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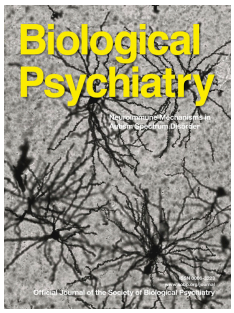

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ATYPICAL FUNCTIONAL CONNECTIVITY IN TOURETTE SYNDROME DIFFERS BETWEEN CHILDREN AND ADULTS

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ABSTRACT

Background

Tourette syndrome (TS) is a neuropsychiatric disorder with symptomatology that typically changes over development. Whether and how brain function in TS also differs across development has been largely understudied. Here, we used functional connectivity MRI to examine whole brain functional networks in children and adults with TS.

Methods

Multivariate classification methods were used to find patterns among functional connections that distinguish TS from controls separately for children and adults (total N=202). We tested whether the patterns of connections that classify diagnosis in one age group (e.g., children) could classify diagnosis in another age group (e.g., adults). We also tested whether the developmental trajectory of these connections was altered in TS.

Results

Diagnostic classification was successful in children and adults separately but expressly did not generalize across age groups, suggesting that the patterns of functional connections that best distinguished TS from controls were age-specific. Developmental patterns among these functional connections used for diagnostic classification deviated from typical development. Brain networks in childhood TS appeared “older” and brain networks in adulthood TS appeared “younger” in comparison to typically developing individuals.

Conclusions

Our results demonstrate that brain networks are differentially altered in children and adults with TS. The observed developmental trajectory of affected connections is consistent with theories of accelerated and/or delayed maturation, but may also involve anomalous developmental pathways. These findings further our understanding of neurodevelopmental trajectories in TS and carry implications for future applications aimed at predicting the clinical course of TS in individuals over development.

INTRODUCTION

Tourette syndrome (TS) is a developmental neuropsychiatric disorder characterized by motor and vocal tics (1) that affects 1-3% of children (2–4). Tics are brief, unwanted, repetitive movements or noises that can be intrusive in daily life. On average, tic onset occurs at age 5-7 years, with tic severity peaking during late childhood/early adolescence (10-12 years). Tics usually continue into adulthood (5, 6), but with marked improvement or even remission after adolescence (7–11). However, symptom progression varies substantially across individuals, with a sizeable subgroup of patients (~60%) experiencing moderate to severe tics that persist into adulthood (9, 12). Understanding how the brain changes over the course of development in TS may provide insight into its clinical manifestation across development and aid prediction of the disorder's trajectory in individuals.

Most neuroimaging studies of TS treat it as a singular disorder, unchanging across development, by grouping together patients from a wide age range (13–17) or focusing on a single age cohort (18–22), often by necessity. However, there is evidence that differences in brain structure and function in TS vary by age (23–25). Comparing the brain differences observed in children and adults with TS is necessary to reveal effects that are present in both age groups ("age-invariant" TS effects) as well as effects that differ between age groups ("age-specific" TS effects). Critically, a more complete understanding of the differences observed in children or adults with TS also requires taking into account typical maturational changes in the brain. Given a context of typical development, one can examine whether brain differences reflect atypically shifted development (e.g., accelerated or delayed maturation) and/or an anomalous difference or trajectory not observed in typical development, potentially providing clues into etiology. While several TS neuroimaging studies have interpreted their findings in the context of brain maturity (23, 24, 26–28), few have included typical developmental comparisons to contextualize the differences observed in TS (29–31).

The potential presence of both maturity- and disorder-related differences in the brain in TS is made more complex by considering where these differences are localized. While many studies of TS have primarily identified differences within a select few brain regions or networks, the findings together suggest that TS involves many cortical and subcortical brain regions (for reviews, see (32, 33)). Thus, capturing the

developmental trajectory of brain function in TS might be facilitated by a multivariate approach that combines information from many brain regions and identifies complex patterns in the data that distinguish individuals by diagnosis and/or age. Multivariate machine learning techniques have been applied to neuroimaging data in an attempt to identify patterns of diagnosis-related differences in neuropsychiatric disorders (for a review, see (34)) and age-related differences in typical development (35–38). Notably, these methods require validation in an independent group of subjects to ensure that the identified differences do not represent idiosyncratic or spurious group differences (39), which is often not possible in small sample studies.

Here, we used a whole-brain, multivariate approach to investigate whether and how brain networks in TS differ from controls in children and adults. Functional connectivity MRI, which measures the temporal correlations between spontaneous fluctuations in the blood oxygen level-dependent signals across the brain (40), was used to examine functional brain networks in separate cohorts of children and adults with TS. We previously demonstrated that multivariate approaches applied to functional connectivity can distinguish children with TS from controls (41) and typically developing children from adults (42, 43). In the present work, we use a similar approach to test whether the patterns of functional connections that differ in TS in one age group (e.g., children) can also distinguish individuals with TS in the other age group (e.g., adults), and place these differences in the context of typical development.

