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Identifying obsessive-compulsive disorder and obsessive-compulsive symptoms using neuroimaging derived phenotypes

뇌영상기반 표현형을 이용한 강박장애 및 강박증상 예측

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이 논문을 심리학석사 학위논문으로 제출함
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Abstract

Obsessive-Compulsive Disorder (OCD) is a prevalent and frequently chronic psychiatric disorder. Despite the findings of OCD-related brain structure and function based on the mass univariate approach, there are limitations in predicting OCD and the developmental trajectory of OCD symptoms at the individual level, complicating precise diagnosis and personalized interventions. With machine learning approaches, large-scale neuroimaging consortium enable research into the potential predictive value of neuroimaging in identifying OCD, going beyond traditional mass univariate results. In addition, while recent studies adopting a developmental perspective have begun to focus on pre-OCD obsessive symptoms, there is limited research on how OCD influences subsequent symptom severity. In this thesis, we leveraged two large-scale neuroimaging datasets for investigation: first, we used data from the ENIGMA OCD working group to explore whether white matter microstructure could predict OCD and its associated clinical traits. Our models showed low-to-moderate and site-generalizable accuracy in classifying "OCD vs. healthy controls" (Adults, receiver operator characteristic-area under the curve = 57.19 ± 3.47 in the replication set; Children, 59.8 ± 7.39). Second, using child data from the Adolescent Brain Cognitive Development, we examined the individual differences in the influence of OCD risk on later obsessive symptoms, as well as the moderation of resting-state functional connectivity that contribute to these differences. We hope our findings will bridge the critical gap in knowledge to advance biologically informed understanding of OCD, and ultimately improving targeted interventions.

Keyword: obsessive-compulsive disorder, obsessive-compulsive symptom, diffusion magnetic resonance imaging, obsessions, resting-state functional magnetic resonance imaging

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Table of Contents

Chapter 1: General Introduction

General Introduction to OCD

Obsessive-compulsive disorder (OCD) is a highly debilitating mental disorder, which often leads to a chronic course. OCD is characterized by the presence of obsession and compulsion. According to the Diagnostic and Statistical Manual of Mental Disorder (DSM, version 5), obsessions refer to recurring and persistent thoughts, urges, or impulses that are intrusive and unwanted, and cause considerable anxiety or distress. Compulsions are repetitive behaviors or mental acts that an individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.

OCD shows a lifetime prevalence of around 1-3% (Carmi et al., 2022). Symptoms may wax and wane in severity, but if left untreated, can persist throughout the lifespan leading to significant academic, occupational, and social impairment and reducing the quality of life (Colucciaa et al. 2016; Stewart et al. 2004). A recent meta-analysis study reported that the prevalence of obsessive-compulsive disorder in women was higher than that in men (Fawcett et al., 2020).

Most male cases occur during childhood, while most females show the onset of OCD during adolescence (Torresan et al., 2009). Despite the early age of onset, diagnosis often follows several years after the start of clinical symptoms (Hezel et al., 2022). OCD typically involves a chronic course persisting for decades. Remission is common, and few patients experience a full recovery (Fineberg et al., 2013).

Although the core symptoms of OCD are obsession and compulsion, individuals with OCD show heterogeneous symptom profiles. Studies applying a factor analysis approach have consistently reported a four-factor or five-factor model of OCD symptoms (Bloch et al., 2008). The factor model includes (1) a contamination dimension (contamination or cleanliness obsession and cleaning compulsion), (2) a harmful thoughts dimension (thoughts of harm to self and others and checking compulsion), (3) a forbidden thoughts dimension (aggressive, sexual, religious obsession with mental rituals or praying), (4) a symmetry dimension (symmetry obsession, and repeating, ordering and counting compulsion), (5) a hoarding dimension (hoarding or saving obsessions and related compulsions).

Neurobiological model of OCD

Structural abnormalities

The efforts to identify correlates of OCD began by identifying differences in morphology between OCD and healthy controls. While initial studies showed inconsistent findings due to the limitation of small sample sizes or methodological inconsistency, recent neuroimaging studies have overcome those problems and conducted mega-analysis leveraging large sample sizes.

Neural correlates of obsessive-compulsive disorder. The first voxel-based morphometry (VBM) study showed that patients with OCD had reduced grey matter volume in the medial frontal gyrus, the medial orbitofrontal cortex, and the left insulo-opercular region (Pujol et al., 2004). Patients with OCD also showed increased grey matter volume bilaterally in the ventral part of the striatum and in the anterior

cerebellum. Moreover, OCD patients with aggressive obsession and checking compulsion showed reduced amygdala volume, suggesting different neural mechanisms might underlie different symptom profiles.

While initial VBM studies showed promising results, relatively small sample sizes might lead to false positive and false negative cases. The first meta-analysis study of OCD included 12 different VBM studies (401 people with OCD and 376 healthy controls) (Pujol et al., 2004). They found increased grey matter volumes in bilateral lenticular nuclei (extending to the caudate nuclei) and decreased volumes in the bilateral dorsal medial frontal cortex. However, the decreased dorsal medial prefrontal volume was not specific for OCD and was also observed in people with anxiety disorders (Radua et al., 2010).

Because of the limitations of meta-analysis that could not perform analysis with raw neuroimaging data, the OCD Brain Imaging consortium began for mega-analysis. OCD patients showed reduced volume in the dorsomedial prefrontal cortex, the anterior cingulate cortex, and the inferior frontal gyrus, and increased volume in the cerebellum (de Wit et al., 2014). They also found group-age interactions, suggesting OCD showed relative preservation of volume in the putamen, insula, and orbitofrontal gyrus and a relative loss of volume in the temporal cortex bilaterally compared with healthy controls with increasing age. Moreover, another study also found age and group interaction in the parietal cortex, indicating increased thinning in the parietal cortex with age in the OCD relative to healthy controls (Subirà et al., 2016).

Large-scale mega-analyses were conducted within the ENIGMA-OCD consortium, which allowed the investigation of age-specific morphological differences. In a sample of 1,950 OCD patients (adult 1,498, pediatric 407) and 1,760 healthy controls (adult 1,436, pediatric 324), OCD patients showed a thinner parietal cortex across age groups (Premika et al., 2018). Medicated adult OCD patients showed a more widespread pattern of reduced cortical thickness compared with unmedicated adult OCD. In addition, pediatric and adult OCD showed distinct subcortical volume abnormalities (Boedhoe et al., 2017). Adult OCD patients showed smaller hippocampal and larger pallidal volumes, compared with adult healthy controls. Unmedicated pediatric OCD patients showed larger thalamic volumes, while adults did not show any differences in the thalamus.

Alterations in white matter microstructure were also identified in several studies. One meta-analysis study reported widespread white matter alterations, particularly in the anterior midline tracts (crossing between the anterior parts of the cingulum bundle and the body of corpus callosum), and in samples with a higher proportion of medicated patients (Jenkins et al., 2016). A recent mega-analysis by the ENIGMA working group found that adult OCD patients showed reduced FA in the sagittal stratum and its association with a younger age of onset, longer duration of illness, and a higher percentage of medicated patients; however, they did not find any significant white matter abnormalities in pediatric patients compared to healthy controls (Piras et al., 2021).

Neural correlates of obsessive-compulsive symptoms. A few neuroimaging studies found neural correlates in subclinical levels of OCD. Weeland et al. (2021) investigated morphological differences between children with probable OCD (OCS over

the clinical cutoff) and the control group with a population-based large sample (N = 2,551). They found a larger thalamus in children with probable OCD compared with the control group. The most recent meta- and mega-analyses by the ENIGMA OCD working group found larger thalalums only in pediatric unmedicated patients with OCD (Boedhoe et al., 2017). Larger thalamus was observed not only in unmedicated pediatrics but also in probable OCD pediatrics who did not have a diagnosis of OCD. These findings suggest that larger thalamus would be a potential biomarker of OCD.

Another population-based OCS study also found neural correlates of OCS (N = 11,876) (Pagliaccio et al., 2020). While they failed to find any significant morphological associations with OCS, they found that higher OCS was associated with lower FA in the left superior cortico-striatal tract (SCS). These studies suggest that structural alterations can be detected in youths with OCS.

Neurocircuits involved in obsessive-compulsive disorder.

Initially, OCD has been linked to dysfunctions within cortico-striatal-thalamo-cortical (CSTC) circuits. However, it's now understood that other circuits, including fronto-limbic, fronto-parietal, and cerebellum, also contribute (Shephard et al., 2021). Abnormalities in these different neurocircuits likely interact with each other to generate the complex OCD phenotype.

This section summarizes the previous model of the neurocircuitry involved in OCD. **The fronto-limbic circuit** includes subcortical and cortical brain regions involved in generating (amygdala) and evaluating (ventromedial prefrontal cortex (vmPFC))

emotional responses (van den Heuvel et al., 2016, Kohn et al., 2014) amongst other functions. Additionally, this circuit links to cortical areas, such as the dorsolateral and dorsomedial prefrontal (dlPFC/dmPFC) regions of the dorsal cognitive circuit, which are implicated in emotion regulation (van den Heuvel et al., 2016, Kohn et al., 2014). A consistent observation in OCD is the dysfunctional activity within the fronto-limbic circuit during emotional processing (Thorsen et al., 2018).

The sensorimotor circuit includes cortical and subcortical regions involved in the generation and control of motor behaviors and the integration of sensory information (van den Heuvel et al., 2016). Sensory phenomena and altered habit formation are involved in the sensorimotor cortex. Sensory phenomena, often experienced by a significant portion of patients (60-70%), refers to uncomfortable sensations or perceptions that induce repetitive behaviors, aside from the well-known fear-driven OCD symptoms related to potential threats (Shephard et al., 2021). The term "altered habit formation" relates to habits, which are rigid, largely subconscious behaviors indifferent to motivation and outcomes. Excessive habit formation, possibly due to heightened activity in the sensorimotor circuit or an over-dependence on the habit-learning system rather than the goal-oriented system, could be a factor underlying certain compulsive behaviors (e.g., checking) in OCD (Shephard et al., 2021).

The ventral affective circuit encompasses the orbitofrontal cortex (OFC), ventral striatum (particularly the nucleus accumbens), and thalamus. This circuit might be associated with disrupted reward responsiveness, a term indicating changes in the

capacity to anticipate, symbolize, and react to rewards, such as diminished sensitivity to rewards and overgeneralization of punishments.

The dorsal cognitive circuit supports executive functions essential for efficient goal-oriented behavior, such as planning, working memory, and superior regulation of emotional, motivational, and sensorimotor processes (van den Heuvel et al., 2016). These dorsal cognitive areas link with the inferior parietal regions, constituting the fronto-parietal network.

The ventral cognitive circuit comprises prefrontal and striatal regions that are instrumental in self-regulatory behaviors (van den Heuvel et al., 2016). One critical function of this circuit implicated in OCD is response inhibition—the capacity to suppress inappropriate actions. This function is partly controlled by the inferior frontal gyrus (IFG) and the subthalamic nucleus (STN) (van den Heuvel et al., 2016, Aron et al., 2014), with additional involvement of regions beyond the ventral cognitive circuit, such as the inferior parietal lobule and insula (Swick et al., 2011). The persistence of maladaptive, repetitive thoughts and actions in OCD, despite the individual's recognition of their excessiveness, irrationality, and negative impacts, points to possible inhibition deficits. These dysfunctions might contribute, at least in part, to the manifestation of obsessions and subsequent compulsive behaviors.

Developmental perspective on symptoms and disorder onset

During normative development, children show repetitive, ritualistic, and compulsive-like behavior that resembles OCS. Evans et al. (1997) found that many OCSs were found in

children aged 2 to 4 years when targeting normal children aged 8 months to 6 years. They classified compulsive-like behavior into two groups: repetitive behaviors (e.g., insistence on the same routines and schedules, repeating actions over and over again), and 'just right' behavior (e.g., insistence on symmetry and ordering). This suggests that obsessive-compulsive behavior may also occur in normal children who do not have obsessive-compulsive disorder.

Subsequent studies report that OCS is a risk factor that increases the incidence of OCD and is associated with decreased cognitive function. A longitudinal population-based study found that 8% of children at age 11 reported having OCS, and children who reported subclinical OCS at this age were more likely to develop OCD at follow-up assessments that occurred at 26 and 32 years (Fullano et al., 2009). Moreover, studies also showed that OCS was associated with a deficiency in cognitive ability (e.g., cognitive flexibility, response inhibition) (Sternheim et al., 2014, Abramovitch et al., 2015).

However, not all children who report OCS will go on to develop OCD. In fact, ritualistic and compulsive behavior is also present in normal developments (Evans et al., 1997). Further, a recent longitudinal study found different developing trajectories for youth with OCS (Luke et al., 2021). The authors assessed the occurrence of OCS in the study participants from pre-kindergarten to high school. The findings indicated that the progression of OCS could be categorized into three distinct paths (i.e., pre-kindergarten peak, high school peak, no peak groups). The study demonstrated that OCS fluctuates over time, and individuals with OCD may exhibit diverse onset patterns. Given the

dynamic brain development during childhood and adolescence, different patterns of brain development may correspond to specific OCS progressions, though this hypothesis remains unconfirmed.

To summarize the developmental perspectives on OCD presented above, children show compulsive-like behaviors during normative development that coincide with the maturation of the neural systems responsible for among others behavioral inhibition. These normative compulsive behaviors mirror clinical OCD symptoms in terms of their phenomenology and proposed neuropsychological basis. Early OCS can predict clinical OCD in later life and the earliest signs of OCD can often be traced back to early normative compulsive-like behaviors, suggesting a potential continuity between the normative symptoms and clinical OCD. Though mechanisms underlying these risk factors are poorly understood, it is proposed they are mediated by alterations in the structure and function of OCD-relevant neural circuitry.

Rationale, research question, and thesis outline

The overarching goal of this study is to contribute to early interventions and the understanding of the developing mechanism of Obsessive-Compulsive Disorder (OCD). To achieve this, I have extensively reviewed OCD neuroimaging studies and, consequently, have identified two major gaps in the literature.

Literature gap 1. The extent to which cerebral white matter microstructure can differentiate obsessive-compulsive disorder has not been definitively established in large datasets.

Previous neuroimaging research has disclosed anomalies in the brain structure of OCD patients, providing a basis for a plausible neural circuit model elucidating OCD. These studies primarily highlighted pervasive morphometric alterations and white matter microstructural aberrations in OCD individuals. Although this body of research has significantly contributed to our understanding of the neuroanatomical characteristics associated with OCD, the potential of these characteristics in accurately identifying OCD patients remains ambiguous.

A considerable proportion of this research has relied on mass-univariate analyses and linear interactions. This approach bears inherent limitations as it fails to encapsulate the brain's intricate nature as a complex system underpinned by non-linear interactions. This, in turn, casts doubt on the feasibility of implementing early intervention strategies grounded in these studies.

To actualize an early intervention for OCD based on neuroimaging, there is a pressing need to assess the disability prediction efficacy using the most comprehensive

neuroimaging dataset of OCD patients available currently. This endeavor will provide valuable insight into the practicability of OCD prediction based on neuroimaging. Furthermore, by discerning the variables that substantially contribute to the predictive model, we may ascertain if they correspond with the previously unveiled brain regions. This could potentially refine the neurobiological model of OCD, ensuring a more holistic understanding of this disorder.

