoparietal connectivity in 22qDel increased between ages 7.5 and 12.8, relative to TD controls, while somatomotor and cingulo-opercular TCC decreased between ages 6 and 22.7. Based on the 95% CI for the group difference in age curves (see **Supplemental Results**), 22qDel frontoparietal connectivity was significantly lower than TD in childhood, from ages 6 to 9.6, but higher in late adolescence, from age 16.8 to 19. In 22qDel, Somatomotor TCC was higher than TD prior to age 14.5, but switched to lower than TD after age 14.8. Cingulo-opercular TCC did not differ between groups at any age. See **Figure 3** for a visualization of frontoparietal and somatomotor age effects. Visualizations of all nine networks, and tabulation of age ranges with significant group differences are included in the **Supplemental Results**.

*Secondary analyses*

Various iterations of the final model were tested to confirm robustness to potential confounds (see **Supplemental Methods**). Test statistics and probabilities are reported in the **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) prior to testing GAMMs, and the exclusion of one scanner (i.e., using only Trio data, excluding Prisma).

*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, there was no longer a significant age-associated effect on TCC in either group. The smoothed age effect on TCC no longer met multiple correction adjusted ɑ=0.05 for any network in 22qDel or TD. Despite the inclusion of motion scrubbing and nuisance regression of motion parameters, quality control functional connectivity (QC-FC) analysis showed that inclusion of GSR additionally reduced the relationship between motion and whole-brain FC in this sample (see **Supplemental Results**).

**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, those at CHR for psychosis, and 22qDel (11,13,14). However, little is known about how thalamic connectivity develops with age in genetic high-risk conditions such as 22qDel. This is the first study to investigate developmental trajectories of thalamic FC in in this population. We used a powerful and flexible GAMM approach to map linear and non-linear age-related changes in network-level thalamocortical connectivity, assessed via rs-fMRI in an accelerated longitudinal cohort of individuals with 22qDel and matched TD controls, ages 6 to 23 years. This novel GAMM approach has only recently been applied for the first time to case-control neuroimaging investigations, and has identified altered developmental trajectories of structural MRI phenotypes in 22q11.2 CNVs (38).

We found that 22qDel patients exhibited significant 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 controls. TCC in the cingulo-opercular network was also found to significantly decrease across the age range in 22qDel, while the TD group trended towards significance in the same direction.

*Development of thalamocortical functional connectivity in 22qDel and TD youth*

These results expand on our prior findings from a cross-sectional analysis in a smaller subset of this dataset where, controlling for age, whole-thalamus FC in 22qDel relative to controls was found to be significantly increased to somatomotor regions and decreased to regions involved in the frontoparietal network (14). Our new longitudinal analysis suggests that the younger 22qDel patients were likely driving the previously observed finding of somatomotor hyper-connectivity and frontoparietal hypo-connectivity, and that this phenotype may normalize or even reverse to an abnormal extent during adolescence. Here, the bi-directional pattern of somatomotor and frontoparietal thalamocortical disruptions in 22qDel can be seen to extend to developmental trajectories. In 22qDel; frontoparietal TCC increases significantly with age, particularly prior to age 13, while somatomotor TCC decreases across the age range, intersecting with the TD curve in early/mid adolescence (see **Table 2** and **Figure 3**). Notably, GAMMs were analyzed across all nine 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 5-25 (28). Another recent study of thalamocortical FC in a large community sample (Philadelphia Neurodevelopmental Cohort), which included 1100 total scans, comprised of TD youth as well as individuals with psychosis spectrum disorders and other psychopathology, found a negative linear association between age and somatosensory thalamic connectivity, but no age by psychiatric group interactions (27). Unlike the previous two 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 to children (43). In the context of this literature, our results can be seen to generally replicate the finding of normative age-related decreases in salience network connectivity (28) in both 22qDel and TD (for whom the effect of age on cingulo-opercular TCC trended towards significance and the 95% CI of the first derivative didn’t include zero; see **Table 2** and **Supplemental Results**). It is still not clear how much age-related change is to be expected in typical development of somatomotor and frontoparietal thalamocortical networks (27,43). Our finding of significant age effects in these networks for 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 may shed light on genetic and cellular mechanisms and potential interventions for age-related FC disruptions.

