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Honors Thesis Final Write-Up

Background

Tourette's Syndrome (TS) is a complex developmental neuropsychiatric disorder characterized by involuntary repeated behaviors known as tics, which are preceded by premonitory urges[1]. Tics are often broken down into two subtypes: motor and vocal tics. Motor tics can look like simple or repeated eye blinking, to complex tics that involve multiple motor regions. Vocal tics can look like simple sounds such as throat clearing to complex speech. Tics are highly heterogeneous and specific tics differ between and within individuals. Children often begin by exhibiting motor tics around ages 5-6, followed by vocal tics, which generally occur 1-2 years later. While symptoms can continue from childhood to adulthood, TS symptoms peak during adolescence, and often, though not always, improve in late adolescence and early adulthood. Common conditions that co-occur with TS are Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), and Generalized Anxiety Disorder/Anxiety[2]. TS is a highly complex and heterogeneous condition associated with periods of significant development, particularly adolescence.

Previous work investigating the neural bases of TS suggests involvement of subcortical brain structures including the basal ganglia and thalamus[2]. The basal ganglia, known for involvement in motor control and other movement disorders, is made up of several structures, including the caudate, putamen, globus pallidus, and nucleus accumbens. The caudate nucleus is involved in motor planning/control and integrating sensory and environmental information to produce movement[3]. Dysfunction in the caudate has been known to be involved in movement disorders, such as Parkison's and Huntington's disease, as well as other psychiatric conditions such as ADHD, obsessive-compulsive disorder, and schizophrenia. The putamen is also known to be highly involved in motor control and producing movement, and specifically, producing coordinated and complex movements due to its direct connection to primary motor cortex and supplementary motor area[4,5]. Putaminal dysfunction includes motor and cognitive deficits, including conditions like Parkinson disease, Huntington disease, Alzheimer disease, OCD, and Wilson disease (characterized by uncontrolled movement). Other areas in the basal ganglia are also known to contribute to motor function - the globus pallidus is primarily responsible for controlling conscious movement[6], and the nucleus accumbens is known for involvement in reward-processing, locomotion, and impulse control[7]. Given its role in modulating motor systems, the basal ganglia is a region of interest in better understanding the neural areas involved in TS. The thalamus is also a crucial subcortical structure that is highly interconnected with the basal ganglia and cortex[8,9]. Signals, particularly inhibitory signals from the globus pallidus, are integrated in the thalamus and projected to other areas of the cortex to control motor outputs. The thalamus is composed of multiple nuclei, including motor nuclei, which are responsible for conveying motor control information from the globus pallidus and striatum to the motor cortex[9]. By investigating these structures, we can better understand the factors that are involved in atypical behaviors like involuntary movement and vocalizations as a part of TS

Typical growth of these regions can inform what differences in growth look like in other conditions. Subcortical structures grow consistently from childhood to adolescence with the most changes

occurring early in life (ages 1-2). In normative development, the adjusted volume caudate, putamen, globus pallidus, and nucleus accumbens increase until age 13 and decline linearly for the remainder of early adulthood. Peak volumes of the striatum, pallidum, and thalamus all occur between ages 8 and 18[10]. Palladium development occurs the fastest, with peak volume occurring around age 8 in males and age 10 in females and decreases after this age. In the striatum, peak volume occurs around age 12 in females and age 14 in males. Thalamus development occurs the latest, with peak volume occurring around age 14 in males and 17 in females.

While previous work has investigated the presence of structural abnormalities in these regions of interest with functions involved with TS, there have been generally inconclusive results - several studies have indicated that in both adults and children with TS, striatum, and specifically globus pallidus volume is smaller[11,12]. Previous studies on the caudate have shown that the interneuron density of the caudate is decreased in TS, implying a smaller volume[13]. However, other studies have found no difference in basal ganglia volume overall, and in work conducted in a larger sample, evidence for caudate differences were not significant[14]. In postmortem subjects, however, striatal structures in TS samples had a lower density of neurons, implying smaller volumes[15]. Other work studying the putamen in TS showed enlargement of this region in boys aged 9 to 15[16]. However, this work found no significant differences in the volume of the caudate, globus pallidus, or thalamus. More work has supported enlargement of the putamen in TS, showing increased grey-matter volumes in the putamen in boys around 12.5 years old[17]. However, in previous work studying the thalamus in children and adults aged 6 to 63 with TS, the thalamus has been found to be 5% more enlarged in TS[18]. However, this was averaged across ages and did not focus on specific age ranges. The nucleus accumbens has also been studied in animal models, showing that disinhibition of this area is involved in vocal tic expression and disinhibition of the putamen elicits motor tics in a monkey sample, indicating possible involvement in TS as it presents in human TS[19].