Considering the literature gap, we proposed **research questions** as follows: Utilizing the most extensive existing neuroimaging dataset for OCD patients, can white matter microstructure have utility for OCD identification and associated clinical factors? Is there a notable correlation between brain-based OCD risk and clinical variables? Which white matter tracts contribute to the recognition of OCD?

In Chapter 2, we developed machine learning models that classified OCD and related clinical variables, such as medication status and unmedicated OCD, leveraging data from 1,336 adult and 317 pediatric participants in the ENIGMA-OCD working group. This dataset represents the largest neuroimaging collection of OCD patients currently available. Our approach involved utilizing H2O Driverless AI (version 1.8.7.1) for automated machine learning, applying anisotropy and diffusivity estimates of white matter (FA, MD, AD, RD; N=252; 4 * {(19 fascicules * 3 (left, right, total) + 5 fascicules (total; e.g., corpus callosum, fornix) + average metrics across all fascicules)} as well as biological variables such as age and sex. We then assessed the performance of these models using metrics like ROCAUC, sensitivity, specificity, and accuracy. To explore associations between brain-based OCD risk and clinical variables such as severity and

age of onset, we implemented a generalized linear model. Additionally, we employed k-LIME (k-Local Interpretable Model-agnostic Explanation) to analyze feature significance. Our hypothesis suggested that our models would outperform the morphometry model (Bruin et al., 2020), examine a link between brain-based OCD risk and clinical characteristics of OCD, and demonstrate the contribution of the CSTC-related tract to diagnosis classification.

Literature gap 2. Individuals with Obsessive-Compulsive Symptoms (OCS) are heterogeneous, and underlying factors have yet to be investigated.

Based on current research findings, it is limited to predict the symptomatic changes in children at risk for OCD. In the absence of intervention, OCS do not necessarily escalate over time. OCS is prevalent among numerous normative developing children during their formative years (Evans et al., 1997). Often, these symptoms decrease as the child grows, underscoring the potential for spontaneous alleviation of symptoms over time (Zohar & Felz, 2001). Indeed, longitudinal studies monitoring OCS from pre-kindergarten to high school have identified a symptom reduction trend in high-risk pediatric OCD cases, despite an elevated risk in adolescence among initial low OCS risk groups (Luke et al., 2021). Thus, it is not definitively inevitable for children with OCS to experience symptom worsening.

Heterogeneity in prognoses is anticipated among children presenting with OCS. The body of research on OCS prognosis is sparse, with even fewer studies investigating individual outcome differences. Previous OCS studies primarily concentrated on the OCD risk group, identified by surpassing thresholds on OCS measures. This group

exhibited diminished neurocognitive capabilities, including cognitive flexibility and response inhibition (Sternheim et al., 2014, Abramovitch et al., 2015). Recent neuroimaging studies have suggested potential abnormalities in youth demonstrating high OCS, who are generally considered at risk for OCD. Some reports have indicated an enlargement of the thalamus and ventral nuclei in children who may develop OCD (Weeland et al., 2020, Weeland et al., 2022), and possible abnormal functional connectivity in the putamen and thalamus among adolescents (Suñol et al., 2021). These findings could imply a link between OCS and neurocognitive deficits, suggesting the possibility of underlying brain changes. Yet, it should be noted these studies often treat the OCS group as homogenous, potentially neglecting individual prognosis variations, and the factors influencing such variations warrant further research.

Given this literature gap, we proposed **research questions** as follows: What are the patterns of symptomatic changes in children at risk for OCD over time? What factors contribute to the spontaneous alleviation or exacerbation of OCS in children, particularly in the transition from childhood to adolescence? To what extent does the prognosis vary among children presenting with OCS, and what factors influence these variations?

In Chapter 3, we used a generalized random forest to identify the individual differences in the influences of OCD risk on OCD symptom severity in preadolescents and whether neural and psychosocial factors contribute to the individual differences. We defined a risk for obsessive-compulsive disorder if symptoms exceed a certain threshold. We build generalized random forest models to identify variance in OCD risk effect on

OCD symptom severity. We statistically tested whether there is heterogeneity in OCD risk effect on OCD symptom severity.

Chapter 2: White matter diffusion estimates in obsessive-compulsive disorder across 1,653 individuals: Machine learning findings from the ENIGMA OCD Working Group

This chapter was jointly written with the following principal co-authors; Gakyung Kim†, ENIGMA-OCD working group, Paul M. Thompson, Willem B. Bruin, Guido A van Wingen, Federica Piras, Fabrizio Piras, Dan J. Stein, Odile A. van den Heuvel, H. Blair Simpson, Rachel Marsh, Jiook Cha

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Introduction

Obsessive-compulsive disorder (OCD) is a common, often chronic psychiatric disorder, affecting 1.0-1.5% of the global population over their lifetime (Fawcett et al. 2020). Extensive neuroimaging research suggests structural and functional abnormalities in cortico-striato-thalamo-cortical (CSTC) circuits in OCD (Boedhoe et al. 2017; de Wit et al. 2014; Norman et al. 2016; Stein et al. 2019; Chamberlain et al. 2008; Menzies et al. 2008). The field has also started to address the question of whether multivariate analyses of neuroimaging data can be used to classify OCD (W. Bruin et al. 2019; W. Bruin et al. 2020).

Prior OCD studies with relatively small to modest samples show mixed findings, with OCD classification accuracies varying from 66% to 100% (W. Bruin, Denys, and van Wingen 2019). However, the generalizability of such findings has rarely been tested, and reproducibility failures have been a major challenge in psychiatric neuroimaging

(Zhou et al. 2018; W. Bruin et al. 2020; Yun et al. 2015; Hoexter et al. 2013). Indeed, typical single-site neuroimaging studies seeking brain-wide associations with psychopathology using small sample sizes of tens to hundreds of individuals may report inflated effect sizes, decreasing reproducibility (Marek et al. 2022).

The ENIGMA OCD consortium has allowed rigorous mega-analyses and meta-analyses based on the largest international multisite neuroimaging datasets to date (W. Bruin et al. 2020). A machine learning analysis of regional measures of cortical thickness, surface area and subcortical volume found that model performance did not exceed chance-level, but that classification performance was improved when individuals with OCD were grouped according to medication status.

Altered white matter pathways have been implicated in the neurobiology of OCD (Radua et al. 2014). An ENIGMA-OCD study using diffusion tensor imaging reported significantly lower fractional anisotropy (FA) in the sagittal striatum (SS) and posterior thalamic radiation (PTR), higher mean diffusivity (MD) in the SS and higher radial diffusivity (RD) in SS and PTR (Piras et al. 2021). However, the question of whether white matter diffusion tensor imaging findings can be used to classify OCD has not yet been explored in large and multisite studies.

In this study, we therefore used ENIGMA-OCD on diffusion tensor imaging to test the classification power of such measures in a large multisite sample of individuals with OCD and healthy controls. We tested several machine learning algorithms to distinguish those with OCD versus healthy controls, as well as to distinguish OCD individuals off medication versus healthy controls, and to distinguish OCD individuals on

versus off medication. We also assessed the site-variability and reproducibility of predictive models using leave-one-site-out cross-validation and evaluated the utility of a post-processing harmonization tool (i.e., NeuroComBat). Finally, we employed a machine learning interpretation framework to assess which features were most relevant to the various classifications.

Methods

ENIGMA-OCD Working Group

Data from the ENIGMA-OCD Working Group recruited from 18 international research institutes were used. We analyzed data from 1,653 participants, including 1,336 adult participants (429 unmedicated OCD, 261 medicated OCD, 646 HC) and 317 pediatric participants (70 unmedicated OCD, 105 medicated OCD, 142 HC) (Table 1). Here, we defined pediatrics as under the age of 18 years old, consistent with previous work from the ENIGMA-OCD working group (Boedhoe et al. 2017, 2018; W. Bruin et al. 2020). The diagnosis of OCD and other comorbid conditions (i.e., anxiety disorders and major depressive disorder) were assessed using DSM-Ⅳ criteria (American Psychiatric Association, 2000). Clinical characteristics included medication status, childhood-onset, disease duration (in years), symptom severity (total scores ranging from 0-40 on the (Child) Yale-Brown Obsessive-Compulsive Scale ((C)Y-BOCS) (Goodman, 1989; Scahill et al. 1997) and current or lifetime history of symptom dimensions (i.e., aggression/checking, cleaning/contamination, sexual/religion, hoarding,

ordering/symmetry). Participants who did not have medication information were excluded from the medication classification analysis.

Image Acquisition and Processing

Image preprocessing, including brain extraction, eddy current correction, movement correction, echo-planar imaging-induced distortion correction, and tensor fitting, was conducted at each site, and Tract-Based Spatial Statistics (TBSS) was performed using protocols and quality control pipelines provided by the ENIGMA-DTI working group (http://enigma.ini.usc.edu/protocols/dti-protocols/) (Piras et al. 2021). For the entire skeleton in each hemisphere, four DTI measures (FA, MD, AD, and RD) were estimated within 25 tract-wise regions of interest (ROIs) based on the Johns Hopkins University (JHU) white matter parcellation atlas (Piras et al. 2021).

OCD classification with Machine Learning

We conducted automated machine learning (AutoML) with H2O Driverless Artificial Intelligence (AI) (DAI, 1.8.7.1 version) using white matter anisotropy and diffusivity estimates (FA, MD, AD, RD; N=252; 4 * {(19 fascicules * 3 (left, right, total) + 5 fascicules (total; e.g., corpus callosum, fornix) + average metrics across all fascicules)} and biological variables (age, sex). Three classification models were built in adult and pediatric samples, separately: (1) OCD vs. HC, (2) unmedicated OCD vs. HC (to test the effects of pure OCD–not confounded by medication effects–on the white matter), (3) medicated OCD vs. unmedicated OCD (to test the medication effects on the

white matter). To prevent data leakage and reduce model overfitting, we split the entire data into a discovery set (80%) and a replication set (20%) (stratified by diagnosis). In the discovery set, we used leave-one-site-out (LOSO) cross-validation (11 sites for adults, seven sites for pediatrics) (Figure 6). With this scheme, within the discovery set, we evaluated the cross-site variability (or generalizability); within the replication set, we tested the overall model generalizability considering potential site variability. The test samples of the discovery data were not used during model optimization. The machine learning pipeline in AutoML involves the estimation of several base models (e.g., XGBoost, LightGBM, the general linear model (GLM)) and stacked ensemble models (Laan et al. 2007) derived from base models. The AutoML pipeline performs random hyperparameter tuning along with feature transformation (e.g., interaction encoding, numeric to categorical target encoding). Firstly, in each iteration, models learn and update the weights of the features and select important features based on the prior iteration. Then, the pipeline searches for the best feature transformations and model parameters using genetic algorithm (Whitley, 1994). In DAI, this procedure is called "feature evolution". In genetic algorithm's evolution can be seen as a competition between mutating parameters to find best "individuals" refering to information about feature transformations and hyperparameters. The feature evolution procedure is not completely random and is informed from the variable importance interactions obtained from the modeling algorithms. So, this model training procedure including feature selection, transformation, and hyper-parameter tuning was performed using 11-fold-cross-validation scheme. In each fold, 10 folds were used for training the model, while

the remaining 1-fold was used to (cross)validate the best training model. Finally, the best cross-validation models from each fold were combined and tested on a held-out replication set. In this way, the validation data within the 11-fold cross validation was not used for model optimization and feature evolution. Likely, replication data was not used for data preprocessing, model training or optimization. We used the ROC-AUC as the primary performance metric and accuracy, sensitivity, and specificity as additional metrics. pROC v. 1.16.2 in the R programming language was used to calculate the metrics (Robin et al. 2011).

NeuroCombat Harmonization

To reduce potential biases caused by site and scanner effects, we employed NeuroComBat harmonization (Fortin et al. 2018). ComBat, a short name for combatting batch effects when combining multiple batches (Fortin et al. 2017, 2018), corrects potential scanner/site effects on brain data by harmonizing the mean and variance of brain measures across scanners. We separately harmonized the diffusivity measures in the discovery and replication data while also including age and sex as covariates in the model matrix. Non-parametric empirical Bayes adjustments were used to adjust for batch effects.

Model Interpretation

To interpret the machine learning classifiers, we calculated the relative weights of DTI features contributing to OCD classification. We used two steps to determine the

relative weights of DTI features contributing to OCD classification. First, we calculated the relative weights of each base model according to the model-specific algorithm. For LightGBM and XGBoostGBM, DAI computed the average reduction in impurity across all trees. Second, the importance of each base model was multiplied by its weight and normalized. We further implemented a machine learning interpretation framework, K-Local Interpretable Model-agnostic Explanation (K-LIME) (Ribeiro, Singh, and Guestrin 2016). This method fits surrogate linear models to data to extract the important features either positively or negatively associated with a target outcome: (1) OCD vs. HC, (2) unmedicated OCD vs. HC, and (3) medicated OCD vs. unmedicated OCD.

Statistical Analysis

To assess the effects of sites on diffusion white matter estimates, we performed principal component analysis (PCA). We tested the association between predicted OCD probabilities and clinical variables (e.g., medication status, childhood-onset) using stepwise regression models (Ganesh et al. 2021). Additionally, we tested site effects on individual classification performances (i.e., whether participants were correctly classified as OCD or HC). To adjust for potential confounding factors, we included the following variables as covariates: age, sex, site, and average DTI metrics (i.e., mean FA, AD, RD, MD).

Results

Demographic Characteristics

This study included 1,336 adult participants (690 OCD, 646 HC) and 317 pediatric participants (175 OCD, 142 HC). Out of the adult OCD samples, 37.8% were taking medication, while 60% of the pediatric OCD sample were taking medication. OCD patients showed comorbidity with lifetime anxiety disorders (adult: 11.02%, pediatric: 27.4%) and major depressive disorder (adult: 12.2%, pediatric: 10.3%). **Table 1** and **Table 2** contain detailed demographic and clinical characteristics of the participants. Demographic characteristics were not significantly different between OCD and HC (P's> 0.45). However, the clinical characteristics varied across sites, including childhood-onset: X2= 93.66, p<0.001, and symptom dimensions: Aggression/checking: X2=64.33, p<0.001, Cleaning: X2=53.02, p=0.002, sexual/religious: X2= 46.33, p=0.012, hoarding: X2=73.06, p<0.001, symmetry/ordering: X2= 145.03, p <0.001 in adults. Illness duration also varied across sites in the pediatric samples, F = 13.20, p<0.001.

Table 1. Demographic and clinical characteristics of patients with obsessive-compulsive disorder (OCD) and healthy controls (HCs).

Characteristics	Adult sample (n = 690) OCD	Adult sample (n = 646) HC	Pediatric sample (n = 175) OCD	Pediatric sample (n = 142) HC
Demographic Characteristics				
Age (years)	31.6± 9.78	30.8± 9.97	14.5±2.3	14.3±2.4
Male N (%)	397 (25.6)	380 (24.2)	97 (27.8)	77 (22.1)
Clinical Characteristics				
OCD illness severity score	25± 7.11		20.8±8.0	
Childhood-onset N (%)	351 (51.7)			
Duration of illness	12.4± 11.1		3.0±2.5	
Medication use at time of scan N (%)	261 (37.8)		105 (60)	
Lifetime diagnosis				
Anxiety	76 (11.02)		48 (27.4)	
Major depression	84 (12.17)		18 (10.3)	
Current comorbid disorders				
Anxiety	69 (10.0)		29 (16.6)	
Major depression	77 (11.2)		6 (3.4)	
OCD symptom dimension				
Aggressive/checking	411 (59.6)		73 (41.7)	
Contamination/cleaning	355 (51.5)		62 (35.4)	
Symmetry/ordering	370 (53.6)		68 (38.9)	
Sexual/religious	228 (33.0)		55 (31.43)	
Hoarding	114 (16.5)		47 (26.9)	

Note. Symptom score was indicated by total score on the adult and child version of the Yale-Brown Obsessive Compulsive Scales. OCD symptom dimensions were measured with the YBOCS symptom checklist.

