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White matter microstructure in early onset Obsessive-Compulsive Disorder and Tourette Syndrome.

A diffusion tensor imaging study in a population of drug-naïve children and adolescents with long-term clinical follow-up.

Doctoral Dissertation of
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ABSTRACT

Background and Objective

Early onset obsessive-compulsive disorder (OCD) and Tourette syndrome (TS) are frequently associated conditions. Beside the evidence of their high epidemiological cross-prevalence supported by a common genetic liability (Huisman-van Dijk et al., 2016; Yu et al., 2015), little is known on the nature of their close relationship on a pathophysiological level. By analyzing white matter (WM) microstructure through diffusion tensor imaging (DTI), the present study aimed to characterize and compare primary pathophysiological changes in drug-naïve children and adolescents with OCD, TS, and TS+OCD.

Methods

Fifty-one participants (mean age 10.2 ± 2.0 years), including N=10 with OCD, N=16 with pure TS, N=14 with TS+OCD, and 11 age-matched controls were studied cross-sectionally through 3T MRI. We performed tractography and extracted DTI metrics in five WM tracts of interest, i.e., the cortico-spinal tract (CST), the anterior thalamic radiations (ATR), the inferior longitudinal fasciculus (ILF), the corpus callosum (CC), and the cingulum. Relationship between DTI changes and clinical severity was examined through correlational analyses. A clinical follow-up at mean 7.6 years after MRI examination was performed to evaluate clinical outcomes and association to neuroimaging findings.

Results

Significant between-group differences emerged in DTI metrics, specifically in fractional anisotropy (FA), an index of myelination and organization of axon fibers (Johansen-Berg & Rushworth, 2009; Toga et al., 2006). All analyzed tracts of interest except for the cingulum revealed a differential microstructure at group comparisons. The OCD group showed decreased FA within CST, ATR, ILF, and CC in respect to controls. A negative correlation was found between obsessive-compulsive symptoms and FA values in OCD, indicating that more severe clinical phenotypes are likely

underpinned by less organized WM. Compared to controls, TS and TS+OCD groups both displayed remarkably different correlates from OCD and opposite DTI changes, i.e., increased FA in CST, ATR, ILF, and CC. Moreover, TS and TS+OCD had comparable DTI changes within all the investigated WM tracts and FA showed negative correlation with tic severity, revealing a shared pattern of WM organization in TS/TS+OCD with inverse relationship to symptom expression. At follow-up, no significant associations were found between FA values at baseline and long-term outcomes. Substantial symptom remission was achieved in 58.3% of TS, 63.6% of TS+OCD, and 70% of OCD patients, although a significant proportion of patient developed additional psychiatric disorders such as anxiety or depression.

Conclusion

The study highlights differential white matter involvement in pediatric OCD as opposed to TS/TS+OCD. Compared to neurotypical population, children with TS/TS+OCD showed an early increase in axons, fiber density, and/or myelination in WM bundles linking the frontal, occipital, and temporal cortices with each other and with the thalamus. Conversely, children with OCD showed widespread reduced organization of callosal, temporo-occipital, and fronto-thalamic WM tracts. Correlational analysis suggests that DTI changes in TS may reflect a compensatory reorganization in response to the disease pathophysiology, while in OCD they may represent a marker of the overall disease severity deriving from delay or damage to white matter development. Confirmation of these possibilities awaits longitudinal studies. The observation of shared DTI correlates of TS and TS+OCD strengthens the concept that at least some forms of OCD are etiologically related to TS and might therefore be a variant expression of the same etiologic factors that are important for the expression of tics (i.e., TS+OCD as a peculiar subtype of TS). By characterizing and differentiating early-stage neural underpinnings of OCD and TS, future targeted and neuroimaging-informed interventions may be developed.

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1. INTRODUCTION

1.1 Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a common, often unremitting, and highly disabling disorder. OCD is characterized by the presence of obsessions and/or compulsions (DSM-5, American Psychiatric Association, 2013) (Table 1). Obsessions are repetitive thoughts, images, or impulses that are intrusive and unwanted, and that often lead to an increase in the arousal state and a sense of discomfort. Compulsions are repetitive observable acts or mental acts that the individual feels the urge to perform in response to an obsession, in the attempt to extinguish the obsessive thought, or to achieve a sense of 'completeness'. In children, identification of obsessive thought contents might be difficult, whereas most adults can recognize the presence of both core symptoms of the disorder. However, although still a matter of debate, some evidence indicates that compulsive acts may be the primary hallmark of OCD and that obsessions occur as a post-hoc rationalization of these behaviors (Barahona-Corrêa et al., 2015; Robbins et al., 2019).

Several symptom dimensions of OCD exist. Most well-known presentations include washing and checking behaviors, related to excessive contamination fears, or worrying. However, a bewildering variety of symptomatology can occur, as in the case of mental or actual rituals (e.g., counting, thinking of specific words, doing specific gestures) to defeat forbidden intrusive thoughts or to accomplish magical thinking (i.e., the belief of being able to influence the outcome of specific events by doing something that has no rational connection to those events).

OCD lifetime prevalence is around 2-3%, although rates vary across regions (Fontenelle et al., 2006). OCD is more common in females than in males in the community, whereas when males are affected, almost 25% of cases have onset before age 10 (Ruscio et al., 2010). Incidence typically

follows a bimodal pattern, with one peak around 19 years and the other around 11 years (early onset OCD) (Fineberg et al., 2013; Ruscio et al., 2010). Over the last two decades, convergent literature indicated that patients with an early age at onset seem to present with a specific clinical and biological profile, suggesting this form to be a neurodevelopmental disorder with distinctive features (Burchi & Pallanti, 2019). Furthermore, data from longitudinal studies highlight that early onset OCD patients tend to have a worse outcome in respect to adult-onset patients, that duration of untreated illness and number of OCD-burdened years are predictors of a worse outcome, and that early interventions could potentially improve prognosis (Fineberg et al., 2020; Skoog & Skoog, 1999).

OCD is also characterized by substantial comorbidity. Up to 90% of individuals with lifetime OCD meet the diagnostic criteria for another DSM lifetime disorder and, notably, type of comorbidity is related to age at OCD onset. While juvenile-onset OCD patients show higher rates of anxiety and depressive disorders, impulse-control disorders, and substance use disorders (Ruscio et al., 2010), childhood-onset OCD patients often have other neurodevelopmental disorders, such as Tourette syndrome and ADHD (Geller et al., 2001; Selles et al., 2014). Comorbidity between OCD and tic disorders, particularly Tourette syndrome (TS), is so frequent in a specific subgroup of patients that several experts argue that the two disorders, when associated, represent a specific subtype of the illness. This peculiar condition has been captured by the elaboration of the DSM-5 OCD tic-related specifier and might be referred to as Obsessive-Compulsive Tic Disorder (OCTD) (Conelea et al., 2014; Tanidir et al., 2015). Available evidence (Dell'Osso et al., 2017) suggests that OCTD is characterized by earlier onset, male gender prevalence, higher presence of obsessions of symmetry, aggressiveness, hoarding, and exactness, and impulsive behaviors and ADHD comorbidity.

Several cortico–striato–thalamocortical (CSTC) circuits are believed to have a role in OCD. These parallel, partly segregated circuits are involved in habitual behaviors, executive control on behavior, motivation — processes that have been hypothesized as dysfunctional in patients with OCD (Kwon

et al., 2009; van den Heuvel et al., 2016). Variants in genes encoding serotonergic, catecholaminergic and glutamatergic pathway components have been implicated in the disorder, although candidate gene studies have been underpowered and further investigation is required (Taylor, 2013, 2016). In addition, gene–environmental interactions, and modulation of obsessive–compulsive symptoms by general aetiological factors (such as those influencing negative emotionality) have preliminary supporting evidence (Taylor, 2016). Also, some subtypes of OCD might have a higher heritability than others, including early-onset tic-related OCD (Leckman et al., 2010).

Serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs)] or cognitive behavioral therapy (CBT) with exposure and response prevention (ERP) techniques, represent the mainstay of treatment for OCD, while neuromodulation (such as deep transcranial magnetic stimulation - DBS) may be useful for patients with refractory OCD, with accumulating evidence suggesting that early intervention produces better outcomes (Fineberg et al., 2019).