MATERIALS AND METHODS

Participants

Individuals with TS (*n*=172, independent studies=4, ages 7.3-35.0 years, 124 males) were recruited from the Washington University School of Medicine Movement Disorders Center and the Tourette Association of America Missouri chapter. After quality control assessments of the neuroimaging data (see below), 101 children, adolescents, and adults with TS were included (Table 1). A group of 101 control participants was selected from an extant database (*n*=487, independent studies=14, ages 6.0–35.0 years, 206 males; recruited from the Washington University campus and surrounding community) and matched to the TS group on age, sex, IQ, handedness, and in-scanner movement (Table 1). Conditions commonly comorbid with TS (e.g., ADHD, OCD, anxiety) and medication use were not considered exclusionary for the TS group (44) (Table S1), but were for the control group. All participants completed assessments of IQ, and TS participants completed

additional assessments of symptom severity for TS, ADHD, and OCD (Supplement 1.1). Adult participants and a parent/guardian for all child participants gave informed consent and all children assented to participation.

Functional Connectivity Network Construction

Resting-state fMRI data were collected as participants viewed a centrally presented white crosshair on a black background. Participants were instructed to relax, look at the plus sign, and hold as still as possible. The duration and number of resting-state scans varied across participants. Imaging data were collected using a 3T Siemens Trio Scanner with a 12-channel Head Matrix Coil. Images were pre-processed to reduce artifacts (45). Additional pre-processing steps were applied to the resting-state data to reduce spurious correlated variance unlikely related to neuronal activity. Stringent frame censoring (frame-wise displacement>0.2 mm) and nuisance regression (motion estimates, global signal, and individual ventricular and white matter signals) were used to reduce spurious individual or group differences in functional connectivity related to head movement in the scanner (46–48). Participants with at least 5 minutes of low-motion data were included (details in Supplement 1.2-1.4).

For each participant, resting-state time-courses were extracted from a set of 300 regions of interest (ROIs) (Figure 1) covering much of the cortex (49), subcortex (50), and cerebellum (51) (available at https://greenelab.wustl.edu/data_software). Functional connectivity was measured as the correlation (Fisher z-transformed) between the resting-state time-courses for each pair of ROIs.

Support Vector Machine Learning

Support vector machine (SVM) learning was implemented (41–43) to distinguish individuals with TS from controls based on patterns of functional connections (SVM: C=1; SVR: C=Infinity, ε=0.00001; Supplement 1.5). SVM classification is a powerful tool for finding differences across many features in a multivariate dataset (here, functional connections) that, in aggregate, best discriminate groups (here, TS vs. controls). Patterns of features that best distinguish individuals by group in a training set were linearly weighted in the resulting classifier and then subsequently applied to classify new test individuals. All 44,850 functional connections

among the 300 ROIs were included as features. SVM classification was also extended to find linear patterns among features that predict a continuous variable (here, age) with support vector regression (SVR).

Testing for age-invariant or age-specific differences in functional connectivity in TS

Using SVM, two separate diagnostic classifiers were built to distinguish individuals with TS from controls based on functional connectivity from two different training sets (Child or Adult sample; Table 2). A "CHILD" diagnostic classifier was trained to separate the youngest 39 children with TS in our sample from 39 matched controls (7.4-13.1 years). An "ADULT" diagnostic classifier was trained to separate 39 adults with TS from 39 matched controls (18.1-35.0 years). Leave-one-out cross-validation (LOOCV) was used to evaluate the within-sample classification accuracy of the CHILD and ADULT diagnostic classifiers and permutation testing (training/testing classifiers that separate subjects according to permuted subject labels) was used to assess the significance of this accuracy (Supplement 1.6). The remaining 23 adolescents with TS and 23 matched controls were kept as a separate adolescent test set (13.1-16.6 years; Table 2).

We then tested if the patterns of functional connections that distinguished TS from controls in one age group (child or adult) could generalize to accurately classify individuals in another age group (Table 2). Permutation testing was used to assess the significance of the classification accuracy across age groups (Supplement 1.6). For the CHILD and ADULT diagnostic classifiers, we assessed the reliability of the classification accuracy when applied to different age groups across the folds of LOOCV and compared the performance across age groups to the performance within the training sample.

If the patterns of functional connections used to distinguish individuals with TS from controls in one age group are "age-specific," the classifier should not generalize well to the other age group (i.e., the CHILD diagnostic classifier will not accurately distinguish adults with TS from adult controls, and vice versa). If these patterns are "age-invariant," the classifier should generalize well to the other age group. We also directly tested for age-invariant differences using an ALL-AGES diagnostic classifier (Supplement 2.1).

We tested whether the results of the CHILD and ADULT diagnostic classifiers were driven by sex, comorbidities, or current medication status (Supplement 2.2), as these characteristics were not matched

across age groups (Table 1). In addition, even though in-scanner head motion was well matched across age groups and between TS and controls, additional analyses were performed to test for lingering relationships between head motion, age, and functional connectivity in TS that might affect diagnostic classification (Supplement 2.3).