Understanding differences in brain maturation between typically developing individuals and individuals with TS may provide insight into areas in the brain involved in TS. This can be done by evaluating the changes in relative volume of each of these regions of interest (basal ganglia and thalamus) over the peak ages of tic severity. Previous work has used nonlinear models to explore the trajectory of maturation of relative subcortical structure volume across a lifespan (3-90) in an extensive control dataset[20]. In this project, we will use this approach to map similar trajectories of subcortical volumes in TS and control groups during critical time points across childhood to early adulthood.

Previous work has also attempted to define and identify structural abnormalities in TS. Another method of identifying and classifying abnormalities is to use a classification model to predict the presence of TS. Using each of the volumes as a predictor for TS gives us the ability to pinpoint which volumes can provide the most information, and have the most differences between TS and control groups.

Research Question

The main research investigates if there are general differences in the volumes of subcortical structures between control and TS populations. This will be accomplished through three analyses to classify TS based on subcortical volumes, map developmental trajectories of the subcortical structures across TS and control groups, and explore the relationship between tic severity scores and subcortical volume.

Specific Aims

Aim 1: Classify the presence of Tourette's Syndrome using volumes of subcortical structures (caudate, putamen, globus pallidus, nucleus accumbens, thalamus) through a logistic regression classification model.

Aim 2: Characterize developmental trajectories of the volumes of subcortical structures (caudate, putamen, globus pallidus, nucleus accumbens, thalamus), in control subjects and investigate the differences in the developmental trajectories of subcortical volumes in Tourette's syndrome.

Aim 3: Examine relationships between tic severity and volume, through analyzing the YGTSS score and each subcortical volume.

Our goal is to investigate the different factors that may influence the classification and development of TS, including YGTSS and individual volumes.

Methods

Participant Demographics

The dataset includes 202 participants composed of 101 controls and 101 TS participants ages 7-36. Of the total 202 participants, 123 are male and 79 are female. Out of the 101 participants with TS, 66 have known comorbidities including ADHD, OCD, migraines, and anxiety disorders, and 51 are taking medications[21]. The average age of both groups is 17.5.

Data Collections

T1w images were collected on a Siemens 3T scanner with a voxel size of 1mm^3 . All structural images have been processed through volBrain. The volBrain software takes in an unprocessed T1w image input, and outputs an image with defined subcortical area segmentation - the software is trained on an expert group of manually outlined T1w images and is able to apply this trained knowledge to any T1w input. I conducted motion quality assessment of the T1w images, as well as a quality check of volBrain outline accuracy of subcortical regions of interest for all 202 subjects. The volBrain software also outputs the percentage of intracranial cavity volume for each subcortical area (calculation of what percentage of the total intracranial cavity volume is the caudate)[22]. In this project, the regions of interest (ROI) are the caudate, putamen, nucleus accumbens, and globus pallidum which are all part of the basal ganglia, as well as the thalamus which is highly interconnected with the basal ganglia and cortex.

Imaging Analysis

To analyze the volBrain volumetric outputs, I will be using the normalized volumes of each subcortical ROI. I will use R statistical software to organize these normalized values for each subject and each ROI. These 5 sets of values will be used as individual predictors in a logistic regression model where each variable is used as a factor to classify the subject (TS or control) through the model. Given that we

only have 5 predictive variables for 1 dependent variable and not a vast set of data points, a logistic regression is the optimal for lower dimensional analysis.

Then, to map the differences in volume across age for TS and control groups, I will use non-linear models. Older work mapping subcortical growth across the lifespan has indicated that non-linear polynomial models are advantageous compared to linear models due to the continuous nature of the dataset[20]. A newer paper suggests that the trajectory of structural growth across age is best mapped through a generalized additive mixed effect model (GAMM), so both will be used and compared for mapping quality. The GAMM is promising in that it will be able to fit the growth trajectory of each subcortical area as a function of the total volume and surface area as well[23].

A quantitative metric important to studying tic disorders is the Yale Global Tic Severity Scale (YGTSS). This is calculated after participants self-report their distress due to tics that week, and an aggregated score can measure the severity of tics in that individual that week. By examining the relationship between an individual's tic severity score and their subcortical region volume, we might be able to better understand the structural and behavioral links between tics and implicated neural areas.

The YGTSS scores will be used to examine the relationship between volume and tic severity given its quantification of tic behavior. To extract the relationship between volumes and YGTSS, we will use a multiple linear regression and consider the correlation between each of the volumes and YGTSS scores. Multiple linear regression models are optimal for this question because it allows us to directly understand the strength of the relationship with multiple independent variables (5 structural volumes) and one dependent variable (YGTSS score).