Table 2. Demographic and clinical characteristics of each site.

Site	OCD/HC (N)	Age	Male	Medicated N (%)	Childhood-onset N (%)	Duration of illness	YBOCS score	Lifetime anxiety N (%)	Lifetime depression N (%)
(A) Adult									
Amsterdam	38/34	39.2±10.5	16 (42.1)	0	24 (66.7)	23.7 ± 12.8	21.3 ± 6.1	16 (42.1)	18 (47.4)
Bangalore	158/131	28.1±6.2	90 (57)	63 (40)	47 (29.7)	7.2 ± 5.2	25.5 ± 6.5	14 (8.7)	21 (13.3)
Capetown	22/26	30±10.2	11 (47.8)	9 (39.1)	17 (73.9)	17.2 ± 11.5	23 ± 4.2	0 (0)	0
Kyoto	35/41	31.3±8.7	14 (40)	0	10 (28.6)	7.7 ± 6.2	21.9 ± 6.6	3 (8.6)	0
Milan	63/65	34.3±11.4	44 (69.8)	38 (60.3)	41 (65.1)	18.9 ± 11.6	31.4 ± 5.2	1 (1.6)	5 (7.9)
NYC	16/18	27.9±6.9	5 (31.3)	13 (81.3)	13 (81.3)	15.1 ± 6.7	19.9 ± 5.9	8 (50)	3 (18.8)
Munich	73/60	31.1±9.6	47 (64.4)	44 (60.3)	41 (56.9)	13.5 ± 10.3	20.8 ± 6.2	0 (0)	0
Rome	77/111	36.5±11	50 (65.8)	68 (89.5)	42 (56.8)	17.3 ± 12.8	23.2 ± 9.3	8 (10.5)	7 (9.2)
Sao Paulo	37/29	36.3±11.7	16 (43.2)	13 (35.1)	31 (88.6)	26.3 ± 13.5	29.2 ± 6.2	25 (67.6)	28 (75.7)
Seoul	92/86	26±6.5	60 (65.2)	13 (14.1)	41 (46.1)	6.2 ± 7	25.8 ± 6.9	1 (1.1)	2 (2.17)
Shanghai	79/45	29.2±9.2	44 (55.7)	0	21 (26.9)	6 ± 5.9	26.2 ± 4.7	0 (0)	0
(B) Pediatric									
Bangalore	13/12	13.7±2.0	6 (23.0)	11 (42.3)		1.46±1.0	21±7.6	3 (23.1)	1 (7.7)
Barcelona	52/27	14.9±1.8	30 (28.9)	41 (39.4)		2.64±2.2	18.7±7.6	15 (28.9)	3 (5.8)
British Columbia	13/16	13.3±3.2	3 (11.5)	11 (42.3)		3.12±2.7	13.4±6.4	15 (38.5)	0
Calgary	19/18	12.2±2.4	10 (26.3)	0			23.1±4.7	NA	0
Chiba	20/6	14.3±2.0	13 (32.5)	8 (20)		2.1±1.8	26.9±6.2	2 (10)	0
Oxford	21/23	16.3±1.3	11 (26.2)	14 (33.3)		4.46±3.2	19.6±7.4	7 (33.3)	5 (23.8)
Yale	23/22	14.3±2.2	13 (26.3)	12 (28.6)			26.9±4.5	10 (43.5)	9 (39.1)
Zurich	14/18	15.2±1.5	11 (27.7)	8 (30.0)		4.74±2.3	16.1±10.2	6 (42.9)	0

Note. YBOCS Yale-Brown Obsessive–Compulsive Scale, NA not available.

Classification of OCD

The principal component analysis (PCA) of the four-diffusion metrics (FA, MD, AD, RD) across the 18 international sites revealed site variability (**Figure 1**). In the PCA biplot, we observed two sites, one from adults and one from pediatrics, which were distinct from other sites. We then performed three classification tasks using the stacked ensemble machine learning models (LOSO cross-validation): (1) OCD vs. HC, (2) unmedicated OCD vs. HC, and (3) unmedicated OCD vs. medicated OCD (**Table 3**).

In adult samples, the models minimally-to-modestly classified participants with OCD diagnosis from healthy controls in the discovery set (N = 1068, ROC AUC = 67.29 ± 0.26) and the replication set (N = 268, ROC AUC = 57.19 ± 3.47). The models also minimally-to-modestly distinguished unmedicated OCD versus healthy individuals in the discovery set (N = 854, ROC AUC = 63.96 ± 0.43) and the replication set (N = 214, ROC AUC = 62.67 ± 3.84). Finally, the models distinguished medicated OCD versus unmedicated OCD participants in the discovery set (N = 437, ROC AUC = 60.22 ± 0.40) and the replication set (N = 137, ROC AUC = 76.72 ± 3.97).

In pediatric samples, the models classified participants with OCD diagnosis versus healthy controls in the discovery set (N = 270, ROC AUC = 69.54 ± 8.59) and the replication set (N = 64, ROC AUC = 59.80 ± 7.39). The models also classified unmedicated OCD versus healthy individuals in the discovery set (N = 151, ROC AUC = 65.96 ± 12.33) and the replication set (N = 38, ROC AUC = 48.51 ± 10.14). Finally, the models classified medicated OCD versus unmedicated OCD participants in the discovery

set (N = 140, ROC AUC = 61.82 ± 15.50) and the replication set (N = 35, ROC AUC = 72.45 ± 8.87) (**Table 3, C**).

In classifying OCD and HC, the ROC AUC of adult samples ranged from 51.6% (site C) to 79.1% (site F), and pediatric samples ranged from 35.9% (site M) to 63.2% (site L) across sites. Also, mean values of DTI metrics across all ROIs showed significant differences across sites (Fs > 97.4, p<.001). The site variability was significantly associated with the classification performance in OCD patients ($\chi 2 = 57.19$, p< .001) and HCs ($\chi 2 = 50.30$, p< .001) when adjusting for the covariates.

Table 2. Performance of classification of OCD clinical outcomes in (A) adult, (B) adult applied NeuroComBat harmonization, (C) pediatric, (D) pediatric applied NeuroCombat harmonization samples. — mean with 95% confidence interval

(A) Adult sample

	OCD (N = 690) vs. HC (N = 646)		unmedicated OCD (N = 429) vs. HC (N = 646)		unmedicated OCD (N = 429) vs. medicated OCD (N = 261)	
	Discovery set	Replication set	Discovery set	Replication set	Discovery set	Replication set
ROC-AUC	67.29 ± 0.26	57.19 ± 3.47	63.96 ± 0.43	62.67 ± 3.84	60.22 ± 0.40	76.72 ± 3.97
Accuracy (%)	66.37 ± 0.27	57.08 ± 3.22	64.64 ± 0.49	61.68 ± 3.58	66.88 ± 0.32	67.15 ± 12.83
Sensitivity (%)	61.96 ± 0.79	75.36 ± 8.49	65.84 ± 1.66	58.82 ± 19.79	58.7 ± 1.53	92.31 ± 2.95
Specificity (%)	71.87 ± 0.73	37.69 ± 29.44	68.44 ± 1.00	63.57 ± 7.92	73.77 ± 1.44	51.76 ± 16.19

Note. For the classification of medication status among OCD patients, some sites (i.e., Amsterdam, Shanghai) containing only unmedicated OCD were excluded from the discovery set.

(B) Adult sample, NeuroComBat

	OCD (N = 690) vs. HC (N = 646)		unmedicated OCD (N = 429) vs. HC (N = 646)		unmedicated OCD (N = 429) vs. medicated OCD (N = 261)	
	Discovery set	Replication set	Discovery set	Replication set	Discovery set	Replication set
ROC-AUC	64 ± 0.05	51.07 ± 3.54	67.35 ± 0.52	52.8 ± 4.18	66.12 ± 3.63	62.24 ± 5.08
Accuracy (%)	63.87 ± 0.07	53.36 ± 3.64	66.44 ± 0.52	60.75 ± 3.09	74.42 ± 0.65	68.6 ± 3.72
Sensitivity (%)	67.14 ± 1.20	37.68 ± 25.16	63.95 ± 1.80	37.65 ± 17.42	76.14 ± 0.71	48.08 ± 13.79
Specificity (%)	60.96 ± 1.24	70 ± 13.74	71.55 ± 0.87	75.97 ± 9.51	70.31 ± 1.35	81.18 ± 4.19

Note. For the classification of medication status among OCD patients, some sites (i.e., Amsterdam, Shanghai) containing only unmedicated OCD were excluded from the discovery set.

(C) Pediatric sample

	OCD (N = 175) vs. HC (N = 142)		unmedicated OCD (N = 105) vs. HC (N = 142)		unmedicated OCD (N = 105) vs. medicated OCD (N = 70)	
	Discovery set	Replication set	Discovery set	Replication set	Discovery set	Replication set
ROC-AUC	69.54 ± 8.59	59.8 ± 7.39	65.96 ± 12.33	48.51 ± 10.14	61.82 ± 15.50	72.45 ± 8.87
Accuracy (%)	73.56 ± 6.82	62.5 ± 6.38	69.15 ± 8.35	57.9 ± 8.06	69.15 ± 11.18	74.3 ± 5.83
Sensitivity (%)	73.25 ±17.25	65.71 ± 16.03	73.43 ± 14.12	50 ± 25.51	73.43 ± 12.74	95.24 ± 2.43
Specificity (%)	73.03 ± 13.18	58.62 ± 20.58	68.75 ± 9.90	62.5 ± 19.13	68.75 ± 15.95	42.86 ± 29.15

Note. For the classification of medication status among OCD patients, some sites (i.e., Calgary) containing only unmedicated OCD were excluded from the discovery set.

(D) Pediatric sample, NeuroComBat

	OCD (N = 175) vs. HC (N = 142)		unmedicated OCD (N = 105) vs. HC (N = 142)		unmedicated OCD (N = 105) vs. medicated OCD (N = 70)	
	Discovery set	Replication set	Discovery set	Replication set	Discovery set	Replication set
ROC-AUC	66.05 ± 0.41	60.49 ± 7.20	60.71 ± 0.92	55.36 ± 10.15	66.78 ± 0.35	58.2 ± 8.85
Accuracy (%)	67.56 ± 0.38	62.5 ± 6.38	61.46 ± 0.28	71.05 ± 8.06	72.1 ± 0.28	60 ± 5.82
Sensitivity (%)	62.28 ± 1.55	71.43 ± 13.10	84.06 ± 0.91	35.71 ± 25.51	77.5 ± 0.91	47.61 ± 2.43
Specificity (%)	77.16 ± 1.46	51.72 ± 24.63	54.69 ± 2.05	91.67 ± 19.13	68.75 ± 2.05	78.57 ± 29.15

Note. For the classification of medication status among OCD patients, some sites (i.e., Calgary) containing only unmedicated OCD were excluded from the discovery set.

Classification of OCD with NeuroCombat-harmonized data

Considering the site variability (**Figure 1**), we implemented the ML analysis with NeuroCombat-harmonized data to correct site effects. The NeuroComBat-harmonized data showed slightly lower performance in the adult samples (**Table 3, A**) and slightly higher performance in the pediatric samples (**Table 3, B**).

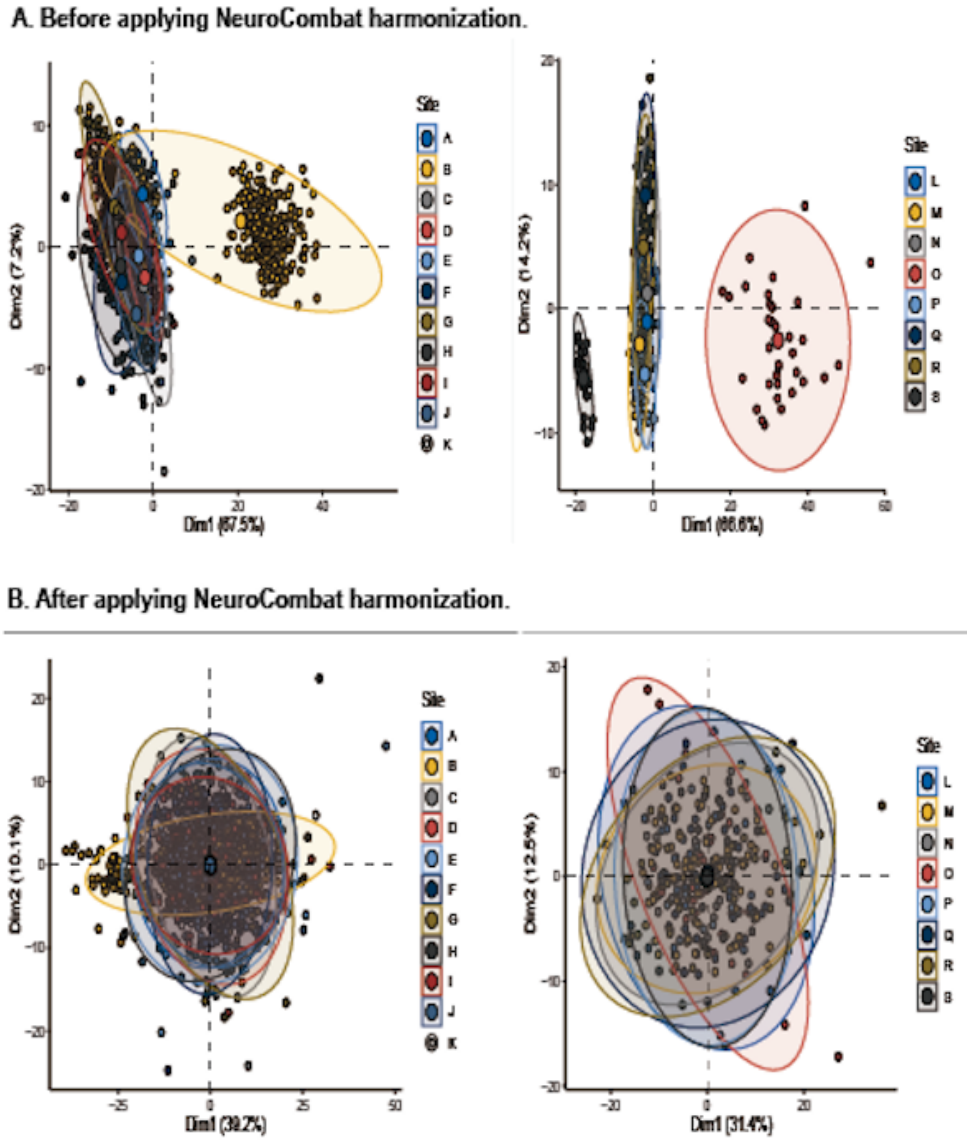


Figure 1. A biplot of principal component analysis (PCA) using the diffusion tensor estimates of the major white matter fascicules across the 18 international sites. (A), PCA biplot before applying NeuroCombat. (Left: Adult, Right: Pediatric). Some sites (e.g., site B) show apparent clusters distinct from the rest of the sites. (B), PCA biplot after applying NeuroCombat. (Left: Adult, Right: Pediatric).