Validating the generalizability of diagnostic classification in an age-matched test set

To ensure that diagnostic classification and the observed generalizability across age groups was not due to idiosyncratic or spurious group differences, we tested the generalizability of diagnostic classification to an age-matched test set. Due to the limited number of subjects within our child or adult group age ranges, we trained a separate "VALIDATION" diagnostic classifier (Table S2) to distinguish a set of 39 children/adolescents with TS from 39 age-matched controls (7.4-16.6 years), and then applied it to classify an independent age-matched test set comprising the remaining 23 children/adolescents with TS and 23 matched controls (8.0-16.6 years). Note that 48 out of 78 subjects used to train this VALIDATION diagnostic classifier overlapped with those used to train the CHILD diagnostic classifier. We also tested whether the VALIDATION diagnostic classifier could accurately classify the adult sample to compare same-age and cross-age generalizability. Subsequent analyses were conducted using the CHILD and ADULT diagnostic classifiers to minimize age effects within the child group, but we also conducted these analyses using the VALIDATION diagnostic classifier to demonstrate consistent results (Supplement 2.4).

Visualization of features from the CHILD and ADULT diagnostic classifiers

By combining the feature weights across training folds, we extracted the top most strongly weighted functional connections in the CHILD and ADULT diagnostic classifiers (e.g. 1000 out of 44,850; range: 100-5000, Supplement 2.5) and examined the percentage overlap of similarly weighted functional connections. Few overlapping connections would suggest age-specific differences between TS and controls, while many overlapping connections would suggest age-invariant differences.

Testing for anomalous or atypically shifted development of functional connectivity in TS

The functional connections that differ by diagnosis (TS vs. controls) may also vary according to age in typical development. To test this, we used SVR to build a developmental model (Table 2) using the top most strongly weighted functional connections (e.g., 1000 features) from either the CHILD or ADULT diagnostic classifier, and tested if those features could also distinguish individuals by age in the control sample (7.4-34.2 years). LOOCV was used to evaluate age prediction within the control sample and permutation testing was used to assess the significance of age prediction with each developmental model (Supplement 1.6).

We tested whether the developmental models built to predict age in the controls could generalize to also accurately predict age in the TS sample (7.6-35.0 years). Permutation testing was used to assess the significance of the age prediction in the TS sample (Supplement 1.6). To benchmark the generalizability of these developmental models to the TS sample, we also tested whether additional developmental models built to predict age in controls could accurately predict age in TS (Supplement 2.6) including using all 44,850 functional connections.

Determining if the most strongly weighted functional connections used for diagnostic classification can also predict age in both the TS and control samples places the disorder-related differences in the context of typical development. If the patterns of functional connections that distinguish TS from controls are purely anomalous such that the patterns associated with typical maturation are unaffected, the CHILD TS or ADULT TS features will predict age equivalently in both the control and TS samples. Otherwise, the maturation of these connections likely differs in TS. Specifically, if the CHILD TS or ADULT TS features predict age well in controls but inaccurately in TS, the patterns of functional connectivity that distinguish TS from controls may involve a unique and/or atypically shifted developmental trajectory. Predicted ages that are systematically older in TS than in age-matched controls and older than expected by chance would be consistent with a theory of accelerated maturation of brain networks, while predicted ages that are systematically younger in TS than in age-matched controls and younger than expected by chance would be consistent with a theory of delayed or incomplete maturation of brain networks. Predicted ages that randomly fluctuate near the mean age in TS as expected by chance would be consistent with unique maturational changes to brain networks (Supplement 2.7).

RESULTS

Patterns of functional connections can classify TS diagnosis in children and in adults, but do not generalize across age groups.

Using SVM, we successfully classified individuals as TS or controls based on patterns of functional connectivity. The CHILD diagnostic classifier (7.4-13.1 years) was 71% accurate (p<0.001, Figure 2A). The ADULT diagnostic classifier (18.1-35.0 years) was 72% accurate (p<0.001, Figure 2B). However, neither classifier accurately classified TS diagnosis in the other age groups (Figure 2). Classification accuracies are displayed as the confidence interval observed across the folds of LOOCV. Specifically, the CHILD diagnostic classifier did not distinguish TS from controls in adolescents (accuracy: 49%±3.5%, p=0.618) or adults (accuracy: 50%±1.9%, p=0.543). Similarly, the ADULT diagnostic classifier did not distinguish TS from controls in adolescents (accuracy: 47%±5.5%, p=0.763), though it was slightly better in children (accuracy: 58%±2.8%, p=0.049). Classification of the other age groups was significantly less accurate than classification in the training sample (see Figure 2). For example, the ADULT classifier was able to classify diagnosis in the children better than chance (p=0.049), but significantly worse than in the adults (p<0.001). These results suggest that the CHILD and ADULT diagnostic classifiers relied on age-specific differences in functional connectivity to best discriminate TS from controls. We also found evidence for age-invariant differences in functional connectivity in TS (Supplement 2.1). However, those age-invariant patterns were not the primary features used to distinguish TS and controls when considering children and adults separately.

Poor generalizability across age groups was not driven by sex, comorbid disorders, medication status (Supplement 2.2, Table S4), or individual differences in head motion in the scanner (Supplement 2.3, Figure S3). Moreover, poor generalizability across age groups was likely not due to overfitting as evidenced by the VALIDATION diagnostic classifier (Figure 3). The VALIDATION diagnostic classifier (7.4-16.6 years) was 64% accurate within the training sample (p=0.006) and generalized successfully to an independent age-matched sample (8.1-15.9 years; accuracy: 64% ± 7.0%, p=0.005), but not to the adult sample (18.1-35.0 years; accuracy: 54% ± 2.3%, p=0.131).