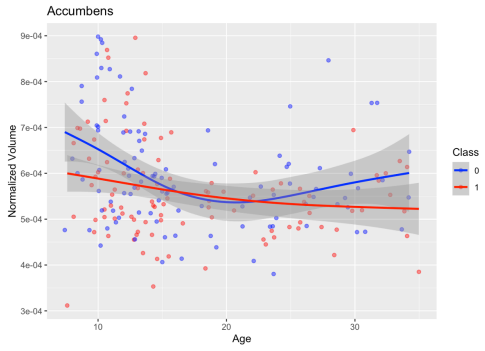
Results

I. A logistic regression model was used to perform a binary classification between TS class and control class in R. The results of this model provided p-values for each of the input variables. Out of the inputs, the p-value for the nucleus accumbens was statistically significant, with a value of 0.0403. Overall, the AUC value for the model with all 5 input volumes was 0.66. When all other variables remain constant, the volume of the nucleus accumbens has a significant effect on predicting the class (TS or control).

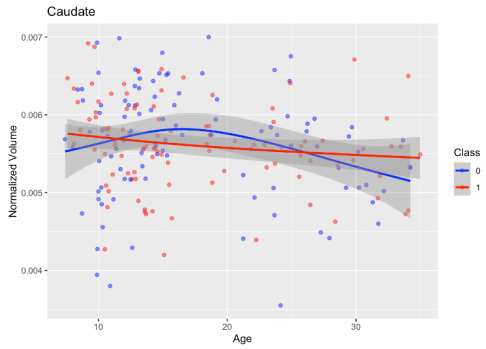
II. A generalized additive model was used to map the nonlinear trajectories of the volumes of each subcortical structure across the TS and control groups. Figures 1-5 show the mapped-out trajectories for the nucleus accumbens, caudate, pallidum, putamen, and thalamus. Each point on the scatter plot represents a subject, with the control group in blue and TS group in red. Generally, it is worthwhile to note that the accumbens and caudate trajectories had non-linear shapes for the control group

Figures A-E. Developmental Trajectory Mapping of Accumbens, Caudate, Pallidum, Putamen, Thalamus

a.



b.



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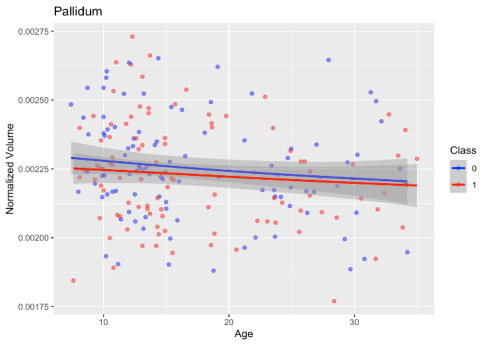

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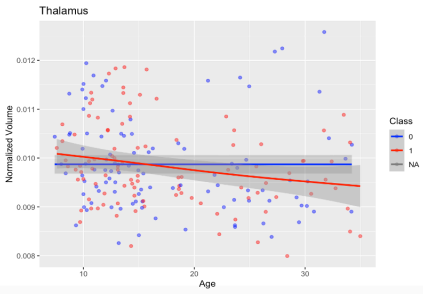
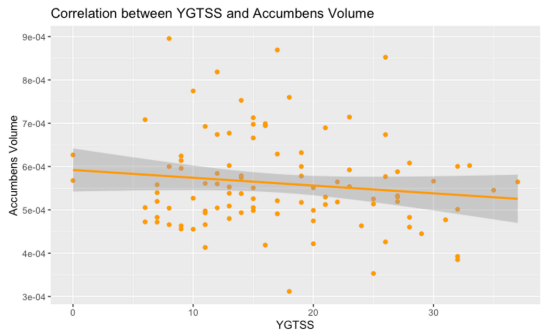


e.

III. The YGTSS scores are provided for all 101 TS group subjects. The scores ranged from 0 to 37, where subjects with a score of 0 presented no tic disruption that week. A multiple linear regression model was used to measure the effects of each subcortical volume on the YGTSS score. Out of the five variables the nucleus accumbens volume had a significant relationship with tics severity, indicated through a statistically significant p-value of 0.02. To further examine the relationships of these volumes with the tic severity score, we computed the correlations of each subcortical volume and YGTSS score. Here, we did not find any strong individual relationships between YTGSS and structure volume. Figures F-J0 show the plotted correlations.

Figures F-J: Correlations of Accumbens, Caudate, Pallidum, Putamen, and Thalamus Volumes and YGTSS Scores

f.