Table 1. DSM-5 diagnostic criteria for OCD

Obsessions are defined by (A) and (B)
A. Recurrent and persistent thoughts, urges or images that are experienced, at some time during the disturbance, as intrusive, unwanted, and that in most individuals cause marked anxiety or distress.
B. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some thought or action (i.e., by performing a compulsion).
Compulsions are defined by (A) and (B)
A. Repetitive behaviors (e.g., hand washing, ordering checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to the rules that must be applied rigidly.
B. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation. However, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.
C. The obsessions OR compulsions are time consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possession, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder], etc.) or due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition.

1.2 Tourette syndrome

Tourette's or Gilles de la Tourette's syndrome (Tourette syndrome, TS) is a complex neuropsychiatric disease with onset in childhood characterized by the presence of multiple motor and phonic tics (Table 2) (DSM-5, American Psychiatric Association, 2013). Tics are unwanted, purposeless movements or vocalizations. Examples include shaking/tilting the head, turning the eyes, sniffing, throat clearing sounds, snorting, and more complex phenomena such as finger tapping, touching, or saying words or phrases (Sanger et al., 2010). Several characteristics set tics apart from other hyperkinetic movement disorders: they are brief, repetitive, stereotyped, discrete and nonrhythmic, most frequently involve the upper body, and are typically perceived by most patients as the result of surrendering to an almost irresistible urge (Sanger et al., 2010).

Table 2. DSM-5 diagnostic criteria for TS

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	A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization	
A.	Both multiple motor and 1 or more vocal tics have been present at some time during the illness, though not necessarily concurrently	
2	The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset	
3	The onset is before age 18 years	
4	The disturbance is not due to the direct physiologic effects of a substance (eg, cocaine) or a general medical condition (eg, Huntington disease or postviral encephalitis)	

Affecting about 1% of children, adolescents, and adults worldwide (Robertson et al., 2009), TS represents just one entity in the spectrum of tic disorders, which range from transient forms with remission after few months to forms associated with rare neurodegenerative disorders (secondary

tic disorders). The latter are not considered further in this thesis, since most tic disorders are primary (Schlaggar & Mink, 2003). Motor tics usually occur at 4-6 years of age and show a cranio-caudal progression pattern, with the head district most involved at onset and later appearance of tics in inferior body areas (e.g., shoulders-arms-hands, trunk, legs, feet) (Robertson, 2008) (Fig. 1). Tics fluctuate significantly in severity, frequency, and distribution, resulting in tic undulations and migration over weeks and months throughout the course of the disease. Phonic tics usually follow motor tics several months to a few years later (Robertson, 2008). The severity of tics usually peaks in mid childhood and early adolescence (~ 9 to 11 years) and then decreases, often leading to complete or near-complete symptom remission towards the end of the second decade of life in 60-85% of cases (Bloch & Leckman, 2009; Hassan & Cavanna, 2012).

Tics in TS show a variable degree of frequency and complexity both intra- as well as inter-individually, and may negatively impact on psychosocial, academic, and occupational functioning (Rizzo et al., 2012). Furthermore, TS clinical presentation is often dominated by its frequent comorbidities, which remarkably influence clinical outcome and quality of life of affected individuals. In this regard, a particular association between TS, Obsessive-Compulsive Disorder (OCD), and Attention-Deficit Hyperactivity Disorder (ADHD) has been established (Hirschtritt et al., 2015; Yu et al., 2019), but anxious-depressive disorders, affect regulation disorders (rage attacks, oppositional defiant disorder, etc.), and other neurodevelopmental disorders such as autism and specific learning disabilities, are also highly frequent (Conte et al., 2020; Cravedi et al., 2017; Mol Debes et al., 2008). Clinical appearance of tics may be preceded in preschoolers by symptoms of ADHD (Fig. 2), such as impulse control problems/hyperactivity and/or inattention, with usual persistence into adulthood and as many as 60–80% of TS patients fulfilling diagnostic criteria for ADHD (Robertson, 2000; Simpson et al., 2011). OCD symptoms generally display a pre-pubertal onset with variable symptom pattern (Geller et al., 2021), although, need for symmetry, and

inappropriate sexual or aggressive thoughts are relatively more common in people with TS than contamination/washing symptom dimensions (Cath et al., 2001; Worbe et al., 2010).

Figure 1. Clinical course of TS and its major comorbidities
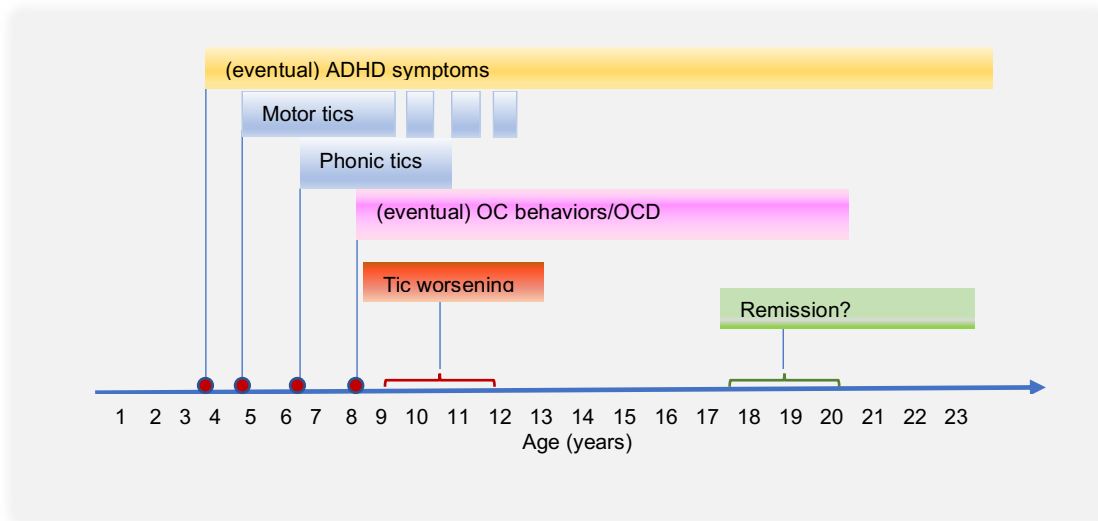
In preschoolers, symptoms of ADHD may precede tic onset. Motor tics usually occur at 4-6 years of age with a cranio-caudal progression pattern. Tics fluctuate significantly in severity, frequency, and distribution (exemplified by separate light-blue boxes) throughout the course of the disease. Phonic tics usually follow motor tics several months to a few years later. OCD onset appears in TS commonly before 10 years of age.

In terms of pathophysiology, there is broad consensus that the functional alteration of TS resides within cortical-striato-thalamo-cortical (CSTC) circuits, however, the definition of which is the neurochemical abnormality or functional pathway primarily involved the disease remains to be determined. Multiple TS known risk genes (Qi et al., 2019; Willsey et al., 2017) and epigenetic modulation of gene expression, particularly within CSTC circuits (Yu et al., 2019), are implicated in TS pathogenesis and high heritability.

From a therapeutic point of view, cognitive-behavioral psychotherapy is considered as first-line treatment, followed by various pharmacological options and, in the most severe cases, by intracranial brain stimulation with DBS (Deep Brain Stimulation) (Müller-Vahl et al., 2022).

1.3 The relationship between OCD and TS

Several lines of research suggest that TS and OCD are related, with many shared clinical characteristics. Both hallmarks of the two disorders belong to the domain of "compulsivity", i.e., acts/actions persisting inappropriate to the situation, and that can result in undesirable consequences (Dalley et al., 2011). In OCD and TS, patients similarly feel compelled to act upon tics, compulsions, and obsessions, which all are exacerbated by stress or anxiety. However, these urges can also be suppressed at the expense of internal tension and according to the individual's ability. Furthermore, tics and obsessions/compulsions share a chronic waxing and waning course; a childhood or juvenile onset; and a familial occurrence (Leonard et al., 2001; Steingard & Dillon-Stout, 1992).

Regarding epidemiology, a series of observational studies have documented high cross-prevalence of OCD and TS across first-degree relatives (Pauls et al., 1991, 1995). In early-onset OCD, chronic tics occur in around 18-46% of individuals (do Rosario-Campos et al., 2005; Nissen et al., 2016), whereas in TS, about 14-61% of individuals meet diagnostic criteria for OCD (O'Rourke et al., 2011; Sambrani et al., 2016).

Genetic studies give additional support for this relationship, showing common genetic background (Mathews & Grados, 2011), although conclusive data on shared genetic polymorphisms predisposing to the association of TS and OCD are still lacking (Yu et al., 2015).