Top functional connections that distinguish TS and controls were distinct in children and adults.

Regions associated with the top weighted functional connections from the CHILD and ADULT diagnostic classifiers involved many different functional networks (Figure 4, Figure S6). Only 25 (2.5%) of the top 1000 functional connections (range across feature sets: 0%-7.4%) overlapped and shared the same sign between the CHILD and ADULT diagnostic classifiers (Figure 4C), indicating different patterns of region involvement (Figure 4A-B) and providing further evidence that the functional connections involved in TS differ in children and adults.

Functional connections that differ in TS reflect altered maturation.

Using SVR, the top weighted functional connections from the CHILD diagnostic classifier and the ADULT diagnostic classifier were each able to predict age well in the controls (CHILD: r=0.62, R^2=0.39, p<0.001; ADULT: r=0.74, R^2=0.54, p<0.001; Figure 5, *red)*. By contrast, these developmental models did not predict age well in TS. Age prediction (correlation between predicted age and true age) is reported with the confidence interval observed across the folds of LOOCV. The developmental model built to predict age in controls using the CHILD TS features did not predict age in TS significantly better than chance (r=0.11±0.028, R^2=0.012±0.0015, p=0.379), such that the children with TS were inaccurately predicted as older than age-matched controls (Figure 5A, *blue*). Visually, these predicted ages were shifted above the age expected if predicted spuriously (Figure S8A). While the magnitude of this shift in the average predicted age of the children with TS was not significant by permutation testing (p=0.177), a sign test confirmed that these predicted ages were consistently shifted older than the null distribution (p<0.001; Supplement 2.7). The developmental model built to predict age in controls using the ADULT TS features also did not predict age in TS significantly above chance (r=-0.11, R^2=0.013, p=0.176), such that the adults with TS were inaccurately predicted as younger than age-matched controls (Figure 5B, *blue*). The average predicted age of the adults with TS was significantly shifted below the mean age expected by chance (p=0.005), and the sign test confirmed this difference (p<0.001; Supplement 2.7).

Not all development of functional connectivity was disrupted in TS. We found that additional developmental models could accurately predict age in the TS sample (Supplement 2.7), importantly including the developmental model using whole-brain functional connectivity (r=0.71, R^2=0.50, p<0.001).

DISCUSSION

In the present work, we applied multivariate machine learning methods to resting-state functional connectivity MRI data to understand how functional brain organization is altered in TS over development. We found that the patterns of functional connections that best distinguished TS from controls generalized to an age-matched independent sample, but not to other age groups. Rather, the patterns of functional connections involved in TS differed between children and adults, suggesting they are age-specific. In addition, we found that these functional connections reflected atypical development in TS. Specifically, those functional connections that differed the most in childhood TS resembled brain networks of older subjects, while those that differed the most in adulthood TS resembled brain networks of younger subjects. By directly examining TS across a wide age range (7-35 years), comparing children to adults, and contextualizing these results with typical development, our findings provide evidence that the neural underpinnings of TS differ in childhood and adulthood, and may involve atypical maturation.

It has been argued that childhood and adulthood TS are fundamentally different, given the commonly described clinical trajectory in which many patients experience significant improvement or remission in adulthood (52). Our results extend this argument to the brain's functional connections. Past studies have also identified age-specific effects in TS, yet primarily within single brain regions. For example, some cortical regions (dorsal prefrontal, orbitofrontal, parieto-occipital cortex) exhibit distinct, even sometimes opposing, volumetric differences in children and adults with TS (26). Previous research has also shown that motor excitability is selectively altered in children with TS (23) and atypical development of fronto-striatal self-regulatory signals only emerges in adulthood TS (24). These findings in combination with ours suggest that treatments may need to be tailored differently for children and adults with TS.

We also characterized functional connectivity in TS in the context of typical development. In childhood TS, we found differences, albeit small, suggestive of accelerated development. It has been proposed that living with chronic tics accelerates the maturation of control systems in children with TS as a result of the need to regularly suppress tics (52, 53). Alternatively, the functional connections that characterize childhood TS may undergo a unique developmental trajectory in TS. That is, differences in brain function early in the disorder

may lead to a developmental trajectory that is distinct from that in healthy controls. In line with this idea, previous studies have reported enhanced cognitive control as well as putatively adaptive changes in brain function and structure in children with TS (54–56). In typically developing children, cognitive training yields modifications of the intrinsic connectivity among brain networks (57). Thus, it is possible that the development of compensatory tic-suppression mechanisms, either accelerated or anomalous, is reflected in the patterns of functional connectivity that best distinguish children with and without TS, and that these alterations support the improvement of tic symptoms experienced by many patients during adolescence and early adulthood (58).