*Strengths, limitations, and future directions*

This study has several key strengths that support the reliability of our findings. The sample size of 112 scans from 65 22qDel patients is large for this population or similar rare disorders (44). 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 thalamocortical FC development have relied on cross-sectional samples (27,28,43). Our GAMM analyses took advantage of this longitudinal design, with the additional benefit of being able to capture developmental trajectories whose shapes differ between cohorts (39). Potential confounds were addressed through multiple complementary approaches. To minimize the impact of scanner type, we used the longitudinal ComBat algorithm, which was specifically adapted for longitudinal neuroimaging data and represents the state-of-the-art in batch correction methods (36). Our secondary analyses showed that our primary results were robust to outliers via Winsorization, scanner effects via exclusion of data collected on one of two scanners, and to inclusion of movement parameters, antipsychotic medication status, and congenital cardiac diagnosis as covariates of no interest in the final model. Together, these results support a robust finding in a unique clinical population that allows for genetics-first 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. Similarly, this sample is not well powered for analyses of brain-behavior relationships, particularly as effect size estimates can be artificially inflated for brain-behavior relationships in small samples (45). An additional limitation is that the GAMM results were significantly different if fMRI inputs were used that had not been subject to GSR as a preprocessing step (see **Supplemental Results**). Without GSR, no age effects remained significant after multiple comparison correction, although 22qDel somatomotor connectivity trended in the same direction. QC-FC analysis, developed by Power et al. to quantify the effect of participant movement on FC (46), 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 field (14,28), we present our primary results with GSR included.

Future research directions include mapping thalamocortical FC development in other clinical populations including autistic individuals, youth at CHR for psychosis, and individuals with other neuropsychiatric CNVs. Characterizing changes across the lifespan, including early through late adulthood, in these populations will also be valuable. Other methods for assessing TCC related phenotypes, such as EEG and sleep spindle detection, will be highly informative in 22qDel and related conditions (47). 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 characterize longitudinal age-related changes in thalamocortical functional connectivity in children and adolescents with 22qDel. Using a novel functional atlas approach to investigate network-specific thalamocortical connectivity, we found that children with 22qDel exhibit a pattern of increased thalamocortical FC in the somatomotor network, concomitant with decreased connectivity in the frontoparietal network relative to TD controls. This pattern normalizes by early/mid adolescence, and potentially reverses by late adolescence. TD controls 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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**Table Legends**

**Table 1. Baseline demographics.** 22qDel and TD controls with *p*-values for between group comparisons (based on ANOVA for continuous variables and chi-squared tests for categorical variables). Baseline cohorts are statistically matched based on age, sex, dominant hand, and fMRI movement, as well as mean number of longitudinal visits and interval between visits. Cognition was measured with the Wechsler Abbreviated Scale of Intelligence (WASI). Prodromal symptoms were assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS). Psychosis Risk Symptoms are determined as having any score of 3 or greater on any SIPS positive symptom item. Psychosis diagnosis based on structured clinical interview (SCID) for DSM-IV and includes schizophrenia, schizoaffective disorder, brief psychotic disorder, and psychotic disorder not otherwise specified.

**Table 2.** **Effects of age on thalamocortical connectivity (TCC).** Generalized Additive Mixed Model (GAMM) predicting 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 22qDel and TD control groups. *F*-values and *p*-values are reported for each age effect, as well as FDR-corrected *q*-values (calculated from the set of n=18 *p*-values). “sig\_age\_range” denotes age ranges with significant change in TCC, determined where zero is not included in the 95% confidence interval for the 1st derivative of the TCC vs age GAMM.

**Figure Legends**

**Figure 1. Participant age distribution.** Typically developing controls in blue, 22qDel in red, with lines connecting follow-up visits from the same individual. Scanner type (Siemens Trio or Prisma) indicated by circle or triangle, respectively.

**Figure 2. Cortical and thalamic regions for functional connectivity analysis.** *Left:* nine cortical functional networks from the Cole-Anticevic Brain-wide Network Partition (CABNP) (35). *Right:* the same functional networks in the thalamus. Network thalamocortical connectivity (TCC) was computed between the mean fMRI time series in corresponding cortical and thalamic regions.

**Figure 3. Age trajectories of frontoparietal and somatomotor thalamocortical connectivity (TCC).** TCC vs age curves in 22qDel and typically developing controls. **A)** *Upper:* smoothed age curves and partial residuals for frontoparietal TCC from the GAMM 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:* 1st derivatives of the TCC vs age curve in patients and controls, with intervals of significant change determined where the 95% confidence interval for the 1st derivative does not include zero, marked with brackets and asterisk. No change in frontoparietal TCC across the age range for controls, but 22qDel increases across ages 7.5-12.8. *Lower:* cortical and thalamic regions used for TCC measure. **B)** Same as **A** for the GAMM predicting somatomotor thalamocortical connectivity, showing no change across the age range in controls but a negative slope across the full age range for 22qDel.

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*Data availability*

Data are publicly available from the National Institute of Mental Health Data Archives: <https://nda.nih.gov/edit_collection.html?id=2414>   
To facilitate reproducibility and rigor, analysis code is publicly available on GitHub: <https://github.com/charles-schleifer/22q_tcc_longitudinal>

**Disclosures**

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