From a pathophysiological point of view, fronto-striatal-thalamic circuits are most implicated in the repetitive behaviors of TS and OCD (Eddy & Cavanna, 2014), with overlapping neuroanatomical sites of dysfunction (Baxter, 1990; Cummings & Frankel, 1985).

1.3.1   Criticism of OCD and TS juxtaposition

In drafting the DSM-5, it was debated upon including TS in the chapter "Obsessive-compulsive disorder and related disorders" (OCDR), a spectrum of psychiatric disorders sharing "repetitiveness" of thoughts and behaviors as a main feature (Hollander et al., 1996). To capture the overlap between OCD and TS, a tic-related specifier was introduced in DSM-5 (see Table 1) to categorize OCD cases with current or past comorbid TS (OCD+TS), and some authors have posited that it would be reasonable to group OCD-related conditions together along a spectrum (OCDS), on the basis of extant co-morbidity and familiarity data (Bienvenu et al., 2012) (Fig. 2). However, in the DSM-5, TS was ultimately included in the chapter of neurodevelopmental disorders (NDD), due both to its demographic-epidemiological characteristics as well as for its comorbidity with other NDD.

Figure 2. Obsessive-compulsive spectrum disorders
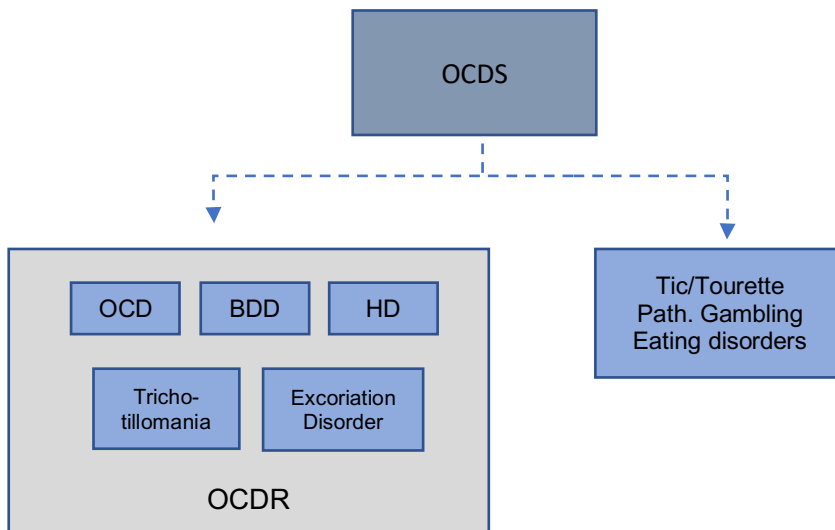
BDD, body dysmorphic disorder; HD, hoarding disorder
Adapted from Nakao & Kanba, 2019 *Psychiatry Clin Neurosci*

To date, several arguments have been pointed out against a nosologic equivalence between TS and OCD (Walkup et al., 2010). These include the following:

a) *OC clinical phenotype in TS.* OC symptoms in the context of TS are predominantly represented by sexual/aggressive obsessions and hoarding, repeating, touching, and counting compulsions compared to OCD alone (Cath et al., 2001; Nestadt et al., 2009).

b) *Types of events preceding motor symptoms*. Tics and compulsions, although both characterized by "internal experiences" that precede them (obsessions in OCD vs "premonitory urges" in tics), are distinguishable by the characteristics of such phenomena, being obsessions highly complex cognitions and urges basic sensitive experiences (such as tickling, pressure-like feeling, etc.) (Martino et al., 2013) (Table 3).

c) *Onset and clinical course.* Although both disorders have an onset in childhood or adolescence, OCD also frequently occurs in young adult age (>18 years) (Grant et al., 2007), which for tics is extremely rare (Chouinard & Ford, 2000) and excludes a diagnosis of TS according to criterion C of the DSM-5 (see Table 2). Tics also tend to peak in prepubertal age with remission in adulthood (Bloch & Leckman, 2009), while OCD can displays also a more persistent and may worsen in adulthood (Bloch et al., 2006).

d) *Neuroimaging correlates.* Several neuroimaging studies have highlighted distinct patterns of CSTC involvement in the two conditions, with greater abnormality of sensory-motor pathways in TS (Baxter, 1990; Cummings & Frankel, 1985), as opposed to alterations mainly in cognitive and action-control pathways in OCD (Mataix-Cols et al., 2004; Mataix-Cols & van den Heuvel, 2006).

e) *Pharmacological treatment.* Although treatment with serotoninergic drugs (SSRIs) is effective for most patients with OCD, presence of tics may predict a worse response to SSRI monotherapy (McDougle et al., 1993, 2000). However, contrasting findings also exist in this regard, showing that tic comorbidity does not increase risk of poor response to SSRIs in OCD (Shavitt et al., 2006). Also, antidopaminergic medications, which are the mainstay of treatment for TS, failed to show benefit in the treatment of OCD in a small study with subjects

with comorbid tics (Carey et al., 2005). Overall, there is limited data indicating that patients with TS+OCD may exhibit different responses to common therapeutic strategies used for OCD alone, which has been allegedly linked to different monoaminergic alterations in TS+OCD as compared to those typical of "pure" OCD (dopaminergic vs serotoninergic, respectively) (Maia & Conceição, 2018).

Table 3. Differences in clinical features of tics and compulsions

	Tic	Compulsion
Onset age	4-6 years	8-10 years
Subjective perception	Ego-syntonic *	Ego-dystonic
Sensory experience	Premonitory urge	Anxiety-generating thought/imagery
Will for action	Involuntary	Voluntary
Duration	Short (e.g., jerks)	Prolonged (e.g., rituals)

(*) tics may be perceived as movements that alleviate aversive sensations (premonitory urges)
Adapted from Martino et al., 2013

1.3.2   *Hypothetical models of OCD and TS co-occurrence*

Despite lack of neurobiological understanding of the exact relationship between OCD and TS, different theoretical models have been hypothesized to explain their common co-occurrence. The following points summarize the main theoretical approaches proposed in this regard.

a) *The phenotypic variant hypothesis.* According to some authors, the condition of OCD accompanying TS would constitute a phenotypic variant of TS based on shared genetic, neurobiological, and pathophysiological determinants (Pauls et al., 1986). The difference between TS and the TS "plus" form (i.e., TS+OCD) would lie not in the quality of neurobiological underpinnings but in the degree of their abnormality in the "plus" phenotype (Coffey et al., 1998).

b) *The hybrid condition hypothesis.* According to this model, TS+OCD would result from the combination of shared vulnerability factors for both TS and OCD. This has lent some authors to term the condition of TS and OCD comorbidity as "Tourettic OCD" (Mansueto & Keuler, 2005), a condition in which the factors determining the clinical appearance of tics and OC symptoms would act synergistically. Accordingly, the resulting "mixed" phenotype is characterized by the combination of the two basic phenotypes of both OCD and TS, that is: onset in childhood, execution of compulsions in response to sensory perceptions rather than to suppress anxiety and obsessive thoughts, partial or absent response to SSRIs, and presence of other comorbidities such as ADHD, Specific Learning Disorders, Impulse Control Disorders.

c) *The independent condition hypothesis.* According to this model, TS+OCD would be a nosologic entity different from both TS and OCD and therefore characterized by specific neurobiological and pathophysiological abnormalities different from the mere combination of those of TS and OCD (Dell'Osso et al., 2017).