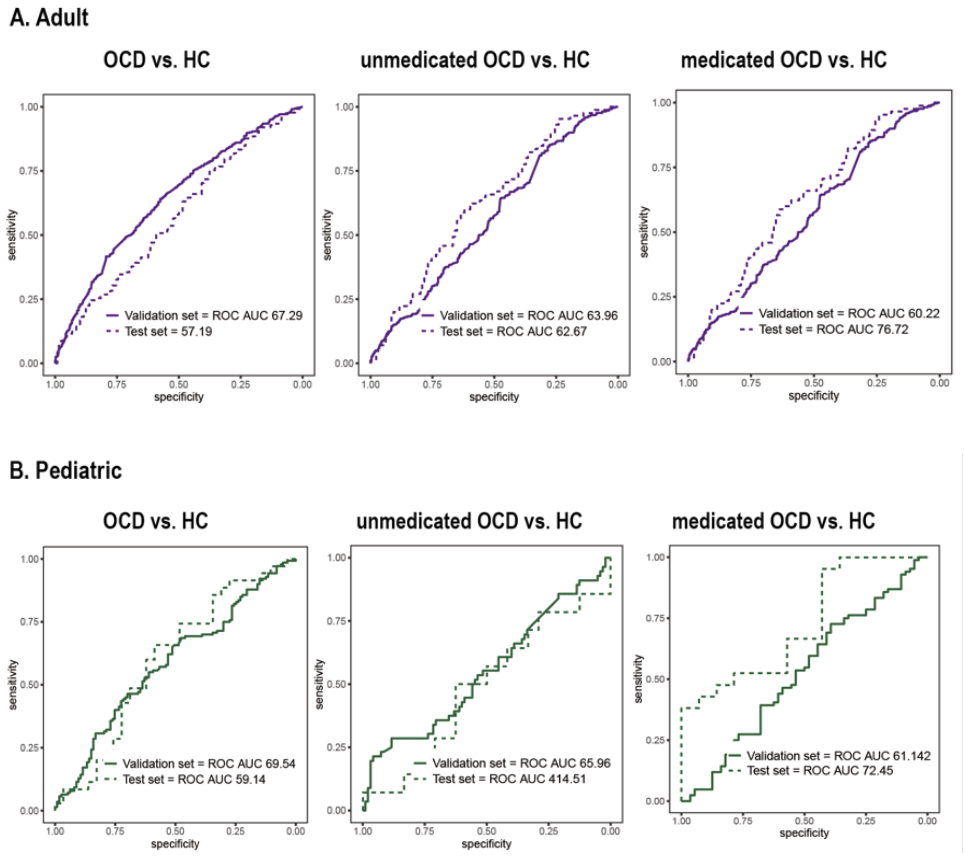


Figure 2. Classification of OCD diagnosis and medication status using diffusion tensor estimates. (A), classification performances in adult samples. (B), classification performances in pediatric samples.

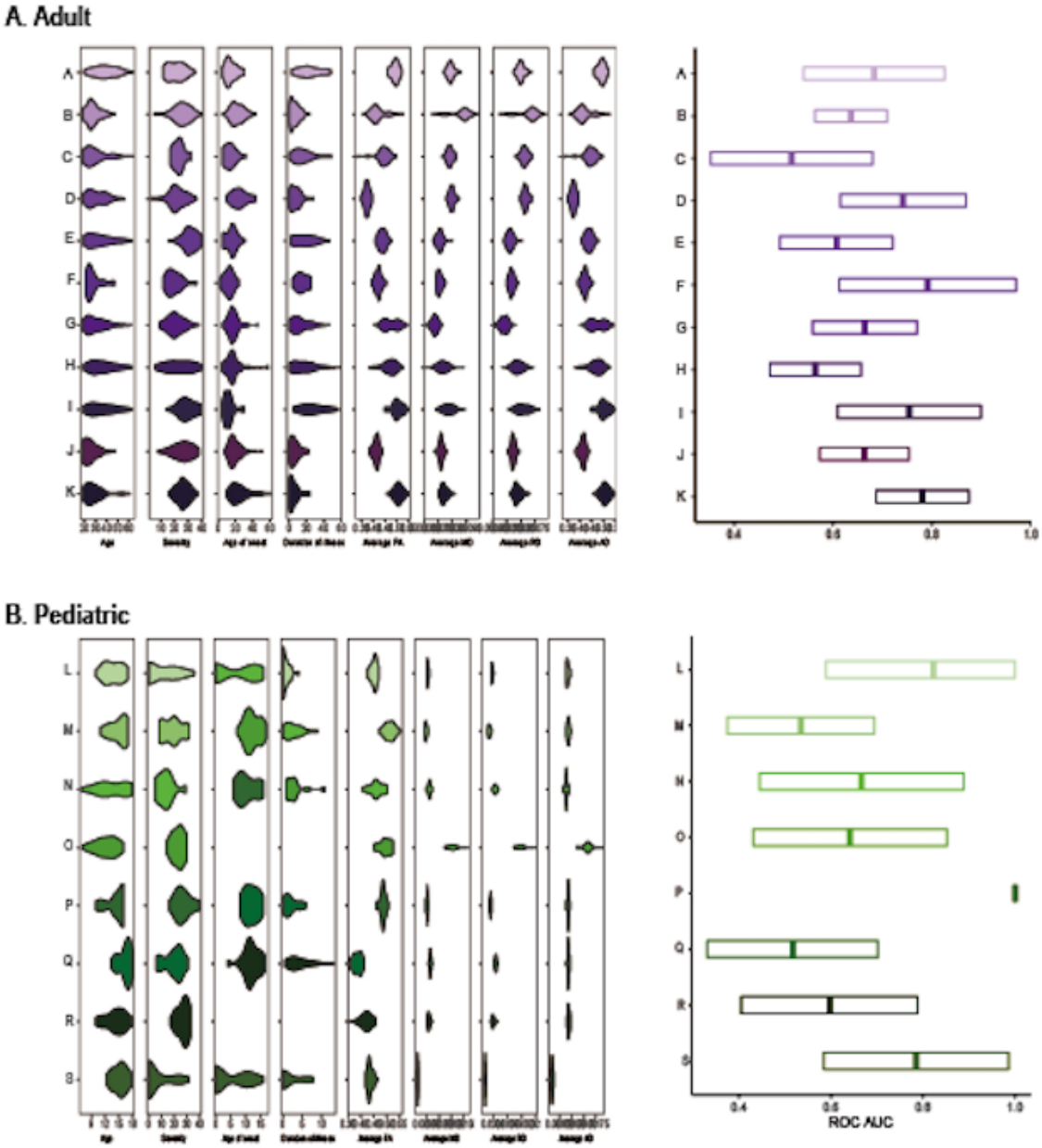


Figure 3. Sample characteristics and prediction performance (ROC AUC) across sites. (A), in adult samples. (B), in pediatric samples. Left: Violin plots of sociodemographic, clinical, and brain features across sites, Right: Box plot of the area under the receiver operating characteristic curve (ROC AUC) for the leave-one-site-out (LOSO) cross validation in the diagnosis classification task (OCD vs. HC).

Variables Associated with OCD Classification

Results of stepwise regression analysis indicated that, in adults, site (e.g., site H, site I), higher age, hoarding symptoms, and adult-onset were significantly associated with estimated OCD probabilities ($t > 2.04$, $p<.05$) (**Table 4**). In pediatric samples, site (e.g., site M, site S), lifetime diagnosis of depression, and aggression/checking symptoms significantly correlated with predicted OCD probabilities ($t > 2.15$, $p<.05$).

Table 4. The association between brain-predicted OCD risk probabilities and clinical features in a discovery set (stepwise regression).

(A) Adult sample, Discovery set (OCD = 379) (Adjusted = 15.15%)				
Variable	Beta	F	*P* value	η^2
Site		6.996	7.72E-08	0.118
Age	0.011	16.152	7.10E-05	0.042
Hoarding	0.017	8.316	0.004	0.022
Childhood-onset	-0.010	4.172	0.042	0.011
Current Depression	0.015	2.372	0.124	0.006
(B) Pediatric sample, Discovery set (OCD =55) (Adjusted = 32.89%)				
Variable	Beta	F	*P* value	η^2
Site		11.796	6.57E-05	0.325
Depression	-0.13142	5.062	0.029	0.094
Aggression, Checking	-0.0645	4.619	0.037	0.086
Age	0.02355	1.896	0.175	0.037

Machine Learning Interpretation

Our machine learning interpretation models showed that various specific diffusion white matter features contributed to the OCD classification (**Figure 4**). For the classification of OCD from HC in adult samples, the top 10 features included the superior corona radiata (MD), age, posterior thalamic radiation (FA), and posterior limb of the internal capsule (FA, AD). In the pediatric samples, the cingulum (MD, AD), uncinate fasciculus (MD), fornix (FA), corticospinal tract (FA), and anterior corona radiata (AD) were important in classifying OCD diagnosis (**Figure 7**). In classifying unmedicated OCD and HC, the internal capsule contributed to both adult (FA, AD of posterior limb) and pediatric samples (FA of the retrolenticular part, AD of anterior limb, FA of posterior limb) (**Figure 4**). In classifying medicated OCD and unmedicated OCD in adult samples, the top 10 features included the corpus callosum (total, genu), average FA, and average RD (**Figure 7**). For the pediatric samples, fornix and stria terminalis, cingulum (cingulate gyrus, hippocampus) were included in the top 10 features (**Figure 7**).

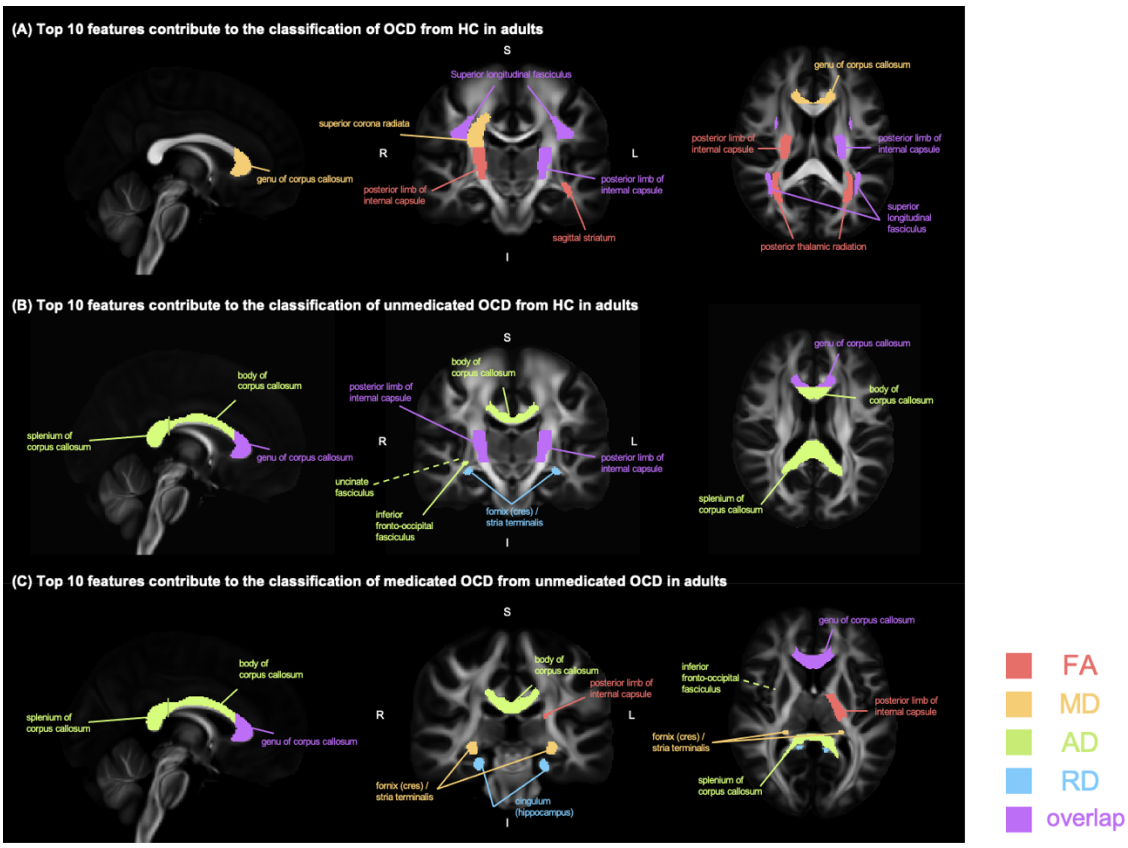


Figure 4. Top 10 features of classification models in adults.

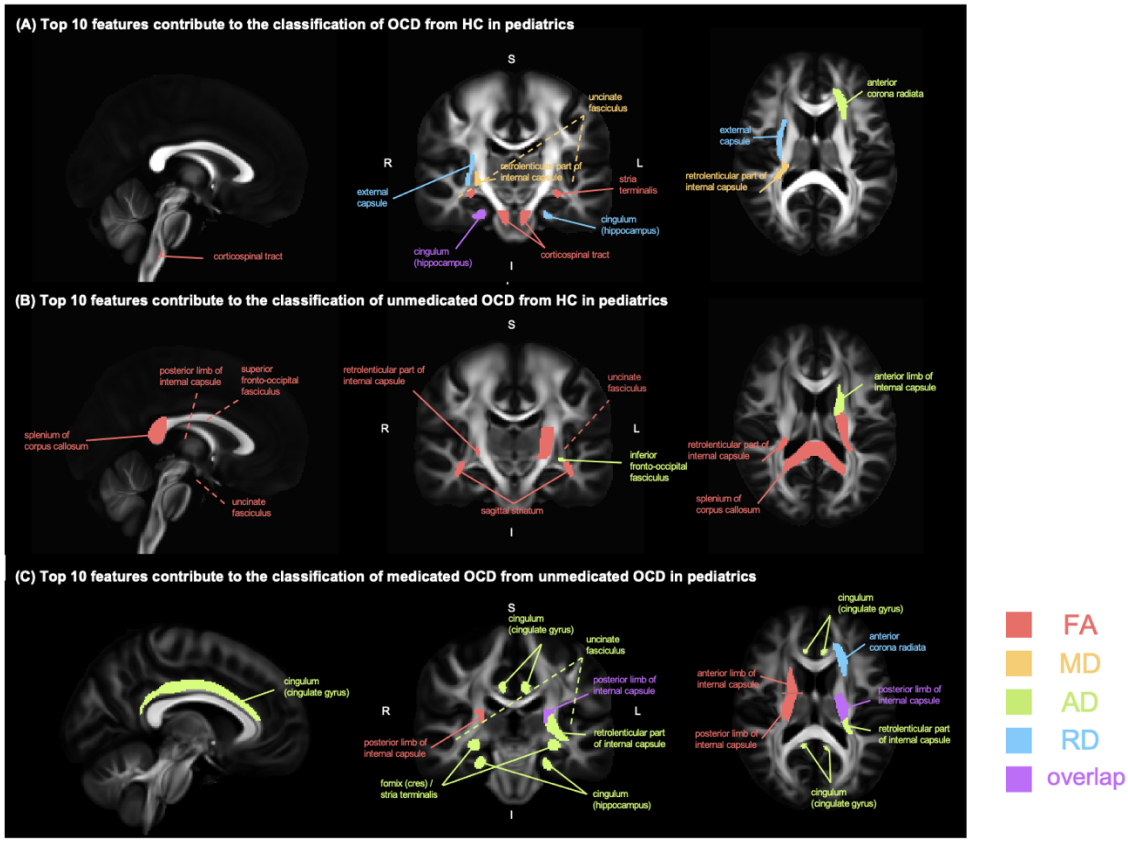


Figure 5. Top 10 features of classification models in pediatrics.