In adulthood TS, we found differences in functional connectivity suggestive of delayed maturation. Adults that experience persistent tics may have maladaptive brain function that either developed with prolonged symptoms or led to the prolonged symptoms. As mentioned above, some argue that childhood TS and adulthood TS are fundamentally different, given the commonly held belief that most patients with TS experience substantial symptom improvement or remission into adulthood (9). Therefore, by studying a sample of adults with current tics, we may have captured the subsample with worse outcomes. By contrast, any sample of children with TS will include a mixture of individuals whose tic symptoms will go on to improve and those whose tics will persist. However, there is evidence that remission is likely much rarer than previously estimated (10%, rather than 40%; (12)), and in our sample, many of the adults with TS reported improvement from childhood. Longitudinal data and studies of adults with remitted tics are necessary to determine whether altered maturation of brain function in adulthood TS is a cause or consequence of prolonged symptom burden. There have been previous reports of immature brain structure and function in TS (28, 30, 59, 60). However, methodological concerns related to head motion artifact in MRI data have called some of these conclusions into question (46, 61–64). In the present study, we implemented strict processing methods that have been shown to best mitigate the artifactual effects of motion (46, 48), yet evidence for altered maturation of functional connectivity in TS remained.

Notably, not all maturation of functional connectivity was altered. The complete set of functional connections predicted age well in both TS and controls. Thus, only specific patterns of functional connections – those that best discriminated TS and controls within each age group – exhibited atypical developmental

trajectories in TS, while much of the typical maturation of functional connectivity was preserved. This finding may correspond to the clinical observation that although TS can involve diminished quality of life and academic achievement, most individuals with TS lead relatively normal lives (65, 66).

It is important to note that our TS sample was heterogeneous with respect to comorbid neuropsychiatric disorders and medication status, representative of the TS population (44, 67). The diagnostic classifiers here may have included medication-induced or comorbidity-related differences in brain function between the TS and control groups (68, 69). Additionally, our child sample included more boys than girls, while the adult sample was more balanced. This difference reflects epidemiological data, as the sex imbalance (4:1 male:female) reported in childhood TS is attenuated in adulthood TS (70). Examination of the misclassified individuals demonstrated that poor generalizability across age groups was likely not driven by these factors. However, given our limited sample size, the possibility for lurking confounding factors remains, and future studies with larger samples will be useful for directly parsing the influence of medications, comorbidities, and sex on brain function in TS.

The success of multivariate machine learning classification applied to functional brain networks holds promise for clinical application of these methods. Given the heterogeneity in the developmental course of TS symptoms, there is a great need to predict future clinical outcome for individuals. Being able to predict whether a given child with tics will go on to improve or not would have high clinical utility, providing important information to families, guiding treatment plans, and affording the opportunity for early intervention. Our findings suggest that functional connectivity contains signals that may be used for these types of predictions, and that the best predictions will likely rely upon modeling these effects in a rich typical developmental context.

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FIGURE & TABLE CAPTIONS

Table 1. Participant characteristics.

Table 2. Overview of participants in the training and testing sets for each diagnostic classifier and developmental model.

Figure 1. Regions of interest. Cortical regions were previously defined from a combination of task fMRI activation and resting state fMRI data (49). Subcortical and cerebellar regions were defined from a combination of resting state functional connectivity and review of the anatomical literature (50, 51). Cortical regions have been previously characterized as organizing into distinct functional networks (denoted by color).

Figure 2. Functional connections that best distinguished TS from controls were age-specific. A.) Performance of the CHILD diagnostic classifier was not significantly better than chance in adolescents (accuracy: 49%±3.5%, sensitivity: 93.1%, specificity: 4.4%, p = 0.618) or adults (accuracy: 50%±1.9%, sensitivity: 97.1%, specificity: 2.3%, p = 0.543) and was significantly less accurate classifying adolescents and adults than children (p-values < 0.001). B.) Performance of the ADULT diagnostic classifier was not significantly better than chance in adolescents (accuracy: 47%±5.5%, sensitivity: 19.2%, specificity: 74.8%, p = 0.763), was marginally significant in children (accuracy: 58%±2.8%, sensitivity: 29.9%, specificity: 85.6%, p = 0.049), and was significantly less accurate classifying children and adolescents than adults (p-values < 0.001).

Figure 3. Diagnostic classification was successful in a same-age, but not cross-age test set. Performance of the VALIDATION diagnostic classifier was significantly better than chance in an independent age-matched test set (accuracy: 64%±7.0%, sensitivity: 73.5%, specificity: 54.2%, p = 0.006), but not in a cross-age (adult) test set (accuracy: 54%±2.3%, sensitivity: 91.2%, specificity: 17.2%, p = 0.131). Classification of the same-age test set was not significantly different than the within-sample classification of the training set (p=0.715), but was significantly better than in the cross-age test set (p < 0.001).

Figure 4. Functional connections that best distinguished TS from controls differed between children and adults. A.) Regions are shown from the top weighted 1000 functional connections used to distinguish TS from controls in the CHILD diagnostic classifier. The size of each sphere represents region involvement (i.e., number of functional connections in the feature set involving a region). Region colors indicate the network to which that region belongs, labeled in Figure 1. B.) Regions are shown from the top weighted 1000 functional connections used to distinguish TS from controls in the ADULT diagnostic classifier. The size of each sphere represents region involvement and the color represents network affiliation. C.) The overlap of the top weighted functional connections that shared the same sign from the CHILD and ADULT diagnostic classifiers was only 25 out of 1000.