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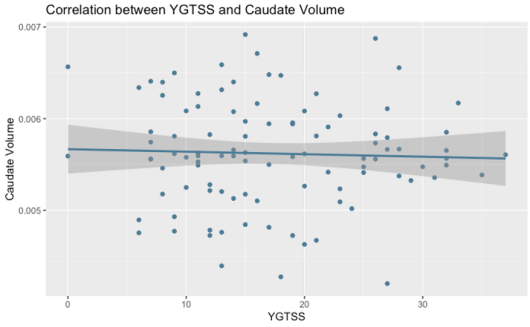

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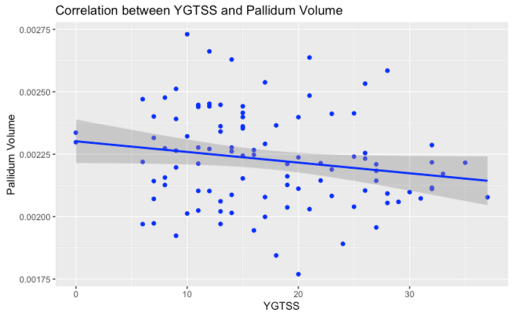
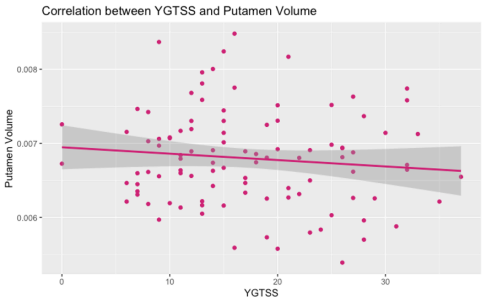


i.



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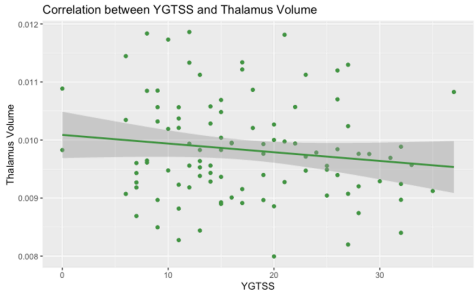

Discussion

Based on these results, we can frame our discussion around the three original aims. First, we asked if we could predict Tourette's Syndrome (TS) based on subcortical volume - when applying the logistic regression model to our data, we found that the nucleus accumbens is a significant predictor of TS classification. In the context of the model, this indicates that the volumes of the nucleus accumbens in the TS group and control group have a significant effect on the model's ability to distinguish the class. Since the other regions' volumes were not statistically significant, this indicates that they do not have a meaningful ability or effect on predicting the class of the volumes in this dataset. Next, we addressed our second aim through mapping the volumetric trajectories of each structure. We were not able to distinguish

any significant differences, meaning that in this sample the development of these structures were relatively similar. Something interesting was the shapes of the nucleus accumbens and caudate curves - it was interesting to see those nonlinear curves in the control group development while the TS group had steadily linear developmental trajectories. While these nonlinear shapes were expected given previous work mapping these areas and their growth trajectories[24], it is interesting to see that in this age group (compared to lifespan studies), there are differences in curves arising in the two groups. In our third aim, we aimed to understand the relationship between YGTSS and volumes. In our regression analysis, we found that the nucleus accumbens was a significant variable in influencing the YGTSS score - meaning that out of the 5 variables, changes in the YGTSS are best explained by changes in the volume of the nucleus accumbens. However, when examining the individual correlations between ROI volumes and YGTSS, no strong correlations emerged.

Overall, we identified that the nucleus accumbens was a significant predictor for the presence of TS as well as had a significant relationship with tic severity, meaning that when all other variables are controlled, the volume of the nucleus accumbens can indicate TS. This can be best explained by the nucleus accumbens' known role in tic expression. Tics can be understood as overlearned habits, and involve abnormal activity of cortico-striatal circuitry[25]. The involvement of the nucleus accumbens in the habitual and reward cycle implications of tics may provide explanation accumbens structural abnormalities given its functional differences.

Understanding the nucleus accumbens result better in the context of TS is a natural next step in this project, given that there was little previous research investigating structural abnormalities in the NA in Tourette's Syndrome. Next steps to specifically look at the NA may include isolating the NA volumes and running similar analyses as this explorative study. Generally, we did see that there was value in considering the nucleus accumbens volumes in both classifying TS and better explaining tic behaviors. Other future directions might include asking similar questions on a longitudinal data set, where we are able to map similar trajectories of growth within the same subject. This might remove individual differences that were present in this cross sectional study. Further work might also benefit from both a larger and better balanced dataset, where ages after adolescence have a higher number of subjects to fill in some of the gaps in this dataset.

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