1.4 Brief introduction to white matter development and its role in neuropsychiatric disorders

White matter (WM) is a widespread area of the central nervous systems composed of millions of bundles of axons (nerve fibers) that connect neurons located in different brain regions into functional circuits. Axons coated with myelin are central components of WM structure and myelin is produced by nonneuronal cells, the oligodendrocytes, through a specific developmental pattern (Barkovich et al., 1988), which begins early during gestational age and continues through adolescence and adulthood, reaching a maximum in the 2nd or 3rd decade of life (Yakovlev & Lecours, 1967) (Figure 3). Myelination has an essential role in brain development and communication by increasing the

conduction speed of electrical impulses, improving prompt connectivity between brain areas. This process undergoes refinement throughout the lifespan and is significantly influenced by learning (Xin & Chan, 2020), motor training (Huang et al., 2015) and sleep (de Vivo & Bellesi, 2019). Thus, over the last decades, it has been increasingly recognized that plasticity in the human brain occurs not only at the level of synapses but also at the level of myelin. Therefore, WM architecture modeling through myelin plasticity has increasingly been recognized as an essential partner of brain plasticity, which mediates brain structure and function.
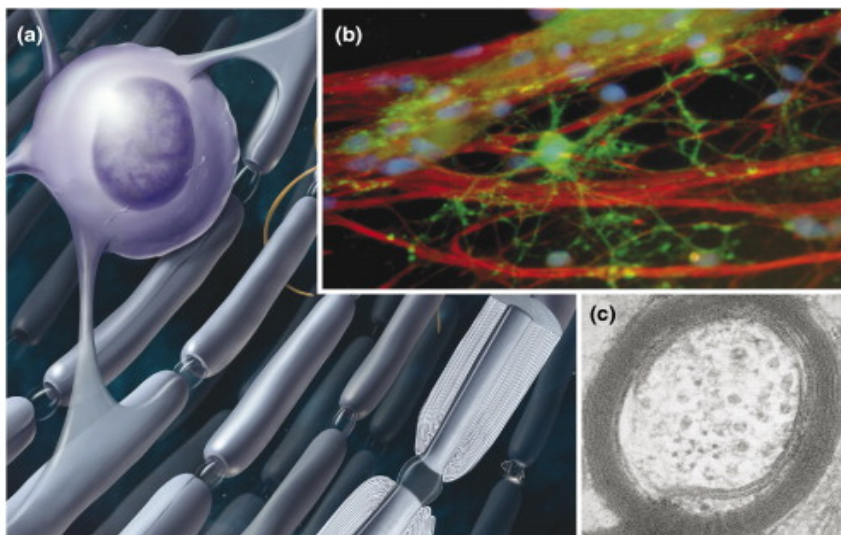
Fig. 3 (a) Myelin is the cell membrane of oligodendrocytes multiply wrapped around axons to form electrical insulation that speeds conduction of nerve impulses. Each oligodendrocyte of the human brain provides insulation of multiple axons through circa 20 or more membrane extensions. **(b)** An oligodendrocyte (green) is shown at the initial stage of wrapping myelin membrane around several axons (red). **(c)** An electron micrograph cross-section of an axon in the rat brain revealing the multiple layers of myelin membrane surrounding the axon. *Fields, 2008, Trends in Neuroscience.* Image reused with permission.

Neuropsychiatric disorders are currently understood and pharmacologically treated as disorders of synaptic transmission, but alterations in WM microstructure have been increasingly associated to their pathophysiology.

WM microstructural changes have been identified in a wide range of psychiatric disorders, including depression, bipolar disorder, schizophrenia, OCD, and posttraumatic stress disorder, as well as in many neurodevelopmental disorders including autism, dyslexia and attention-deficit hyperactivity disorder (Fields, 2008).

Although still unclear whether intrinsically linked to primary risk factors or secondary to cortical neural dysfunction (Konrad & Winterer, 2008), WM alterations contribute to the pathophysiology of

brain disorders through aberrations in transmissions. The characterization of WM microstructure therefore represents a privileged avenue for the characterization of the neural basis of neuropsychiatric disorders, such as OCD and TS, and to understand their mutual relationship.

1.4.1 Diffusion-weighted imaging (DWI)

DWI takes advantage of principles of water diffusion to estimate brain or other tissues microarchitecture. In a perfect homogenous and unconstrained medium, the water molecules follow the so-called Brownian motion, i.e., they float in a random isotropic pattern of movement (isotropy refers to the capacity of a material to show the same properties – e.g., velocity of movement - when tested in different directions). Conversely, in structured environments, the motion of water molecules is restricted due to the presence of the physical constraints intrinsic to the architecture of that environment. This motion is termed as 'anisotropic' given that it is not equal in all directions. The brain, due to its complex subdivision in grey and white matter components and to the microstructural organization within these, represents a structured environment in which the flow of water molecules is restricted ("anisotropic"). Within white matter, water molecules generally move aligned parallelly to the tract main length/axis rather than perpendicularly, because axon membranes offer a limit to water motion towards them. "Diffusion tensor' is the mathematical term used to calculate the probability of the motion of water molecules in x, y, z planes and the correlation between these directions (Figure 4). Diffusion tensor imaging (DTI) is the derived technique which allows for the assessment of WM architecture through the analysis of water diffusion properties within brain tissue. WM structural and orientational indexes most employed in DTI are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), which are all sensitive to different aspects of tissue microstructure. In particular, FA has been associated with myelination and organization of axon fibers (Johansen-Berg & Rushworth, 2009; Toga et al., 2006) and FA reductions are believed to

reflect less myelinated and less compact WM tracts (Beaulieu, 2002; Hermoye et al., 2006). FA is usually considered as the measure of 'WM integrity' though FA can be modulated by several other factors.
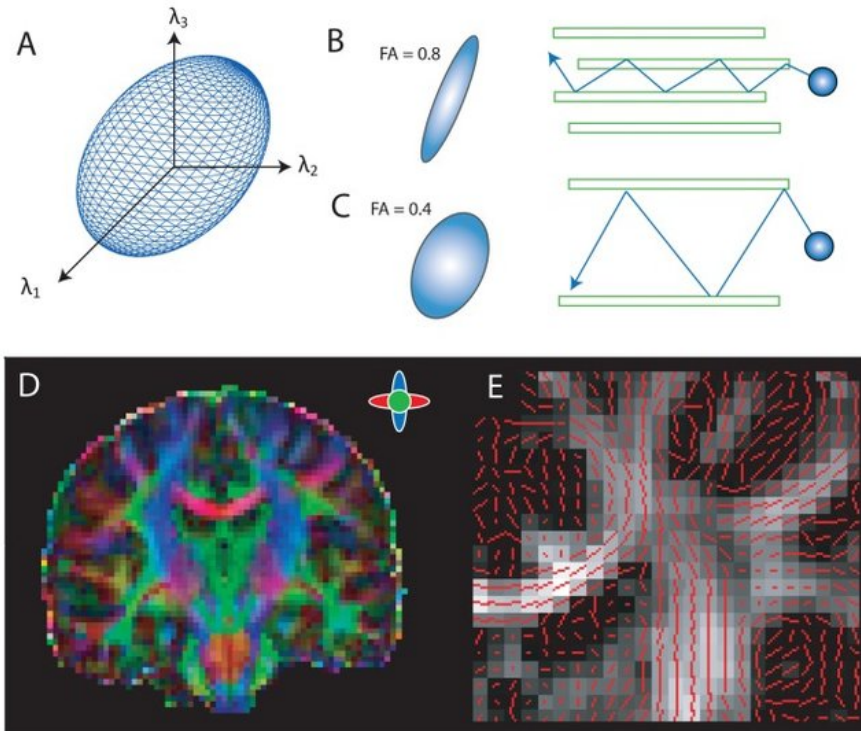
Figure 4. (A) Diffusion tensor ellipsoid represents the probability that water molecules within a voxel will diffuse in a given direction. (B) Fractional anisotropy (FA) is calculated from the diffusion tensor. Areas of high anisotropy have a more elongated probability distribution, reflecting the higher likelihood of diffusion in one direction. (C) Areas of lower anisotropy have a more spherical distribution. (D) FA map that illustrates the principal directions of diffusion within different white matter pathways. (E) Here, the principal direction of diffusion within each voxel (red line) is shown overlaid on an FA map (lighter gray indicates higher anisotropy).
Image reused from *Roberts et al., 2011, The Neuroscientist*

2. THESIS OBJECTIVE AND OUTLINE

The above premises highlight that the relationship between TS and OCD is complex and heterogenous. Disentangling such complexity is unviable without greater characterization of the underlying neurobiology since it is unknown whether, and to what extent, the clinical characteristics of OCD and TS reflect shared pathophysiological pathways. A crucial issue in this regard would be to define which correlates are present when TS and OCD are associated, and which underpin the presentation of TS alone or OCD alone. Thus, comparing the pathophysiology of the comorbid condition (TS+OCD) with each single "pure" phenotype (TS or OCD) would add remarkable understanding on the nature of the association of these two disorders and represents the objective of this Thesis.