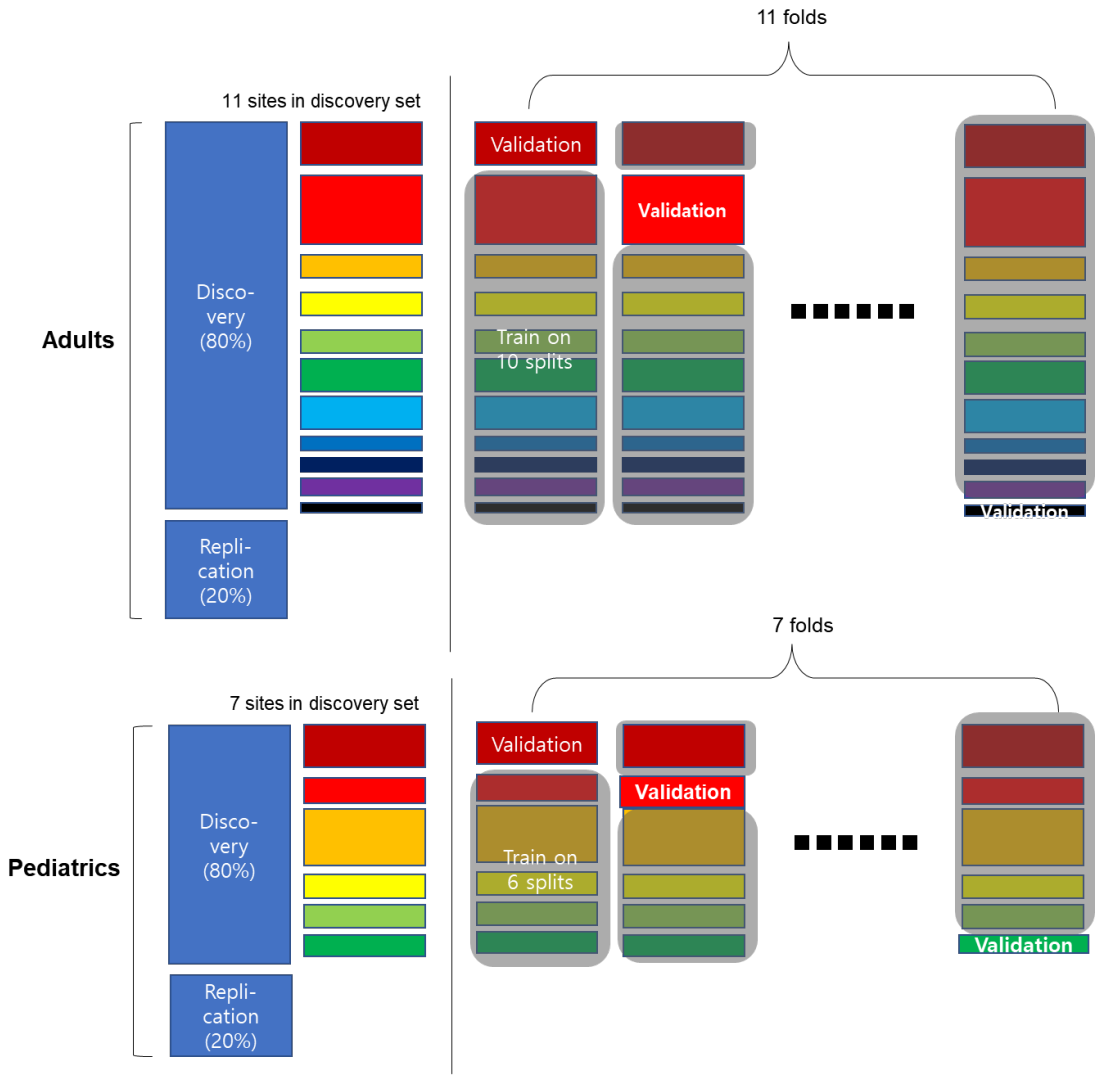
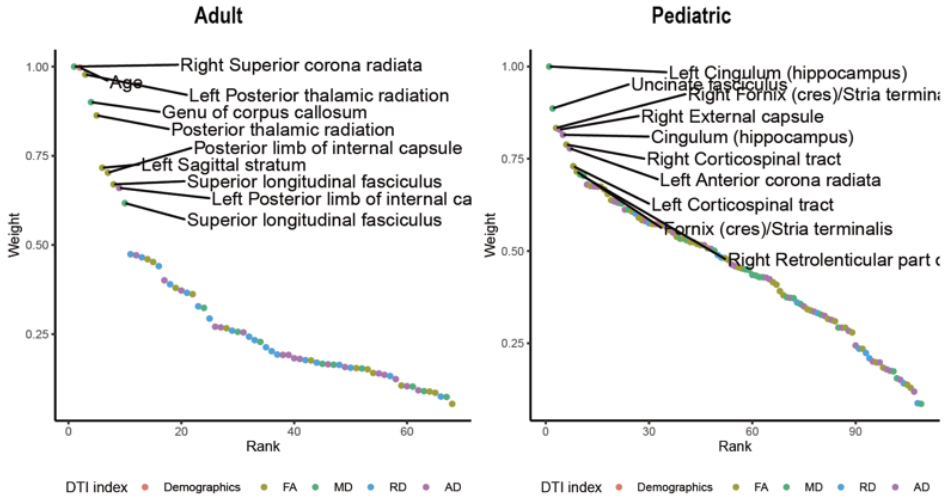
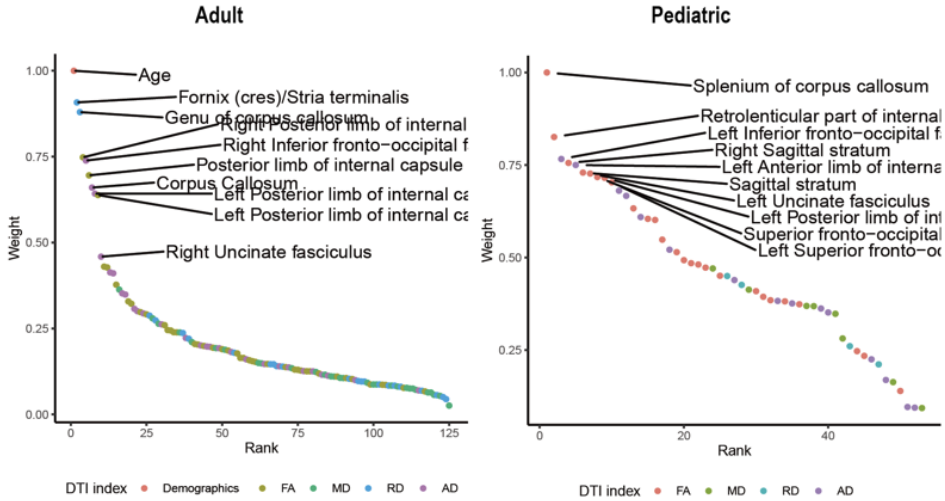


Figure 6. Leave-one-site-out cross-validation.

A. OCD vs. HC



B. unmedicated OCD vs. HC



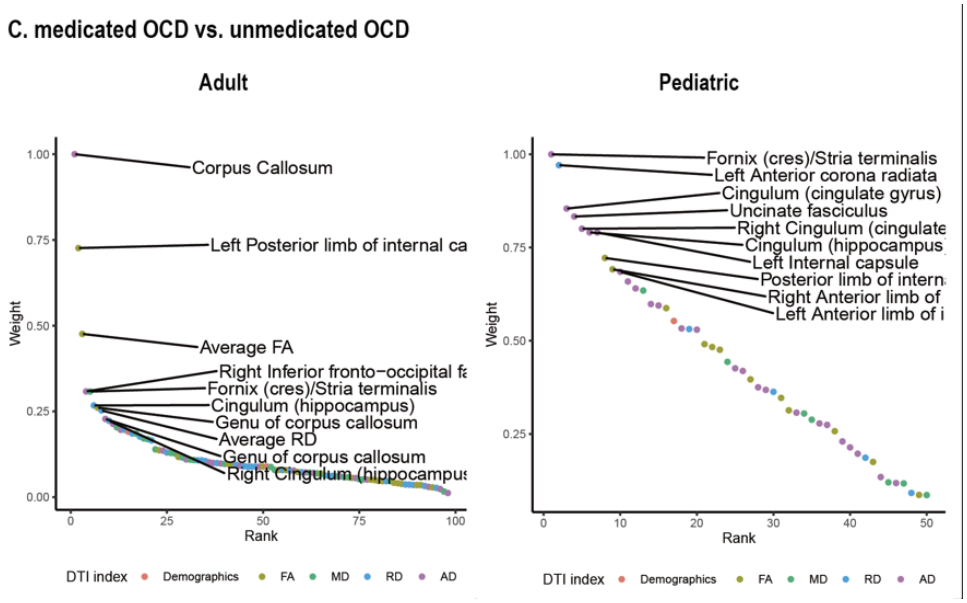


Figure 7. Feature importance plot of the diagnosis and medication models in adult (Left) and pediatric (Right) samples. (A), relative importance plot of OCD vs. HC model. (B), the relative importance of unmedicated OCD vs. HC model. (C), relative importance plot of medicated OCD vs. unmedicated OCD model. The top 10 features are represented.

Discussion

In this study, we tested the extent to the accuracy of machine learning in classifying the diagnosis or medication status of OCD patients based on white matter diffusion estimates obtained using the ENIGMA-matched image analysis pipeline across 18 international sites. Our results showed a low-to-moderate accuracy in predicting OCD diagnosis and medication status. Classification of medicated OCD versus unmedicated OCD had the best classification accuracy (ROC-AUC of 76.72 in adults), followed by unmediated OCD-health control classification (ROC-AUC of 63.96 in adults) and all OCD-HC (ROC-AUC of 57.19 in adults). In all OCD-HC classifications, the performance varied significantly across sites with cross-validated ROC AUC ranging 51.6-79.1 in adults, and 35.9-63.2 in children. Diffusion white matter features contributing to OCD classification (compared with HC) include anisotropy and diffusivity estimates of white matter in the internal capsules, thalamic radiations, and uncinate fasciculus.

The low-to-moderate accuracy of our machine learning models is consistent with prior work. OCD machine learning studies using structural MRI have found that accuracy in classifying OCD and HC, ranges from 60 to 90%, all in small datasets (N < 150) (W. Bruin et al. 2019; Zhou et al. 2018). However, these classification performances from small studies are likely to be inflated and not generalizable, while the true effect size (i.e., the brain-psychopathology association, regardless of the choice of analysis) may be smaller (Marek et al. 2022). Indeed, the recent large-scale ENIGMA OCD study found that machine learning models trained on grey matter morphometric estimates from structural MRI resulted in poor classification of OCD vs. HC (ROC AUC, 0.51-0.54;

leave-one-site CV) (W. Bruin et al. 2020). Our model based on white matter features showed improved classification performance compared with the grey matter morphometry model in adults and pediatric samples, though a direct comparison may not be warranted due to different machine learning pipelines and different subsamples used in this study. Future studies should determine whether multi-modal machine learning using structural and functional MRI can increase classification accuracy (Calhoun & Sui, 2016; Kuo et al. 2021; Guggenmos et al. 2020; Menon & Krishnamurthy, 2021).

We observed significant site variability in classification performance. Firstly, this may be related to the variability of the quality of the diffusion MRI across sites. The aggregated ENIGMA MRI data were harmonized for the post-imaging processing procedure (e.g., TBSS) but not for data acquisition. Though this harmonization method was a best practice when the raw image data were not sharable, nevertheless, given the sensitivity of diffusion MRI to the image acquisition conditions (e.g., magnets types, pulse sequences, such as numbers of gradient directions or b values, etc.; compared with the grey matter morphometry validated across scanners, sites, and pulse sequence designs (Guo et al. 2019)), our approach is limited in controlling potential confounding factors and their impact on the quality of the diffusion white matter metrics. Also, our application of another post-processing harmonization method, NeuroComBat, was effective in matching the distributions of the data across the sites (in our PCA results). However, this method failed to result in a performance gain in the OCD classification (slightly higher AUC in pediatric samples, slightly lower AUC in adult samples) or a reduction of the cross-site variability. The covariate modeling with NeuroComBat also

did not demonstrate a gain in performance. Secondly, our international multisite clinical samples show variability in clinical characteristics such as symptom severity, age, adult-onset, and duration of illness. The sampling variability may have added complexity to the already challenging task of OCD classification.

Our analysis of the machine learning model indicated that OCD probability was significantly associated with several sociodemographic and clinical characteristics. In adults with OCD, a higher age, adult onset, greater hoarding symptoms, and greater depressive symptoms were more likely to be predicted as having OCD. The significant correlation of age and adult-onset with the OCD likelihood might reflect age-dependent patterns in the diffusion white matter estimates. Though there are no significant group differences in age between OCD and HC, the neurobiology of OCD might be related to abnormal aging effects on the diffusion white matter estimates. Indeed, some literature shows that psychiatric disorders, including OCD and anxiety disorders, are linked to accelerated brain aging (Liu et al. 2022; Han et al. 2021). However, the potential association between the neuropathophysiology of OCD and age appears more relevant to adults than to children because, despite the similar effect sizes of age and the OCD likelihood, only adult samples show statistical significance (probably due to a larger sample size). This may reflect the effects of chronicity in adult samples (Koch et al. 2014).

Our machine learning interpretation is consistent with prior white matter studies that have relied on univariate analyses and/or small samples size (Simpson et al. 2020). For example, the well-known CTSC pathway includes the internal capsule (posterior limb

(FA, AD) in adults and retrolenticular part (MD) in children), which has been implicated in habit formation and cognitive control in OCD (Spalletta et al. 2014). In the classification model of unmedicated OCD and HC, the corpus callosum - connecting the two cerebral hemispheres - was important in adults and pediatric samples alike. This finding is in line with the previous ENIGMA-OCD study (Piras et al. 2021) indicating that adult OCD was characterized by lower volume in the genu of the corpus callosum than HC. However, careful interpretation is needed because of differences in the brain metrics used, here based on tensor modeling (FA, MD). In addition, we found that the cingulum bundle contributed to the classification of unmedicated OCD and medicated OCD in both adult and pediatric samples. The cingulum bundle contains short and long connections between the frontal lobe, parietal lobe, and temporal lobe. In short, our machine learning findings suggest common patterns of white matter abnormalities in adult and pediatric OCD, as well as distinct patterns consistent with prior work (Boedhoe et al. 2017).