Figure 5. Functional connections that best distinguished TS from controls are consistent with atypically shifted development. A.) The developmental model built using CHILD TS features was able to predict age well in the control sample (*red*) but not in the TS sample (*blue*). Predicted ages of children with TS were older than the

predicted ages of age-matched controls. B.) The developmental model built using ADULT TS features was able to predict age well in the control sample (*red*) but not in the TS sample (*blue*). Predicted ages of adults with TS were younger than the predicted ages of age-matched controls. A Fisher z-test confirmed that the correlation between true and predicted age differed between TS and controls ($p<0.001$). The curves depict the moving average of the predicted age for each group (window = 5).

Table 1. Participant characteristics.

TS group (N = 101)

	Child sample	Adolescent sample	Adult sample
N	39	23	39
Male/Female	31/8	15/8	16/23
Age (Years)	10.9 (1.6); 7.6-13.1	14.5 (0.86); 13.1-16.6	25.9 (5.3); 18.4-35.0
Handedness (R/L)	36/3	22/1	36/3
IQ	110 (12.3); 87-135	108 (12.9); 89-135	119 (12.7); 83-139
Residual in-scanner movement (mean FD)	0.11 (0.011); 0.092-0.14	0.11 (0.013); 0.086-0.14	0.11 (0.017); 0.063-0.13
Number of "good" frames	241.2 (69.4); 121-363	260.3 (84.5); 156-459	349.7 (103.9); 153-573
YGTSS Total Tic Score	17.5 (5.5); 0-37	17.5 (8.7); 0-35	16.7 (8.3); 0-32
ADHD Rating Scale	11.0 (8.2); 0-34	10.5 (9.4); 0-34	11.9 (12.3); 0-44
CY-BOCS Score	4.8 (5.5); 0-19	4.3 (6.2); 0-22	6.8 (6.6); 0-24
Number on medications	19	14	18
Number with comorbidities	23	16	28

Control group (N = 101)

	Child sample	Adolescent sample	Adult sample
N	39	23	39
Male/Female	30/9	14/9	16/23
Age (Years)	10.7 (1.5); 7.4-12.9	14.6 (1.1); 12.9-16.5	25.9 (4.6); 18.1-34.2
Handedness (R/L)	37/2	22/1	36/3
IQ	115 (12.1); 90-139	109 (12.9); 86-136	119 (14.8); 83-145
Residual in-scanner movement (mean FD)	0.11 (0.013); 0.067-0.13	0.11 (0.015); 0.071-0.13	0.10 (0.012); 0.077-0.13
Number of "good" frames	242.6 (88.2); 139-555	252.1 (61.3); 149-371	311.3 (115.9); 170-668

Where applicable values are displayed as Average (Standard Deviation); Range
All variables did not differ between the TS and control group ($p > 0.1$) within the child, adolescent, and adult samples.
Variables did not differ between the child and adult samples ($p > 0.1$) within the TS and control groups, except for age, sex, and number of "good frames".
FD = Frame-wise Displacement (in millimeters) (45)
YGTSS = Yale Global Tic Severity Score (Total Tic Score) (46)
CY-BOCS Score = Children's Yale-Brown Obsessive-Compulsive Scale (47)

Table 2. Overview of participants in the training and testing sets for each diagnostic classifier and developmental model.

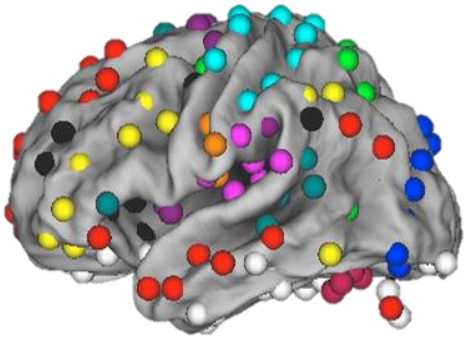
SVM

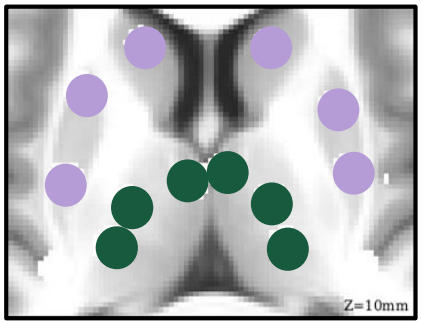
Diagnostic Classifier			N	Ages
CHILD	***Train***	***Children***	**39 TS / 39 Controls**	**7.4 – 13.1 years**
	Test	*Adolescents*	23 TS / 23 Controls	13.1 – 16.6 years
		Adults	39 TS / 39 Controls	18.1 – 35 years
ADULT	***Train***	***Adults***	**39 TS / 39 Controls**	**18.1 – 35 years**
	Test	*Children*	39 TS / 39 Controls	7.4 – 13.1 years
		Adolescents	23 TS / 23 Controls	13.1 – 16.6 years