The present study focuses on the analysis of white matter (WM) in children and adolescents with OCD, TS, and TS+OCD, to gather insight on this central component of structural brain development. MRI with diffusion tensor imaging (DTI) was implemented to assess characteristics of WM microarchitecture, such as fiber myelination, density, orientation, and overall integrity, providing metrics derived from the measurement of water diffusion within WM tracts. The study has included only drug- and treatment-naïve pediatric patients to provide evidence on primary microstructural WM correlates, unbiased by brain plasticity mechanisms potentially induced by pharmacological or psychotherapeutic interventions. Three group categories were identified according to clinical presentation, i.e., "OCD" (OCD without TS), "TS" (TS without OCD), and "TS+OCD" (patients having comorbid OCD and TS), to allow investigation and comparison of structural brain correlates in line with the main objective of the study. All findings were related to clinical severity measures of TS and OCD assessed concomitantly to MRI acquisition (T_1), to verify whether and to what degree the observed correlates translate into clinical presentations. Moreover, participants were reassessed at

a mean follow-up of 7.6 years after MRI examination (T_2) to evaluate clinical outcomes and association to neuroimaging findings uncovered at T_1.

Two different prior studies with resting-state functional brain MRI and cerebellum DTI-MRI are available on the same patient cohort included in the present study. By analyzing other central nervous system areas through different neuroimaging approaches, these prior works have for the first time highlighted that the condition of TS+OCD shares common neural correlates with TS but not with OCD (Tikoo et al., 2020, 2021). Based on this evidence, two main hypotheses are claimed to be verified in the present study, i.e., that: (i) TS+OCD and TS share common microstructural WM alterations and may be regarded as a unitary group, and (ii) OCD is different from TS+OCD/TS in terms of WM correlates. We also hypothesize that the degree of WM structural integrity in patients with TS and OCD may be related to the severity of tics and obsessive-compulsive symptoms at T_1 and may be associated to different clinical outcomes at long-term follow-up (T_2).

2.1 Previous white matter correlates in TS and OCD

To date, TS and OCD have been separately considered in neurostructural studies aimed at investigating correlates of WM involvement. Moreover, for both disorders, a large amount of previous studies relies on findings from adult cohorts (e.g., Cheng et al., 2014; J. Fan et al., 2017; Lochner et al., 2012; Neuner et al., 2010; Ramkiran et al., 2019; Worbe et al., 2015), thereby possibly missing to capture primary correlates of two conditions rooted in the age of neurodevelopment.

In TS, available evidence has yielded variable findings in WM bundles involved in different structural networks (Bruce et al., 2021; Cheng et al., 2014; Debes et al., 2015; Govindan et al., 2010; Jackson et al., 2011; Jeppesen et al., 2014; Liu et al., 2013; Makki et al., 2009; Müller-Vahl et al., 2014; Plessen et al., 2006; Sigurdsson et al., 2018; Thomalla et al., 2009; Wolff et al., 2016; Worbe et al., 2015). With the exception of the study by Jeppesen et al. (2014), all studies examining pediatric TS

populations have revealed widespread WM abnormalities, involving main motor pathways (Bruce et al., 2021; Govindan et al., 2010; Liu et al., 2013; Sigurdsson et al., 2018), interhemispheric connectivity (Bruce et al., 2021; Govindan et al., 2010; S. R. Jackson et al., 2011; Plessen et al., 2006; Sigurdsson et al., 2018; Wolff et al., 2016), prefrontal, and fronto-striatal pathways (Debes et al., 2015; Makki et al., 2009). Both reduced (Jackson et al., 2011; Plessen et al., 2006) and increased (Bruce et al., 2021) FA values have been outlined in children, while AD more clearly and consistently resulted *reduced* in different WM tracts (Debes et al., 2015; Sigurdsson et al., 2018; Wolff et al., 2016).

In OCD, the largest pediatric study to date has shown no differential WM correlates between patients and controls (Piras et al., 2021a), replicating similar findings from previous studies on smaller samples (Jayarajan et al., 2012; Silk et al., 2013). However, contrasting results have been reported by other studies, showing either decreased (Lázaro et al., 2008; Rosso et al., 2014) or increased WM integrity (as indexed by the FA) in pediatric OCD in cortico-spinal, and interhemispheric connections, as well as in several brain areas outside the fronto-striatal neural circuitry (parietal cortex and limbic system) (Fitzgerald et al., 2014; Gruner et al., 2012; Zarei et al., 2011).

Heterogeneous findings are the rule in neuropsychiatric neuroimaging studies, due to variable techniques of MRI acquisition, comorbid disorders, treatments, and, most importantly, age. In childhood-onset conditions such as TS and OCD, studies on drug-naïve populations with definite comorbidity profiles and short disease duration are of crucial importance to identify which primary correlates sustain pathophysiology. Studies of such kind would critically provide evidence for or against shared structural abnormalities, thereby informing current conceptualizations and future research on outcomes and interventions in the two disorders.

3. METHODS

3.1 Study design

The study had two phases: phase T_1 is a cross-sectional evaluation for MRI investigation and clinical assessment, and phase T_2 is a naturalistic clinical follow-up of patients at mean 7.6 years after T_1.

3.2 Participants

Seventy drug-naïve children and adolescents were recruited during phase T_1 at the specialized outpatient clinic for TS and related disorders (Child and Adolescent Neuropsychiatry Unit, Department of Human Neurosciences, Sapienza University of Rome, Italy). The examination procedure for both phases of the study is yielded in Table 4.

Table 4. T_1 and T_2 time-point examinations of participants

Clinical Cohorts	T_1 (2014-15)	T_2 (2022)
Inclusion criteria	OCD diagnosis TS diagnosis TS+OCD diagnosis	All participants included at T_1
Exclusion criteria	IQ<70 ADHD Other psychiatric or NDD conditions Pharmacological treatment/pychotherapy Left-handedness	None
OC symptom severity	CY-BOCS	CY-BOCS/Y-BOCS
Tic severity	YGTSS	YGTSS
Global functioning and wellbeing	GAF	GAF
Handedness	Edinburgh handedness inventory	-
Intellectual functioning	WISC-III	-
Other NDD and/or psychiatric conditions	CBCL and KSADS-PL	KSADS-5-PL and review of medical records
Medication, treatments, psychosocial, and educational	Structured interview	Structured interview

Note: ADHD= Attention-Deficit/Hyperactivity Disorder; CBCL = Child Behavior Checklist; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; GAF = Global Assessment of Functioning; KSADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version; KSADS-5-PL = Kiddie Schedule for Affective Disorders and Schizophrenia – DSM-5 – Present and Lifetime version; OCD = obsessive-compulsive disorder; TS= Tourette syndrome; WISC = Wechsler intelligence tests for children, version III; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale Score.

Patients were diagnosed according to DSM-5 criteria by a child neuropsychiatrist experienced in TS, OCD, and related disorders. Following criteria were set for inclusion: clinical diagnosis of TS (ICD-10: F95.2) and/or of OCD (ICD-10: F42.2), no prior history of pharmacological treatment, no engagement in structured behavioural intervention for tics or OC symptoms (e.g., HRT, CBIT, or ERP) within the previous 12 months, right-handedness as assessed by the Edinburgh handedness inventory (Bryden, 1977). Symptom severity was assessed using the Yale Global Tic Severity Scale (YGTSS, total tic severity scale: max. 50, without impairment score) (Leckman et al., 1989) and the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Goodman et al., 1989). Children diagnosed with TS and CY-BOCS scores above 14 were identified as patients with the comorbid condition and

included in the TS+OCD group. All subjects underwent a cognitive evaluation by means of the Wechsler Intelligence Scale for Children 3rd edition (WISC-III) full scale. All subjects had normal cognitive profile (IQ $\geq$ 70). Other developmental disorders and, specifically, Attention-Deficit/Hyperactivity Disorder (ADHD) or other psychiatric disorders were excluded using the Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (Kaufman et al., 1997) administered to both parents. Parents or guardians provided written informed consent. The study was approved by the Institutional Review Board and conformed to the Declaration of Helsinki.

Nineteen participants received a diagnosis of TS, 19 of TS+OCD, 17 of OCD. As controls, we selected 15 age-matched participants with episodic tension headache who were headache-free during the MRI scans. Importantly, all TS and TS+OCD patients had YGTSS scores above 15 or more than 10 if only motor or vocal tics were present in the past 7 days, thus showing a moderate to severe symptomatology. Typically, patients with YGTSS $\geq$14 seek medical treatment, and this represents a common inclusion criterion for clinical studies including, e.g., the ORBIT trial assessing the efficacy and of online delivered behavioral treatment for children and adolescents with tic disorders (Hollis et al., 2021).