The classification model of unmedicated OCD from HC showed greater accuracies than the model classifying all OCD from HC. This would suggest medication status likely confounds the white matter microstructure of OCD patients. In the literature, the causal effects of medication, Serotonin Reuptake Inhibitor (SSRI), on the white matter microstructure remain unclear: No randomized controlled trial exists. Nevertheless, given the key role of serotonin in neurodevelopment including gliogenesis (Milard et al. 2017, changes in extracellular serotonin levels in the brain owing to SSRI may impact the integrity of the white matter fibers. Prior correlational research supports

this. A cross-sectional study shows a decrease in FA in the sagittal striatum associated with medication use in adults with OCD compared to unmedicated OCD (Piras et al. 2021); longitudinal clinical studies show a decrease in MD of the midbrain white matter bundles after 12-week administration of SSRI (Fan et al. 2012), a decrease in MD in the frontal regions and the corpus callosum (Seiger et al. 2021). Though some of these correlational findings might indicate causal effects of SSRI on the white matter, nevertheless, without direct causal evidence it is still unclear if the associations result from the neurobiological effects of SSRI, symptom improvement, or both. A practical implication of our finding is that the diffusion white matter-based model presents a particular utility in classifying medication naïve individuals with OCD from healthy individuals. Though not reaching the clinical utility yet (e.g., around AUC of 80%), with further research (perhaps with the integration of brain, genetic, and behavioral multi-modal data (Rahaman et al. 2021) the white matter diffusion estimates might be used to predict the risk for OCD. Future research may test whether the models trained on medication naïve OCD patients—perhaps capable of learning the neurobiological patterns underlying the OCD without medication confounding—may be used for related tasks (e.g., via representational learning (Abrol et al. 2021).

There are limitations of this study. Firstly, the imaging acquisition was not harmonized across the sites, so we could not test whether the suboptimal model performance or the cross-site variability might result from the issues of the data or not. Given the sensitivity of the anisotropy and diffusivity estimates depending on the pulse sequence designs (e.g., the number of directions, b-values) (Ni et al. 2006), despite the

harmonized image processing method (TBSS), the remaining data quality and validity issues perhaps may have worked against model performance. Secondly, since only the image-derived phenotypes were available from the ENIGMA consortium, but not the raw images, our results are only limited to a single type of analysis (TBSS) and metrics (diffusivity and anisotropy). Thirdly, our adult samples were larger than the pediatric samples, so our machine learning methods may have resulted in more optimized learning outcomes for adult samples.

In conclusion, using the largest multisite DTI with harmonized image processing, our investigation indicates that machine learning models currently allow only poor-to-modest classification power, but that captures meaningful multivariate patterns of white matter features relevant to the neurobiology of OCD. Accuracy is largely constrained by site variability, indicating room for future improvement.

Chapter 3: Individual Differences in the Influence of OCD on Symptom Severity and the Moderation of Resting State Functional Connectivity

Introduction

Obsessive-Compulsive Symptom (OCS) is common in preadolescence but usually does not meet the diagnostic threshold for obsessive-compulsive disorder. Similar to Obsessive-Compulsive Disorder (OCD), which affects 2% to 4% of adolescents, OCS is characterized by repetitive thoughts and behaviors (Evans et al., 1997). The diagnosis of OCD occurs when the distress and impairment arising from OCS manifest as intrusive and incapacitating, resulting in significant disruption to an individual's functioning. OCD, if untreated, is known to lead to academic, occupational, and social impairments, along with a reduced quality of life (Coluccia et al., 2016). The delay between symptom onset and diagnosis, averaging at 7.1 years (Hezel et al., 2022), exacerbates the distress experienced by individuals manifesting OCD symptoms. Research on OCS facilitates a dimensional approach to the disorder, moving away from binary 'all or nothing' perspectives, and aids in the identification of those at risk.

Without treatment, Obsessive-Compulsive Symptoms (OCS) do not always worsen over time. OCS can be observed in numerous typically developing children during childhood (Evans et al., 1997), with these symptoms frequently diminishing as they mature, highlighting the possibility of spontaneous symptom alleviation over time (Zohar & Felz, 2001). Indeed, longitudinal studies tracking OCS from pre-kindergarten to high school have found a trend of symptom alleviation in high-risk pediatric OCD cases,

though increased risk in adolescence was also observed in those initially presenting with low OCS risk (Luke et al., 2021). Therefore, it cannot be conclusively assumed that children presenting with OCS are destined for symptom deterioration.

Heterogeneity is to be expected in the prognoses of children presenting with OCS; research on the prognosis of OCS is scant, with studies examining individual differences in these outcomes even more scarce. Prior OCS literature focused on the OCD risk group, which exceeds the threshold in OCS instruments. The OCD risk group showed reduced neurocognitive ability including cognitive flexibility and response inhibition (Sternheim et al., 2014, Abramovitch et al., 2015). Furthermore, recent neuroimaging research has discovered abnormalities in youth groups exhibiting high OCS, considered at risk for OCD, based on population-wide samples. These studies reported an enlargement of the thalamus and ventral nuclei in children likely to have OCD (Weeland et al., 2020, Weeland et al., 2022). Additionally, they found abnormal functional connectivity in the putamen and thalamus among adolescents (Suñol et al., 2021). These findings highlight a strong link between Obsessive-Compulsive Symptoms (OCS) and decreased neurocognition, suggesting possible underlying brain alterations. However, these studies consider the OCS group as homogenous. They failed to consider potential individual differences in prognosis among these children, and the factors that could influence such outcomes remain under-investigated.

Individual variability in the influence of Obsessive-Compulsive Disorder (OCD) on symptom severity presents a significant issue for accurate diagnosis and effective treatment. This study aims to explore these individual differences further, with a focus on

the moderating effects of resting state functional connectivity and psychosocial variables. Notably, prior study on children aged 9-11 by Pagliaccio et al. (2020), examining the correlation between OCD symptoms and their neural correlates, discovered differences in resting state brain function between children with severe OCD symptoms and those without (no such differences were found in brain morphology and white matter microstructure). Therefore, based on prior research, this study focuses on exploring the individual variability in OCD's impact on symptom severity, particularly considering resting-state functional connectivity (RSFC) and psychosocial variables.

Methods

The ABCD Study

The Adolescent Brain Cognitive Development (ABCD) Study is a comprehensive investigation being conducted across 21 locations in the United States. Its primary objectives are to examine the differences in adolescent brain and cognitive growth and to comprehend the factors that contribute to such development (Volkow et al., 2018). The ABCD Study has implemented a recruitment strategy focused on elementary schools (both public and private) to gather baseline clinical, questionnaire, behavioral, and neuroimaging data from 9- and 10-year-old participants. This ongoing longitudinal study involves regular follow-up assessments (Garavan et al., 2018) The study employed exclusion criteria to ensure a specific participant sample, whereby individuals lacking proficiency in English, those with substantial medical or neurological conditions, premature birth, contraindications for magnetic resonance imaging (MRI), a history of

traumatic brain injury, a current diagnosis of schizophrenia, moderate to severe autism spectrum disorder, intellectual disability, or an alcohol or substance use disorder were not included. The present study examined the fourth public ABCD data release, which included baseline clinical, questionnaire, cognitive, and neuroimaging data and questionnaire data from the 2-year follow-up assessment.

This study analyzed 5,284 individuals showing at least one OCS for two years recruited from ABCD study **(Figure 1).**

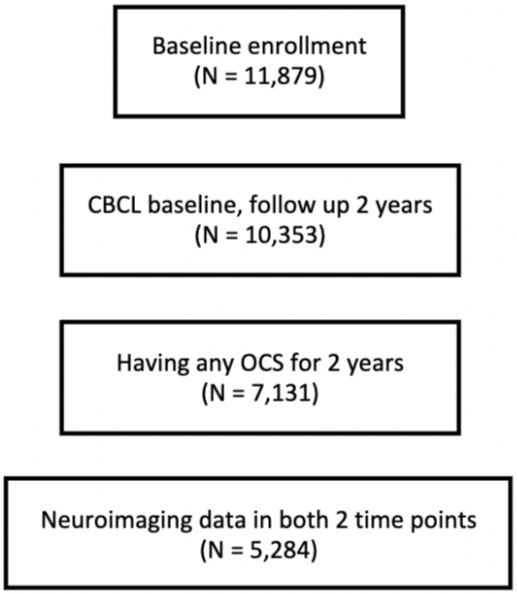


***Figure 1*. Participants flowchart.**

Variables

Obsessive-compulsive symptoms. The Child Behavior Checklist (CBCL) was administered to parents/guardians in order to evaluate the emotional and behavioral functioning of their children. Age- and sex-normed T-scores were used for analyses

based on the prior study showing high correspondence with raw scores (Pagliaccio et al., 2020). Our primary predictor of interest was the 8-item OCS subscale (Nelson et al., 2001, Hudziak et al., 2006, Saad et al., 2017) The Child Behavior Checklist's (CBCL) Obsessive-Compulsive Symptoms (OCS) subscale is an instrument potentially used for evaluating obsessive and compulsive symptoms. It utilizes eight components, each rated on a 3-point Likert scale that ranges from 0 to 2. The prior study confirmed good psychometrics of the 8-item CBCL OCS subscale, including good fit of a once-factor/unidimensional model and moderate/good internal consistency (standardized Cronbach's $\alpha = .71$, $\omega = .87$) (Pagliaccio et al., 2020).

OCD risk. It has been proposed in the literature that a threshold score of four or more on this scale could potentially display superior psychometric characteristics (Hudziak et al., 2006). We used this cut-off of 4 points or higher to define an 'OCD risk' for case-control analysis in generalized random forest models.

Covariates. We included sociodemographic, psychosocial, and neuroimaging features from the baseline. These features were selected as they have the potential to mediate or moderate the effect of OCD risk on OCD symptom severity.

Sociodemographic features. We selected 11 factors from the baseline survey, including four demographic characteristics (age, gender, and race), three socioeconomic statuses (parental education, household income, and marital status), one pubertal status, and one physical development factor. These factors were selected because they are likely to act as confounders (i.e., predictors of longitudinal OCS that are differentially

associated with OCD risk), effect modifiers (i.e., the association between OCD risk and longitudinal OCS depends on the level of these factors), or both.

Psychosocial features. We included potential moderators related to prognosis of OCS; 1) the fluid, crystallized, and total scores from the National Institutes of Health Toolbox Cognitive Battery (NIHTB-CB) tests, 2) sleep problems from Sleep disturbance scale for children, 3) physical activity for one week, 4) parental behavioral problems from Adult Self Report Raw Scores Aseba (ASR), 5) the child-rated UPPS-P (urgency, premeditation [lack of], perseverance [lack of], sensation seeking, positive urgency) for Children Short Form (UPPS-P-CSF; ABCD version), 6) Prodromal Psychosis Severity Score Sum from Prodromal Questionnaire–Brief Child Version, 7) family conflict from ABCD Parent Family Environment Scale-Family Conflict Subscale Modified from PhenX (FES), 8) Residential History Derived Scores from

Neuroimaging features and quality control. We used resting-state functional connectivity features including internal connectivity measures (i.e., Within-network functional connectivities for 12 large-scale brain networks, Between-network functional connectivities between the 12 networks and 10 subcortical regions).

High-resolution resting-state functional MR imaging of children was acquired by multi-band scanning (2.4 mm isotropic, TR=800ms, 6 factors). Standardized fMRI preprocessing included registration, distortion correction, and normalization. Post-processing included regression of 24 temporally filtered motion parameters, frame-wise displacement (FD)>0.3mm outliers, as well as white matter, cerebral spinal fluid, and whole brain signal (Hagler et al., 2019). Within- and between-network connectivity was

extracted by averaging all connections between ROIs assigned to given networks of the Gordon atlas (Gordon et al., 2014).

Quality control of imaging data. Par quality control (QC) information provided by QC file (abcd_imgincl01) from ABCD 4.0 release, data quality control was performed for all brain imaging data according to the quality control parameters recommended by ABCD study (Hagler et al., 2019). The QC criteria for rest-state functional MRI data mainly include the following: No serious MR findings (mrif_score ~=3 || mrif_score ~=4); rsfMRI tfMRI series passed rawQC (iqc_rsfmri_ok_ser > 0); T1 series passed rawQC (iqc_t1_ok_ser > 0); rsfMRI Number of frames > 375 (rsfmri_c_ngd_ntpoints > 375); fMRI B0 Unwarp available (apqc_fmri_bounwarp_flag == 1); FreeSurfer QC not failed (fsqc_qc ~= 0); fMRI Manual PostProcessing QC not failed (fmri_postqc_qc ~= 0); fMRI registration to T1w: less than 19 (apqc_fmri_regt1_rigid < 19); fMRI Maximum dorsal cutoff score: less than 65 (apqc_fmri_fov_cutoff_dorsal < 65); fMRI Maximum ventral cutoff score: less than 60 (apqc_fmri_fov_cutoff_ventral < 60).

Analysis

The Generalized Random Forest (GRF) method was utilized to examine the impact of OCD risk on symptom severity, and to identify variability based on subject-specific covariates. GRF uses the 'honest trees' strategy, wherein it teaches the tree model with one data subset and computes the treatment effect with a different data subset (Wager & Athey, 2018). By splitting data for tree model formation and for effect estimation, we effectively curtail overfitting risks, thereby enhancing the trustworthiness

of the treatment effect we derive. Furthermore, GRF uses a doubly robust estimator (i.e., augmented inverse-propensity weighting) in estimating the treatment effect, thus reducing the likelihood of potential confounding bias (Glynn & Quinn, 2010).

The treatment effect was quantified in terms of the OCS severity. The causal forest method estimated conditional average treatment effect (CATE) for each participant as a conditional OCS severity difference, the difference between weighted OCS severity averages among treated and control participants with similar values for potential effect modifiers (the more similar values, the higher the weights). Positive CATE values indicate a predicted deterioration in OCS severity due to OCD risk exposure, while negative values indicate a predicted improvement in OCD risk exposure.

The analysis process consists of five main steps **(Figure 2).** First, full model fitting. We fitted a causal forest model with preprocessed 134 covariates for the outcome, OCD symptom severity. In this procedure, the ‘causal forest’ function was applied, and 2,000 tree models were composed of each causal forest model. All adjustable parameters, such as the size of terminal nodes and the approach to partitioning input data for constructing each tree model, were auto-tuned through the 'tune.parameters' arguments. Then, we calculated the variable importance of 134 covariates within each causal forest model using the ‘variable_importance’ function. This function computes each feature’s importance based on the frequency of how often the features were chosen to split trees to maximize the heterogeneity of CATEs (Athey & Wager, 2019).