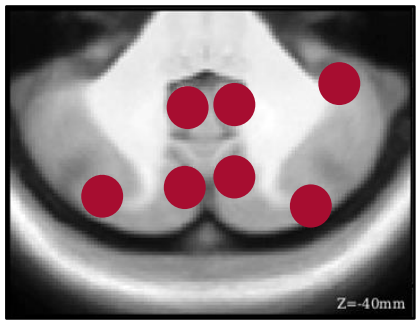
SVR

Developmental Model			N	Ages
Typical Development	***Train***	***Control sample***	**101**	**7.4 – 34.2 years**
	Test	*TS sample*	101	7.6 – 35 years

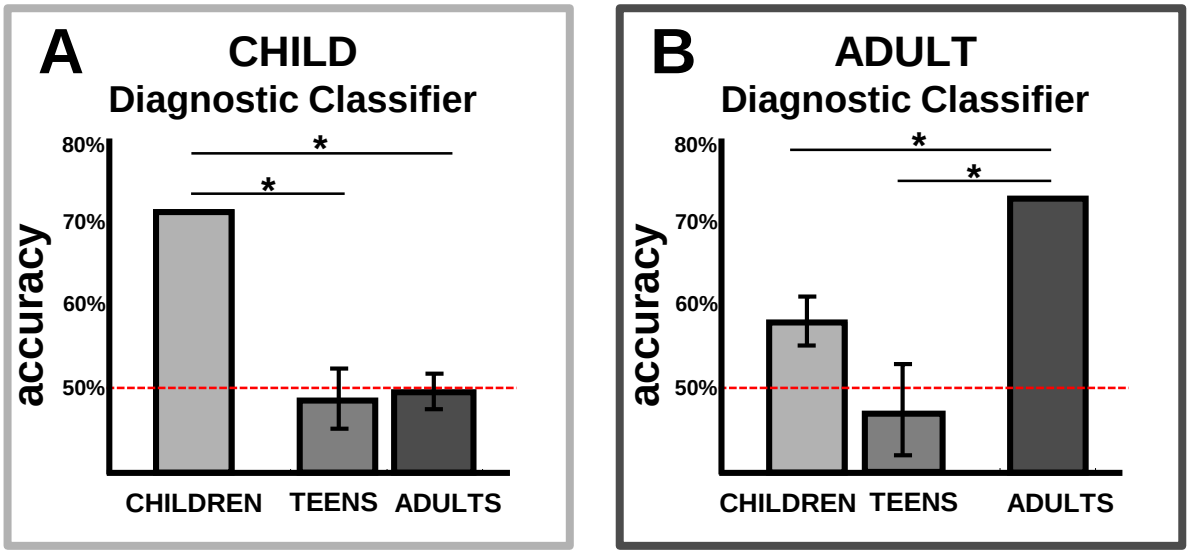
48 out of 78 children in the YOUTH training set were used in the CHILD training set
84 out of 124 children and adolescents (TS and controls) were used in Greene et al. 2016







- salience
- fronto-parietal
- cingulo-opercular
- dorsal attention
- ventral attention
- somatomotor (body)
- somatomotor (face)
- visual
- auditory
- memory
- default mode
- basal ganglia
- thalamus
- cerebellum
- unlabeled