At phase T_2, all patients from the three clinical groups were contacted and offered an in-presence complete neuropsychiatric assessment. The same validated diagnostic methods used at T_1 were implemented at T_2 (Table 4) to assess presence of tics, obsessive-compulsive symptoms, and current or past psychiatric/neurodevelopmental disorders, namely, the YGTSS, the (C)Y-BOCS (CY-BOCS for youth <18 years and Y-BOCS for >18 years), and the KSAD-PL (administered to patients). Careful anamnestic interview with patients and their families provided information on treatments, and clinical course of tics and OC symptoms over the years of follow-up.

3.3 Measures

YGTSS. The YGTSS (Leckman et al., 1989) is a reliable clinician-rated interview (Storch et al., 2005), that allows the notation of the current tics experienced by the patient, based on clinical observation, and child and parent report. Clinicians are asked to evaluate tic severity in terms of number, frequency, intensity, complexity, and interference on a 0–5 scale. Total score is obtained by summing scores from each dimension in total scale (0-50 max.).

CY-BOCS. The children's version of the Y-BOCS (CY-BOCS) (Scahill et al., 1997) is the most widely used measure of clinician-rated obsessive-compulsive symptom severity. Severity ratings range for each domain from 0 (which indicates no illness) to 4 (indicating extremely severe symptoms), on a total score of 0-40 points.

K-SADS-PL. K-SADS-PL (Kaufman et al., 1997) is a comprehensive interview allowing clinicians to diagnose current and past episodes of psychopathology and presence of neurodevelopmental disorders in children and adolescents according to DSM-5 criteria.

GAF. Global Assessment of Functioning is a widely used scale that measures how much symptoms affect the individual's day-to-day life, by also combining domains of occupational, social, and psychological functioning (Moos et al., 2002; Piersma & Boes, 1997). Clinician rate patient's functioning on a 0-100 scale, with 100 representing superior functioning.

CBCL 6-18. The Child Behavior CheckList 6–18. (Achenbach & Ruffle, 2000), is one of the most widely used instruments to assess child and adolescent psychopathology both in population and clinical samples. It is a 113-item informant-report questionnaire, which asks parents to rate specific emotional–behavioral problems of their child during the past 6 months. Items are grouped into eight empirically based syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. These subscales can be combined in two broader scales: internalizing problems scale (that

is comprised of items from the anxious/depressed, withdrawn-depressed, and somatic complaints scores); externalizing problems (that combines rule-breaking and aggressive behavior). Moreover, a total problems scale comprises the scores of all the problem items.

3.4   Outcome definition

Remission of TS. We defined remission of tics as spontaneous substantial remission of tics over a considerable amount of time, which was assumed according to our clinical experience as a period of at least 12 consecutive months. For spontaneous it is meant that tic remission was sustained after at least 6 months from discontinuation of any specific treatment for tics (either or both, psychotherapy, and pharmacotherapy). The issue of actual tic remission has been largely debated in the literature on the clinical course of TS. Some authors argue that some adults with tics are unaware of their tics, therefore, if clinical interviews relying on self-reported information are the only measure to detect tic persistence, there may be risk of overestimation of tic remission (Bruun & Budman, 1997; Leckman et al., 2006; Singer, 2006). Several studies that directly observed adults at follow-up found tics in 82%, 90% and 100% of TS patients previously diagnosed in childhood or adolescence (Goetz et al., 1992; Groth et al., 2017; Pappert et al., 2003). However, subjective perception and impairment are far more relevant for the global functioning and quality of life of the individual with tics than any clinician's direct observation. Moreover, available longitudinal studies on children with clinically problematic tics followed to age 11-25 or 15-29 (Groth et al., 2017; Stárková, 1990) have relied on clinician interviews and described that the most common course (60%) is occasional "relapses" or "minimal tics". Therefore, in this study we opted for self-reported statements of remission at clinical interview (YGTSS) and marked as "remitted" all conditions in which patients reported experience of no residual or of minimal tics (YGTSS<14, or <10 when only one tic type is present) over a period of more than 12 months.

Remission of OCD. Consistent with the definition proposed by Catapano et al. (Catapano et al., 2006) and adopted in longitudinal clinical studies on OCD course (Cherian et al., 2014; Nakajima et al., 2018), full remission was defined as a (C)Y-BOCS total score of <8 for at least 8 consecutive weeks, and failure to fulfill the DSM-5 criteria for OCD.

3.5   MRI parameters

After baseline evaluation at T_1, all participants underwent an MRI scan performed with 3.0 T scanner (Magnetic Verio; Siemens, Erlangen, Germany) with a 12-channel head coil designed for parallel imaging (GRAPPA, Generalized Autocalibrating Partial Parallel Acquisition) using a standardized protocol.

Noise reduction headphones were used to prune the scanner noise. Head positioning was standardized using canthomeatal landmarks, and the head motion was minimized by inserting foam pads between the participant's head and the head coil. Moreover, participants were instructed to lie as still as possible during and between scans. MRI included: (i) Diffusion tensor imaging (DTI, single-shot echo-planar spin-echo sequence with 30 directions, TR = 12.200ms, TE = 94ms, FOV = 192 mm2, matrix = 96 × 96, b = 0 and 1,000 s/mm2, axial 2-mm-thick slices, no gap); (ii) 3D T1-weighted MPRAGE (TR = 1,900ms, TE = 2.93ms, 176 sagittal 1-mm-thick sections, without a gap, flip angle =9◦, FOV=260mm2,matrix=256×256); (iii) dual turbo spin-echo proton density and T2- weighted images (DPT2) (TR = 3,320ms, TE = 10/103ms, FOV = 220 mm2, matrix = 384 x 384, 25 axial 4-mm thick slices, 30% gap) acquired to rule out possible concomitant brain focal lesions.

3.6 Data analysis

3.6.1   MRI preprocessing

MRI preprocessing was performed via FMRIB's software library (FSL), version 5.0.9 (http://fsl.fmrib.ox.ac.uk). Considering that the prevalence of motion in the child population is high in neuroimaging data (Smith et al., 2006), the DTI scan of each subject was first visually inspected and entirely removed in presence of artifacts even in one single volume alone. Secondly, using the FSL tools "eddy" and "topup," correction of the susceptibility-by-movement interactions was performed. Eddy current corrected DTI files were further subjected to DTI Fit using FMRIB's diffusion toolbox to generate fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps.

3.6.2 *Tract–based spatial statistics*

Firstly, FA maps were subjected to the Tract-Based Spatial Statistical (TBSS) tool for the voxel-wise statistical analysis (Smith et al., 2006). To deal with age-dependent skull characteristics, we created a pediatric skeleton template by averaging the FA maps, thresholded at mean FA = 0.2 and binarized, of all participants in the same space of a reference subject. Mean FA derived from the FA of the patients was therefore used as a pediatric template. In order to run the TBSS, linear registration was automatically performed to register FA images of all participants onto the pediatric template. Similarly, MD, AD, and RD maps were registered to the pediatric template to obtain comparable images in the same standardized space. We selected five WM tracts chosen to be of interest (TOIs) (Mori & Zhang, 2006) according to previous findings showing consistent WM bundles alterations in TS or OCD patients (Gruner et al., 2012; Liu et al., 2013a; Piras et al., 2013, 2021a; Sigurdsson et al., 2018a; Wolff et al., 2016b).

The five TOIs, i.e., anterior thalamic radiations (ATR), corpus callosum (CC), cortico-spinal tract (CST), inferior longitudinal fasciculus (ILF), and cingulum, were first selected in MNI standard space using the JHU ICBM-DTI-81White-Matter atlas and then were linearly registered onto the pediatric template space. The TOIs in the pediatric template space were further used to create binarized masks for further voxel-wise intergroup analysis.

3.6.3 Statistical analysis

We performed the Shapiro-Wilk normality test to check for normal distribution of the demographic and clinical data. One-way ANOVA and post-hoc unpaired t-tests (two-tailed, alpha = 0.05, unequal variance) were performed to investigate differences among groups with respect to age. The Chi-square test was also exploited to check for sex distribution among the groups. Differences in clinical scores among pure TS, TS+OCD, and OCD were analyzed with the Mann-Whitney U test. Analyses were performed with SPSS (Statistical Package for the Social Sciences, https://www.ibm.com/analytics/spss-statisticssoftware). Using the FSL Randomize (n = 5,000 permutations), nonparametric statistics were performed to investigate voxel-wise differences within the five pre-selected microstructural WM tracts between pairs of the study cohorts and to further compute correlations with clinical measures (i.e., YGTSS and CYBOCS). Statistical significance was set at $p < 0.05$, corrected for false discovery rate (FDR). Age and sex were included as covariates of no interest.