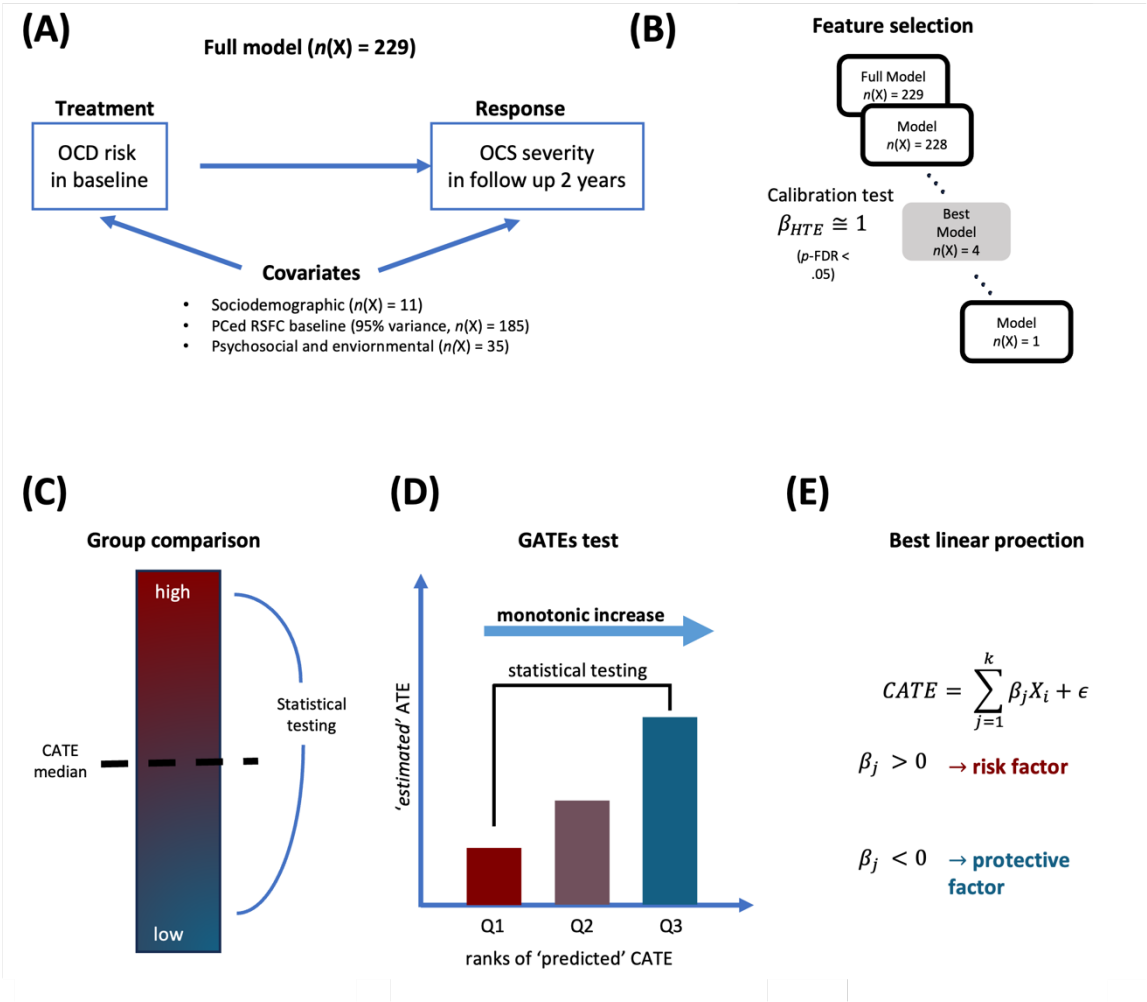


Figure 2. Analysis framework of individually different influences of OCD risk on OCS severity.

Second, feature selection. GRF provides the omnibus criterion to evaluate the model fit of the causal forest with the 'test_calibration' function. It computed the coefficient and p-value of estimated ATE and demeaned predicted CATE respectively from the best linear predictor model. It means that if the coefficients of estimated ATE (ATE) and demeaned predicted CATE (CATE) are significantly close to 1, we can

confirm that ATE is correctly estimated and fitted causal forest detects significant heterogeneity in sample-level CATEs (Athey & Wager, 2019).

Third, estimation of ATE and evaluation of heterogeneity. Using the optimized model, we estimated ATE of OCD risk on children's OCD symptom severity levels with the 'average_treatment_effect' function. In GRF, ATE is calculated by averaging sample-level CATEs. For acquiring doubly robust estimates of sample-level CATEs, we executed an augmented inverse probability weighted (AIPW) estimation using the 'AIPW' option specified in the 'method' argument. During this process, GRF automatically predicts the expected outcome value based on covariates and propensity scores for assignment in the treated group, both being necessary for calculating AIPW estimates of sample-level CATEs. Because AIPW estimates ensure unbiasedness even if one of the two values (i.e., expected conditional outcome or propensity score) is incorrectly specified, we can secure more reliable estimates of sample-level CATEs compared to traditional conditional analysis, which depends on a single prediction (e.g., predicting the propensity score in inverse probability weighting approaches or expected conditional outcome in S-learner).

Fourth, to evaluate significant heterogeneity, we contrasted the characteristics of individuals in the upper and lower 50% of the CATE distributions. Those in the upper half (i.e., those demonstrating a higher level of OCD symptom exacerbation after OCD risk exposure) were classified as the "Vulnerable" group, while those in the lower half (i.e., those showing lesser OCD symptom exacerbation after OCD risk exposure) were categorized as the "Resilient" group.

Last, risk and protective variable analysis. We used the function 'best_linear_projection', fitting a multiple regression model with selected features as regressors to all sample-level CATEs (Cui et al., 2023). Through this method, we can also explicitly understand the effect size and coefficient of selected features on sample-level CATEs.

Results

Demographic characteristics

The final sample were 5,284 preadolescents, including 626 probable OCD and 4,568 controls. Of the probable OCD group, 42.2% had OCD diagnosis based on the KSADS-COMP criteria. The probable OCD group showed higher scores for problem behaviors **(Table 1)**.

Table 1. Demographic characteristics.

Variables	**Full sample (N = 5284)**	**Probable OCD (N = 626)**	**Control (N = 4658)**
Sex, Female	2436 (46.1%)	252 (40.3%)	2184 (46.9)
Age, Months	119 (7.4)	119 (7.5)	119 (7.4)
Pubertal Status	2.25 (10.1)	1.74 (3.1)	2.32 (10.7)
Race, White	4163 (78.8)	515 (80.3)	3648 (78.3)
Race, Black	967 (18.3)	116 (18.5)	851 (18.3)
Ethnicity, Hispanic	984 (18.8)	125 (20.2)	859 (18.7)
Parent's Marital Status, Together/Married	4006 (76.2)	465 (74.6)	3541 (76.4)
Parental Education, Completed Some College	4544 (86.1)	543 (86.9)	4001 (86.0)
Parental Income	7.39 (2.3)	6.96 (2.4)	7.44 (2.2)
NIH Toolbox - Cognition Total (age corrected)	102 (17.4)	100 (18.3)	102 (17.3)

CBCL OCS total problem t-score	46.7 (11.0)	62.3 (8.3)	44.6 (9.6)
KSADS OCD baseline	646 (12.2)	264 (42.2)	382 (8.2)
Probable OCD in follow up 2 years	581 (11)	283 (45.2)	298 (6.4)

OCD risk influences OCD symptom severity in preadolescents

We employed causal forest analyses to estimate the average treatment effect ('ATE') of OCD risk on OCD symptom severity in preadolescents. A full causal forest model was fitted. This model included 229 covariates, including brain functional features and sociodemographic variables measured before the treatment response.

To enhance the estimation of ATEs and detect heterogeneity, it is recommended to include only a limited number of decisive features in the causal forest model (Athey et al., 2019). We excluded covariates with the lowest importance values one by one based on the variable importance of all covariates computed in the full model, resulting in 134 models.

From these models, we identified the best model in terms of model fit indices in the calibration test (Athey & Wager, 2019, Chernozhukov et al., 2018). This test evaluates model fit based on two metrics: the correctness of predicted ATE ('β_{ATE}') and the ability to detect heterogeneity ('β_{HTE}') per causal forest model. We selected the best model among the 134 models based on these metrics. It is worth noting that a value closer to 1 indicates a more precise estimation of ATE and heterogeneity by the causal forest (Athey & Wager, 2019).

Although the model fit indices (β_{ATE} and β_{HTE}) of the casual forest models typically depend on the covariates set (Athey et al., 2019, Athey & Wager, 2019), the model consistently estimated ATEs stably estimated across models **(Figure 3)**. All

models yielded significant estimates of ATEs, even after false-discovery rate ('FDR') correction, demonstrating high coherence in effect sizes. These findings provide robust evidence of the effect of OCD risk on OCD symptom severity with reliable population-level estimations. ATEs were estimated by the full model (ATE =0.932, SE = .047, p-FDR < .001) and the best model (ATE =1.005, SE = .05, p-FDR < .001). This indicates OCD risk increase future OCS severity in preadolescents.

The variable importance plot of the full model reveals that out of 229 variables, RSFC ranks among the top. While socio-environmental variables were generally dispersed, the level of education in the community stood out, ranking 17th highest **(Figure 4).**

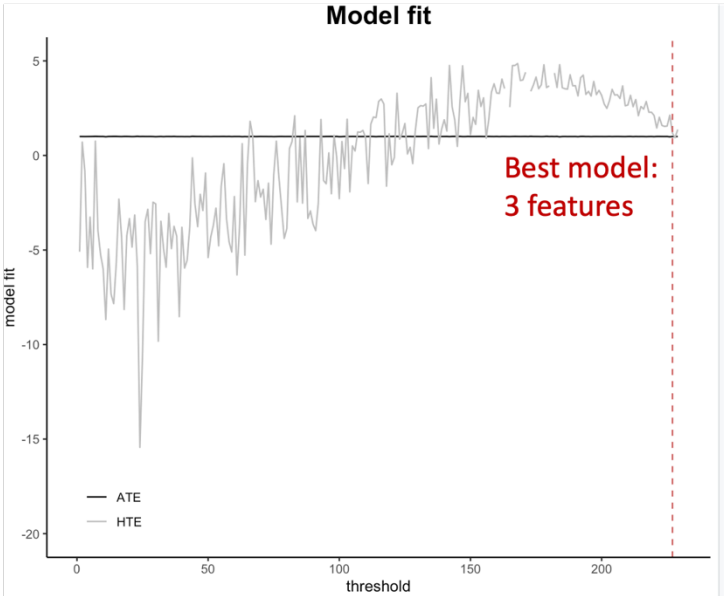


***Figure 3*. Fluctuation in models fits.** The best model included three covariates (i.e., PC 59, PC 184, PC 108 of resting state functional connectivity in the baseline).

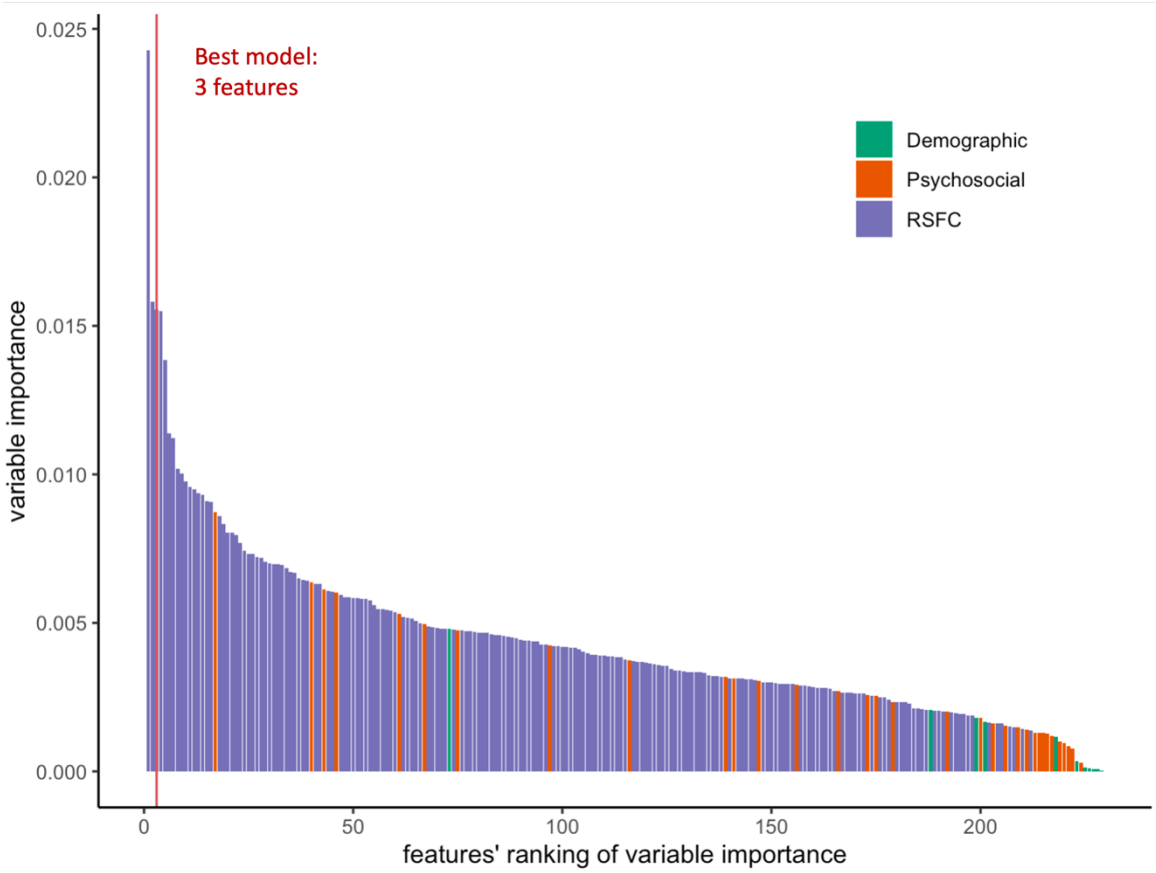


***Figure 4*. Variable importance of the full model.**

The effect of OCD risk is heterogenous, potentially derived from resting-state functional connectivity.

The best model showed significant detection power for heterogeneity (β_{HTE} = 1.132, p-FDR < .001). We performed a Welch-independent t-test between two groups categorized below and above the median CATEs. The results showed significant differences in the CATEs (t(1958.34) = 45.89, p < .001, **Figure 5**). This finding supports the existence of heterogeneity in CATEs from a conventional perspective.

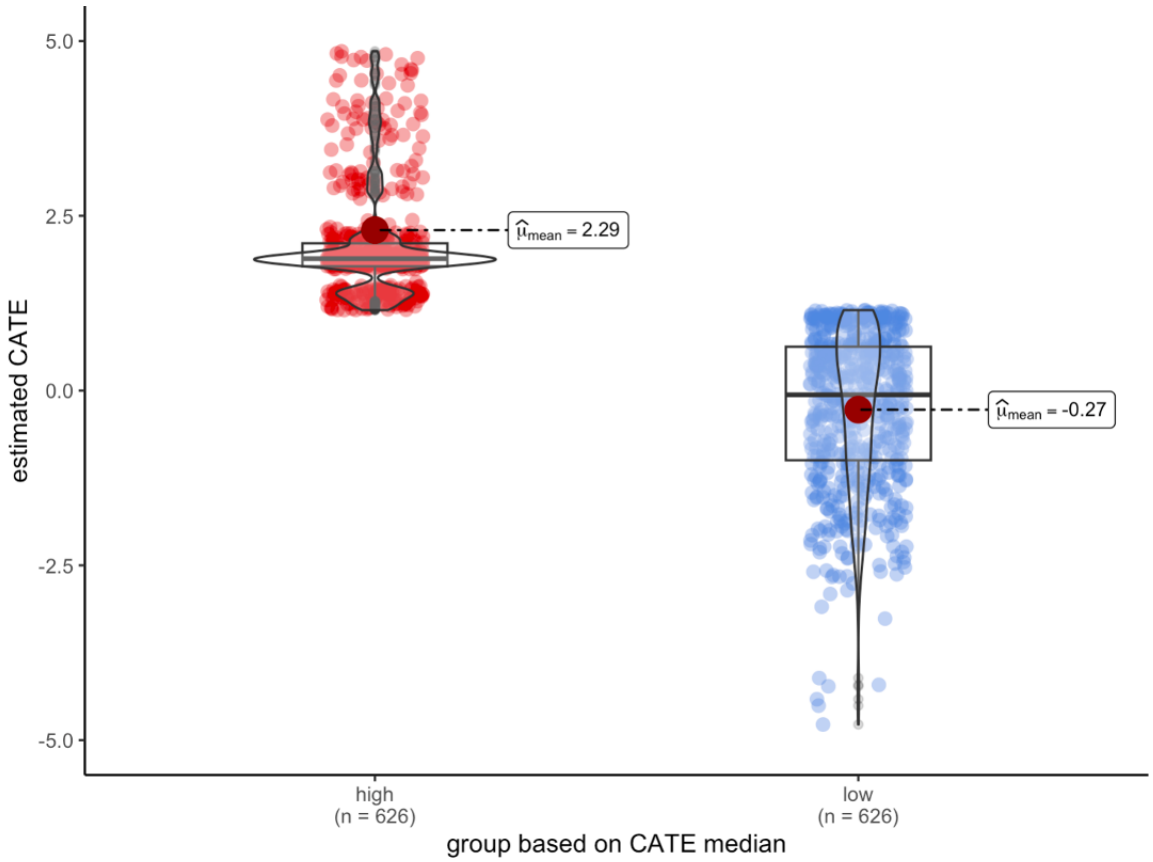


***Figure 5*. Group comparison between high CATE and low CATE**. We identified significant differences in sample-level CATE between vulnerable group and resilient group.