A
CHILD
Diagnostic Classifier
accuracy
80%
70%
60%
50%
*
*
CHILDREN
TEENS
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B
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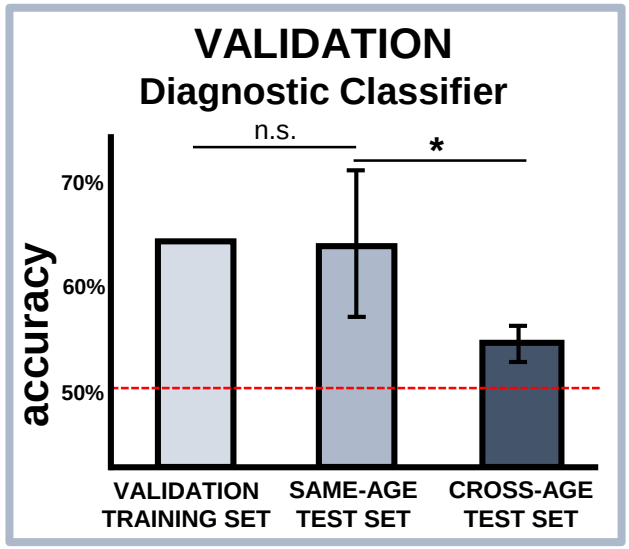
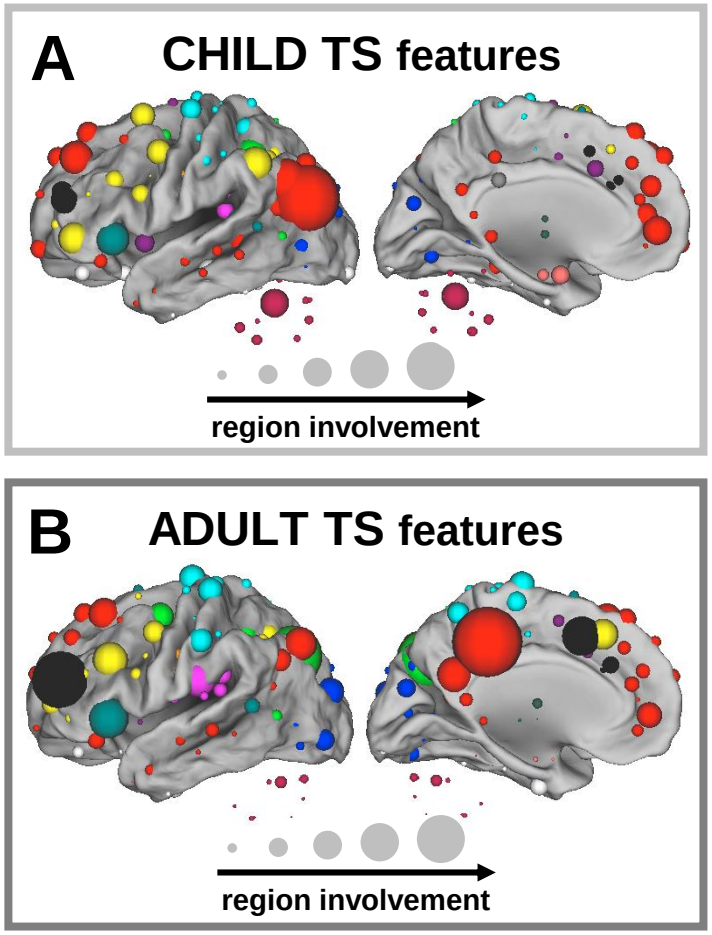
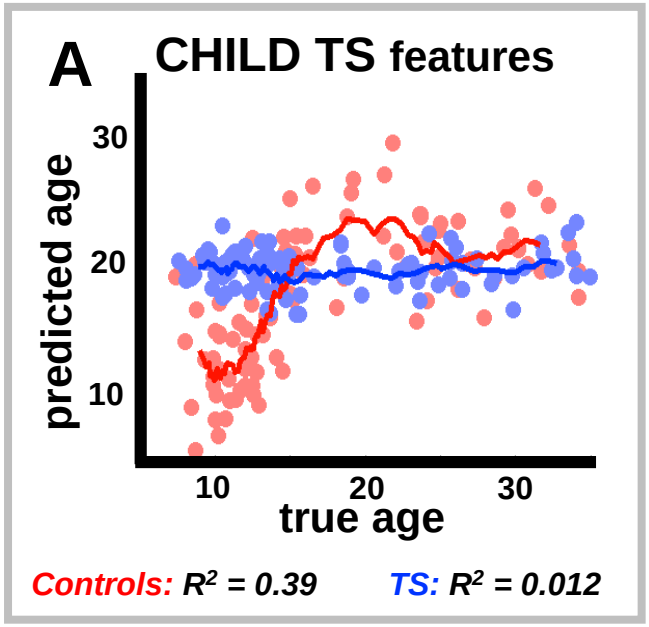
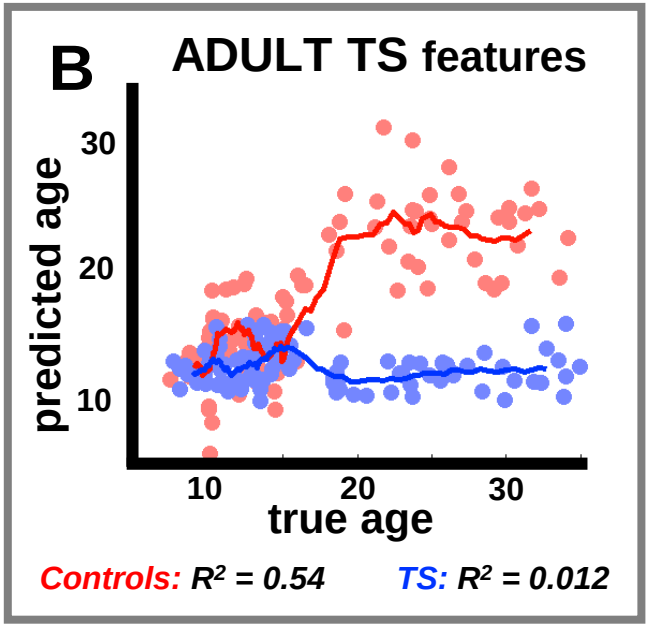
ADULTS


VALIDATION
Diagnostic Classifier
n.s.
*
70%
60%
50%
accuracy
VALIDATION TRAINING SET
SAME-AGE TEST SET
CROSS-AGE TEST SET


A
CHILD TS features
region involvement
B
ADULT TS features
region involvement
C
Overlap of Top Weighted Features
25 / 1000
CHILD TS
ADULT TS


A
CHILD TS features
predicted age
30
20
10
10
20
30
true age
Controls: R² = 0.39
TS: R² = 0.012


B
ADULT TS features
predicted age
30
20
10
10
20
30
true age
Controls: R² = 0.54
TS: R² = 0.012