4. RESULTS

4.1 Clinical and demographic characteristics

4.1.1 At T_1 – time point examination

The clinical details of the study cohorts at baseline (T_1) are summarized in Table 5. From the original population of 70 children, 51 were included in the study. Overall, 19 children were excluded due to excessive head motion (n = 10) or inability to complete the MRI scan (n = 9). Children who excessively moved their head were mainly diagnosed with TS or TS+OCD (respectively 3 and 4 cases), while two children were diagnosed with OCD, and one was a healthy control. On the contrary, 5 children with OCD, one child with TS+OCD and 3 controls could not complete the scan. Sixteen subjects were ultimately included in the TS group (15 males, mean age ± standard deviation: 9.7 ± 2.1 years), 14 in TS+OCD (10 males, 10.2 ± 2.1 years old), 10 in OCD (7 males, 10.9±2.5 years old) and 11 age-matched children in the control group (2 males, 9.9 ± 1.2 years old).

Table 5. Clinical and demographic characteristics at T_1

	TS	TS+OCD	OCD	Controls	TS vs Controls	TS+OCD vs Controls	OCD vs Controls	TS vs OCD	TS+OCD vs OCD	TS vs TS+OCD
	(N=16)	(N=14)	(N=10)	(N=11)						
Age	9.7 ±2.1	10.2 ±2.1	10.9 ±2.5	9.9 ±1.3	p=0.30	p=0.43	p=0.31	p=0.18	p=0.46	p=0.44
Sex (Male/Female)	15/1	10/4	7/3	2/9	p<0.001*	p=0.008*	p<0.001*	p=0.10	p=0.94	p=0.10
YGTSS score (0-50)	17.5 ±6.7	18.1 ±10.8	0.8 ±1.7	--	--	--	--	p<0.001*	p<0.001*	p=0.88
CYBOCS score (0-40)	0.25 ±0.7	16.4 ±6.1	18.6 ±7.5	--	--	--	--	p<0.001*	p=0.53	p<0.001*

TS, TS+OCD, OCD and controls were not statistically different for age [$F_{(3, 46)} = 0.77$, p = 0.51, partial $\eta^2 = 0.048$) (see Table 5). Conversely, chi-square test revealed uneven sex distribution between TS-pure and controls [χ^2 (1, N = 27) = 15.90, p <0.001], and between OCD and controls [χ^2 (1, N = 21) =48.90, p < 0.001]. Mann-Whitney U test revealed no significant difference in YGTSS scores between TS and TS+OCD (U= 108.5, p = 0.88), as well as in CY-BOCS scores between OCD and TS+OCD (U = 65, p = 0.53).

4.1.2 At T_2 time-point examination

Of the 40 participants recruited at T_1 in the clinical groups, 33 participants were contacted for clinical follow-up and underwent in-person reevaluation at our clinic. Of this cohort, only three patients (2 in OCD, 1 in TS group) of the original T_1 group had continued to be routinely followed at our clinic. The remaining 30 individuals were offered a new clinical evaluation and, to limit recall biases, were invited at follow-up together with their parents and asked to provide all medical or psychological records issued in the follow-up period. Mean follow-up duration was 7.6 ±0.8 years. Results are displayed in Table 6.

Table 6. Clinical and demographic data at T_2

		OCD (n=10)	TS (n=12)	TS+OCD (n=11)
Age at follow-up		18.8 ±2.6	17.1 ±1.5	18.7 ±2.7
Sex (Male/Female)		7/3	12/0	7/4
Age at onset		9.8 ±2.9	6.2 ±1.3	9.3 ±2.5
(C)YBOCS		4.2 ±7.0	-	5.3 ±6.1
YGTSS		-	4.3 ±5.3	5.6 ±5.5
GAF		65.5 ±14	68.3 ±13.3	77.7 ±13.7
OC symptoms	Remission	70% (7)	-	63.6% (7) *
	Age at remission (years)	14.1 ±3.9	-	14.5 ±1.3
	Disease duration (years)	4.2 ±1.8	-	5.4 ±1.8
Tics	Remission	-	58.3% (7)	63.6% (7) *
	Age at remission (years)	-	14.0 ±1.6	15.0 ±2.6
	Disease duration (years)	-	7.8 ±1.9	5.8 ±3.1
Pharmacological treatment	Treatment anytime	50% (5)	25% (3)	45.4% (5)
	Currently on treatment	30% (3)	8.3% (1)	9.1% (1)
	Mean treatment duration (years)	3.8	2.6	1.4
Psychotherapy (CBT for tics or OC symptoms/for other psychiatric cmorbidities)	Treatment anytime	80% (8)	50% (6)	72.7% (8)
	Currently on treatment	10% (1)	-	27.2% (3)
	Mean treatment duration (years)	3.8	1.1	4.6
Other psychiatric comorbidity (lifetime)		60% (6)	41.7% (5)	27.2% (3)
Learning disorder		10% (1)	25% (3)	-

Data are presented either as mean ± standard deviation or as percentages (number of cases)
(*) In the TS+OCD, remission of both OC symptoms and tic occurred in 3 patients out of 11 (27.2%)
YGTSS=Yale Global Tic Severity Scale score; (C)YBOCS=(Children's) Yale-Brown Obsessive-Compulsive Scale, GAF=Global Assessment of Functioning scale

TS, TS+OCD, and OCD were not statistically different for age [F (2, 32) = 1.87, p =.172], and for GAF scores [F (2, 31) = 2.35, p = .113]. The three clinical groups were instead statistically different for age at disease onset [F (2, 32) = 8.089, p = .002, η2 = 0.35], and for mean duration

of disease (in those with TS+OCD, the symptoms with the longest time of occurrence were considered to calculate disease duration) [$F_{(2, 32)} = 6.818$, p = .004, $\eta 2 = 0.31$]. Bonferroni-corrected post-hoc group comparisons showed that TS patients had the lowest age at onset in respect to both OCD groups (p=.003), and TS+OCD (p=.009), whereas OCD and TS+OCD did not reveal statistical differences in this regard (p=.364). Moreover, TS and TS+OCD groups resulted different in terms of overall diseases duration in respect to OCD which showed the shortest disease duration (TS vs OCD, p= .006; TS+OCD vs OCD, p= .013).

Mann-Whitney U test revealed no significant difference in YGTSS scores between TS and TS+OCD (U= 2.42, p = 0.495), as well as in CY-BOCS scores between OCD and TS+OCD (U = 4.4, p = 0.20) at follow-up.

Remission of TS and OCD

Tic remission was present in 58.3% of the TS group and in 63.6% of the TS+OCD group. OCD remission was detected in 70% of the OCD group and in and in 63.6% of the TS+OCD. In the TS+OCD group, 3 individuals (27.2%) had remission of both tics and OCD.

No statistical differences emerged either in the remission rate of tics between TS and TS+OCD groups [χ^2 (1, N = 23) =.068, p=.795], or in OC symptom remission between OCD and TS+OCD groups [χ^2 (1, N = 21) =.095, p=.757].

Rate and type of treatment intervention

In the OCD group, 5 (50%) of patients needed pharmacological intervention (mainly SSRIs) for OC symptoms over the follow-up period. Of these, 3 patients were still on medication at follow-up for OCD. Mean duration of treatment was 3.8 years.

Similar rates were detected in TS+OCD group, with 5 (45.4%) of patients having been treated with SSRIs. However, mean duration of treatment was much shorter (1.4 years) and only one patient was still on medication in this group at follow-up.

In the TS group, only 3 (25%) individuals had taken antipsychotics for tics., with mean treatment duration of 2.6 years and one patient still on medication at follow-up.

Psychotherapeutic interventions were more variable across individuals and groups. Only a few individuals received structured cognitive-behavioral therapy for tics and OC symptoms, while one received psychoanalytic psychotherapy, and most patients received other non-specified psychological support for concomitant psychiatric comorbidities.

Other psychiatric diagnoses from T_2 clinical interview

In the OCD group, 60% of patients reported currently diagnosed comorbidities (confirmed by medical files) not including OCD. Four (40%) reported generalized anxiety disorder, one depression (10%), one intermittent explosive disorder (10%). Moreover, one patient was diagnosed with developmental dyslexia and two patients had two associated comorbidities.

In the TS group, 41.7% of patients had another psychiatric condition diagnosed at follow-up. This included depression in 2 individuals (16.7%), performance anxiety with school avoidance in 2 individuals (25%), and social anxiety with gaming disorder in one. Moreover, three patients received diagnosis of a learning disorder (n=2 with dyslexia, and n=1 with dyscalculia).