Best linear projection analysis showed a significant association between PC 59 of RSFC and sample-level CATE of OCS severity (**Figure 6**). The top 5 positive loadings were found in functional connectivity within in sensorimotor network (sensorimotor mouth, sensorimotor hand network) and between cingulo-opercular & cingulo-parietal networks, and retrosplenial temporal network & caudate. The top 5 negative loadings were observed in functional connectivity between auditory network & putamen, cingulo-

opercular network & putamen, retrosplenial temporal network & cerebellum, sensorimotor hand network & cerebellum, sensorimotor hand network & pallidum.

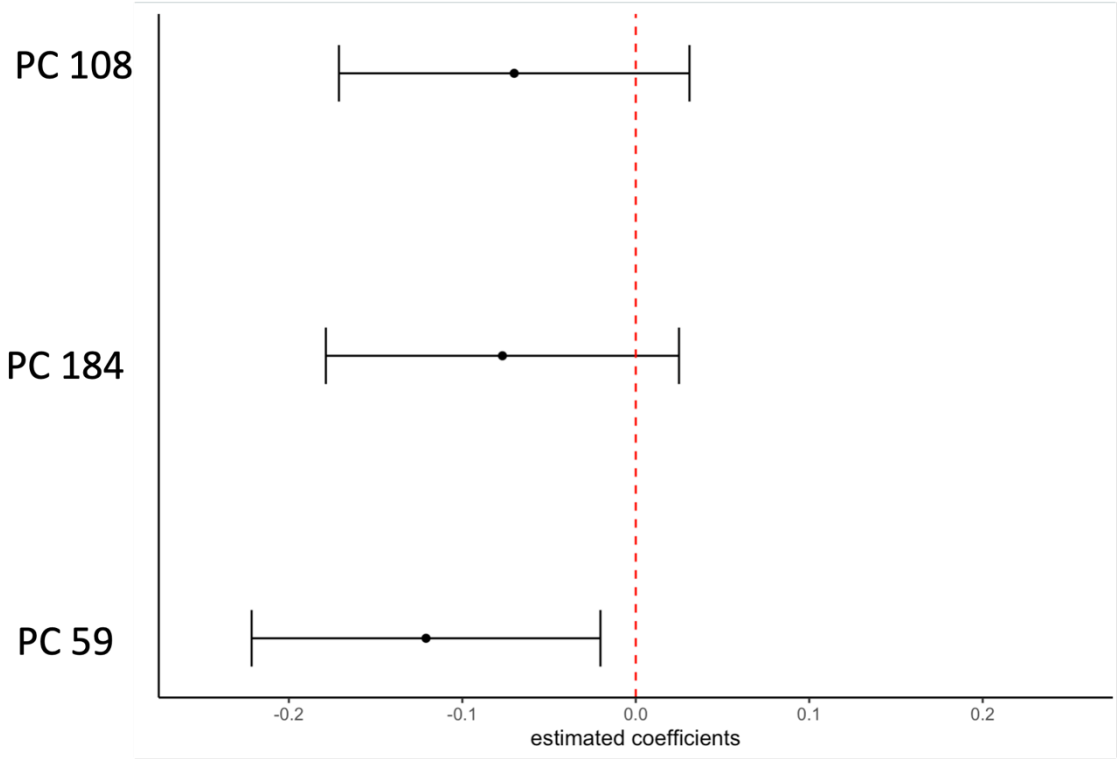


***Figure 6*. Important features contributing to heterogenous OCD risk effect**. Using best linear prediction, we found that PC 59 of resting-state functional connectivity in the baseline significantly contributed to the heterogenous effect of OCD risk on OCD symptom severity.

Table 2. Top 10 features contributing to PC 59 of RSFC

Top 5 positive loading features	
Functional connectivity with	Loading
sensorimotor mouth network & sensorimotor hand network	0.195
auditory network & hippocampus	0.147
retrosplenial temporal network & caudate	0.126
default network & brain-stem	0.114
cingulo-opercular network & cingulo-parietal network network	0.108

Top 5 Negative loading features	
Functional connectivity with	Loading
auditory network & putamen	-0.196
cingulo-opercular network & putamen	-0.13
retrosplenial temporal network & cerebellum	-0.127
sensorimotor hand network & cerebellum	-0.121
sensorimotor hand network & pallidum	-0.11

Discussion

In this study, we detected individual differences in the influence of OCD risk on symptom severity, potentially resulting from resting-state functional connectivity (RSFC). In children at risk for OCD, we observed an increase in obsessive-compulsive symptoms after two years. Our findings revealed that this effect was primarily driven by

neurological factors, with the 59th component of the resting-state functional connectivity (RSFC) found to be involved in individual differences in OCD's impact.

We identified a significant heterogeneous effect of OCD risk on OCD symptom severity. This indicates a variation in the progression severity of obsessive-compulsive symptoms amongst individuals susceptible to obsessive-compulsive disorder. In particular, this heterogenous effect was explained well by three features of RSFC in the baseline. Of note, the 59th principal component (PC) of baseline RSFC significantly contributed to the heterogeneous effect of OCD risk on symptom severity. Specifically, the 2nd PC of baseline RSFC included functional connectivity within sensorimotor networks (sensorimotor hand, sensorimotor tongue) as a resilient factor. Reduced within-network functional connectivity in the sensorimotor network has been associated with OCD; for example, a recent large-scale study from ENIGMA-OCD working group found significant hypo-connections within the sensorimotor network (Bruin et al., 2023). The sensorimotor cortex plays a pivotal role in formulating and managing motor behaviors, as well as amalgamating sensory data (van den Heuvel et al., 2016). Alterations in this network may be related to sensory phenomena, undesirable or distressing tactile feelings, or perceptions inducing repetitive actions (Shephard et al., 2021, Subirà et al., 2015, Brown et al., 2019). The sensorimotor cortex collaborates with the sensorimotor CSTC circuit significant to OCD due to its fundamental role in creating habits (Stein et al., 2019, Shephard et al., 2021, van den Heuvel et al., 2016). Abnormalities in connectivity within the sensorimotor areas could indicate hindered sensorimotor gating, a mechanism for filtering out unnecessary sensory, cognitive, and motor information to support mental and

behavioral adaptability and integration (Cromwell et al., 2008). This could contribute to the inability to inhibit undesired thoughts and images and repetitive behaviors or mental acts (Hoexter et al., 2018, Ahmari et al., 2012, Moreira et al., 2019).

In addition, the 59th PC of baseline RSFC included functional connectivity between the sensorimotor network and subcortical regions (e.g., putamen, cerebellum cortex) as a risk factor. This is consistent with prior studies showing associations between OCD and greater functional connectivity among the somatomotor network, cerebellum, and subcortical network (Sha et al., 2020). These findings suggest that disrupted cerebellar-cortical connectivity is implicated in the pathophysiology of OCD.

Resting-state functional connectivity (RSFC) represents the synchronous activation of distinct, anatomically separated brain regions when at rest, signifying functional communication among these regions (Graybiel & Rauch, 2000). Neurocircuit-based models may be particularly effective in representing OCD. Initially, OCD was linked to dysfunctions in cortico-striatal-thalamo-cortical (CSTC) circuits (Graybiel & Rauch, 2000, Milad & Rauch, 2012), yet, other circuits like fronto-limbic, fronto-parietal, and cerebellar are now acknowledged as contributing factors (Stein et al., 2019). Abnormalities in these different neurocircuits likely interact with each other to generate the complex OCD phenotype and development trajectories (Milad & Rauch, 2012, Stein et al., 2019). Therefore, individuals with OCD may have different degrees and patterns of alterations in these neurocircuits, leading to heterogeneous developing trajectories of OCS.

Confidence can be drawn from these findings for several reasons. This study was unable to control for the effects of treatment. Children at risk for OCD may have been exposed to medication or psychotherapy, potentially influencing subsequent symptom changes. While the study found a significant impact of OCD risk exposure on later symptom worsening, and individual variations were meaningful, it is limited by not being able to control for interventions following OCD risk exposure.

The study also has limitations in not considering children who develop OCD risks over time. Given that obsessive symptoms can evolve during development, the risk group for OCD includes not only children currently having OCD but also those progressively developing symptoms. Through GRF analysis, we identified RSFC characteristics in children with OCD who are vulnerable to future symptom worsening. However, this study did not elucidate the case for children who gradually show obsessive symptoms. Future research is needed to characterize the risk group longitudinally.

Furthermore, the correlation within baseline brain IDPs might potentially amplify the occurrence of false negatives. With two mutually correlated variables, the Gaussian Random Field (GRF) may assign high significance to one while neglecting the other. Despite implementing principal component analysis and utilizing these components as covariates to mitigate this issue, correlations between baseline characteristics and change rates could still skew the accuracy of feature importance.

Overall, we identified OCS developing trajectories and the role of RSFC in influencing OCS in a large normative sample of 9- and 10-year-olds. Our findings underscore the potential of functional connectivity within sensorimotor circuits as a

resilient factor and between sensorimotor-subcortical circuits as a risk factor. Subsequent research can build on this to provide a deeper understanding of these circuits over developmental stages, utilizing future longitudinal data from the ABCD study, and to explore the possibility of focusing on these circuits in clinical trials aimed at preventing the onset of OCD in young people.

Chapter 4. General Discussion

Summary of findings

In this thesis, we leveraged the largest available neuroimaging dataset of OCD patients to determine the current predictive capabilities for OCD, and utilizing a large-scale child data, we discovered individual variations in the aggravation of subsequent symptoms due to OCD risk.

In Chapter 2, we confirmed that using the largest scale of white matter microstructure data, we could accurately classify patients with OCD with an ROC AUC of approximately 0.6. The neuroimaging-based probability of OCD was found to be associated with OCD sub-symptoms. We demonstrated that the white matter microstructure areas within the cortico-striatal-thalamo-cortical (CSTC) circuits, known mechanisms for OCD from prior research, are involved in predicting OCD patients. In Chapter 3, we explored the influence and individual variability of OCD risk on subsequent symptom exacerbation among preadolescents from the ABCD study. Utilizing a generalized random forest, we discovered that OCD risk can intensify symptoms two years later, with significant individual variations. Notably, we found that these individual differences are closely associated with nerual factors.

Neuroimaging based predictive modeling for mental illness

Leveraging the extensive neuroimaging consortium of the ENIGMA OCD working group, we confirmed that brain white matter microstructures could predict OCD

with about 60% accuracy. This outcome, based on the largest dataset to date and accounting for potential performance declines due to site-specific variability, provides a benchmark for the current level of OCD prediction based on neuroimaging. To render this useful in a clinical setting, enhancement of prediction accuracy is essential.

These limitations are not exclusive to OCD, but pervasive across psychiatric disorders. Current predictive performance based on large-scale neuroimaging data remains partial, with no reports of accuracy reaching 90%. Hence, individual psychiatric disorder prediction via neuroimaging holds considerable room for improvement. One factor is potential information loss during feature construction, a conventional process based on domain knowledge. Traditional human neuroimaging studies have utilized phenotype data derived from images rather than the image data itself, applying modeling and assumptions typically deemed appropriate, which can result in information loss. As an alternative, recent studies have begun applying deep learning directly to 3D brain imaging data, bypassing the feature construction stage. Prior study showed that deep learning-based models outperformed traditional machine learning-based models (Abrol et al., 2021). Future research should examine the predictive performance of OCD based on deep learning.

In our study, we identified differences in brain and clinical features within the same OCD patient group depending on the site. Such site variation could potentially hinder the model's ability to learn brain abnormalities in OCD patients. There are various ways to account for site variability in predictive models. For instance, harmonization techniques that alter the data distribution to reduce site variability can be used.

Alternatively, increasing the volume of training data can render the prediction probability independent of site variability.

Large-scale neuroimaging consortia studies have provided benchmarks for the performance of brain imaging-based prediction models when data is voluminously expanded, demonstrating the prediction capabilities when cutting-edge technology is applied to unprecedentedly large data sets. However, their utility in clinical settings still appears insufficient. For qualitative growth in neuroimaging prediction models, one potential approach involves creating foundation models that effectively utilize multimodal neuroimaging data. Foundation models, also known as pre-trained models, are designed to be fine-tuned for various downstream cognitive tasks (Fei et al., 2022). This approach could yield maximum efficiency based on the accumulated data, and it is particularly crucial considering the inherently heterogeneous nature of psychiatric disorders. Future endeavors should aim at constructing foundation models by integrating multimodal neuroimaging data.

Individual differences and developmental trajectories of psychiatric disorders

Psychiatric disorders have a persistent impact on an individual's life, influencing behavior, potentially hindering appropriate treatment, and possibly exacerbating functional impairment. These processes manifest differently across individuals, with some more vulnerable to psychiatric disorders, and others with similar risk profiles experiencing worse prognoses. Identifying individual characteristics that contribute to this vulnerability can inform more effective interventions. In this context, we

demonstrated that the impact of childhood Obsessive-Compulsive Disorder (OCD) on subsequent symptom severity varies among individuals and found that these differences are closely linked to resting state functional connectivity features.

This study built upon previous research by acknowledging that the evolution of OCD symptoms during development can differ among children. However, it did not consider the concurrent development of brain structure and function during this period. Future studies should utilize longitudinal data to explore the relationship between changes in OCD symptoms and developmental factors in the brain.

Future direction

This thesis aimed to construct neuroimaging-based predictive models for obsessive-compulsive disorder (OCD) and identify factors contributing to individual differences among patients. Both individual prediction and elucidating underlying mechanisms strive for ultimate clinical utility. Future research should focus on establishing foundation models adaptable to a variety of cognitive tasks and fine-tuning these to accurately predict specific psychiatric disorders. Furthermore, investigation into individual trajectories of the onset, persistence, and recovery from psychiatric disorders is warranted.

Contribution

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