In TS+OCD group, 27.2% of patients had ongoing comorbidities other than OCD and TS, which for all included generalized anxiety disorder. Other detected comorbidities were social anxiety and disruptive mood dysregulation disorder.

4.2   WM microstructural alterations in TS, TS+OCD and OCD

TS patients showed higher FA and lower MD, AD, RD than controls within the right ATR, the genu, body, splenium of CC, the CST, and the ILF bilaterally (Figure 5a). Since the voxelwise results obtained by analyzing MD, AD, and RD perfectly matched those obtained by FA analysis, the relative

maps of MD/AD/RD are available as Supplementary Material 1-3. White matter regions exhibiting differences in FA between groups are detailed in Table 7.

TS+OCD patients exhibited overlapping DTI features, e.g., FA, MD, AD, RD, as TS-pure in respect to controls (Figure 5b), i.e., DTI parameters were comparable in TS and TS+OCD within any of the investigated WM tracts. Based on such findings, TS and TS+OCD were merged for the following analyses into a joint group named hereinafter as "TS."

OCD patients showed opposite DTI alterations with respect to controls, i.e., lower FA and higher MD, AD, RD within the ATR bilaterally, the genu, body, splenium of CC, the CST and ILF bilaterally (Figure 5c).

The direct comparison between TS and OCD revealed that TS had higher FA and lower MD, AD, RD than OCD within the four aforementioned WM bundles (Figure 5d).

No changes in DTI parameters were found in the cingulum in any group comparison.
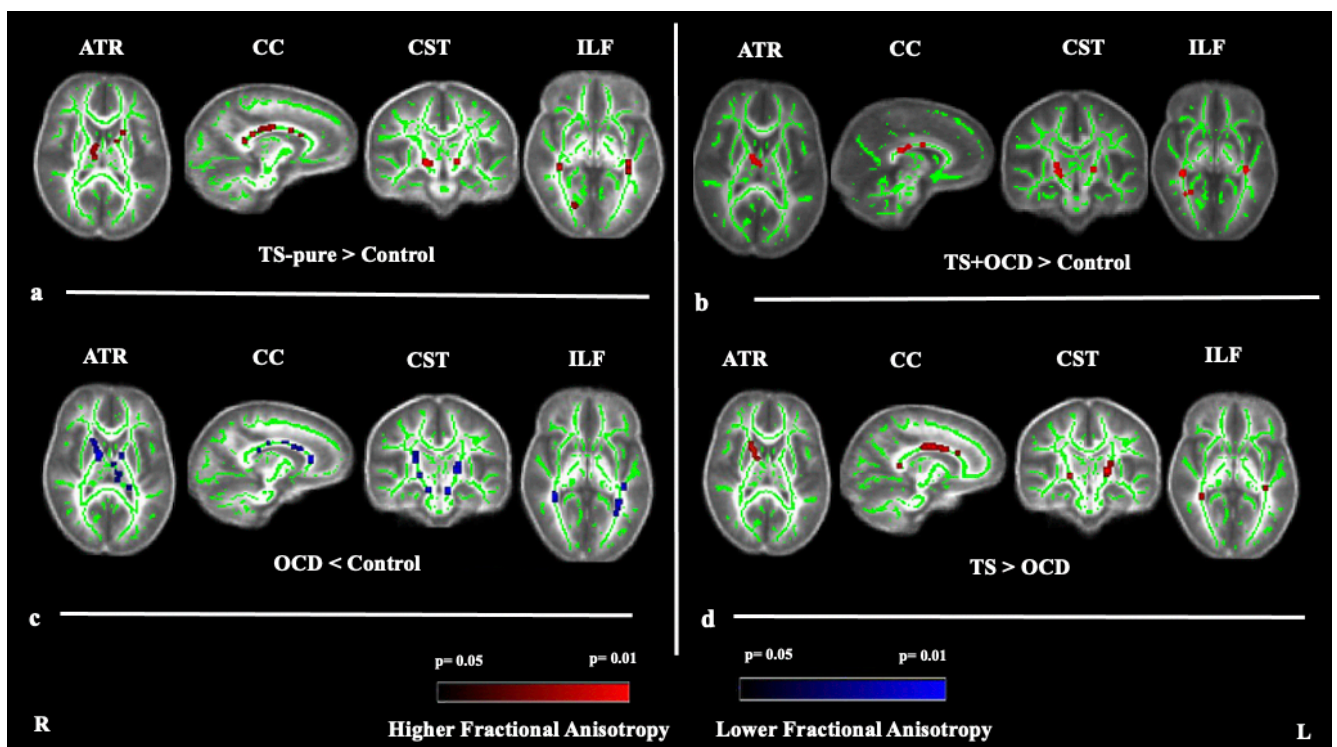
Figure 5. Fractional anisotropy (FA) differences between (a) TS-pure and controls, (b) TS+OCD and controls, (c) OCD and controls, (d) TS and OCD at anterior thalamic radiation (ATR), corpus callosum (CC), corticospinal tract (CST), inferior longitudinal fasciculus (ILF). a: higher FA in TS-pure than in controls, b: higher FA in TS+OCD than in controls, c: lower FA in OCD than in controls, d: higher FA in TS than in OCD. Results were obtained within the mask of ATR, CC, CST, and ILF. Results were presented in the whole brain FA skeleton mask derived from the complete set of participants. FA results were corrected for multiple comparisons at the false discovery rate (FDR) of p < 0.05. Red: Higher FA differences, Blue: Lower FA differences, TS-pure: participants with pure Tourette syndrome (TS), OCD: participants with obsessive compulsive disorder, TS+OCD: TS participants with comorbid condition, TS: participants with TS-pure and TS+OCD.

Table 7. White matter tracts with fractional anisotropic (FA) differences in TS and OCD

Group Differences	Brain Areas within the tract	No of clusters	Clusters Voxels	Coordinates			Peak – t stat
				X	Y	Z	
TS-pure>Controls							
ATR	Right anterior limb of internal capsule	20	10	-19.9	28.1	-25.7	4.15
	Left anterior limb of internal capsule	10	7	-5.97	-33.4	-65.4	3.95
CC	Splenium	20	10	-9.84	-37.5	-19.7	3.10
	Body	14	10	9.32	-10.9	-13.7	2.93
	Genu	5	10	12.1	25.1	-19.7	2.45
CST	Right Cerebral peduncle	6	10	11.5	-18.6	-52.5	2.74
	Left Cerebral peduncle	5	10	-11.7	-18.6	-53.4	2.61
ILF	Right inferior fronto-occipital fasciculus	12	8	34.6	-42.4	-39.7	3.34
	Left inferior fronto-occipital fasciculus	14	10	-31.7	-42.2	-39.7	3.26
	Right posterior thalamic radiation	7	8	28.9	-67.6	-37.3	2.91
TS+OCD>Controls							
ATR	Right anterior limb of internal capsule	20	15	11.2	-6.87	-31.7	4.16
CC	Splenium	19	10	-7.65	-43.4	-27.7	3.11
	Body	15	7	6.55	-6.81	-15.5	3.53
CST	Right cerebral peduncle	14	10	17.6	-17.2	-39.2	3.28
	Left cerebral peduncle	13	5	-17.4	-17.2	-10.3	3.20
	Right Corticospinal tract	20	25	14.3	-16.7	-48.7	2.91
	Left Corticospinal tract	7	10	-13.6	-16.7	-44.0	3.15
ILF	Right inferior fronto-occipital fasciculus	13	10	35	-33.9	-44	3.32
	Left inferior fronto-occipital fasciculus	10	8	-33.8	-31.5	-44	2.94
OCD<Controls							

ATR	Right anterior limb of internal capsule	20	25	13.2	4.62	-28.8	4.34
	Left anterior limb of internal capsule	7	10	-13.4	-5.8	-28.8	2.70
CC	Splenium	10	15	-13.4	-55.2	-22.6	3.88
	Body	5	12	-13.4	-24.3	11.2	4.15
	Genu	25	35	-13.4	23.1	-27.8	3.69
CST	Right corticospinal tract	30	25	24.3	-26.7	-21.2	2.37
	Left corticospinal tract	30	20	-23.1	-26.7	-27.8	3.19
	Right cerebral peduncle	15	12	4.87	-26.7	-70.1	3.64
	Left cerebral peduncle	12	10	-8.41	-26.7	-62.0	2.50
ILF	Right inferior fronto-occipital fasciculus	10	11	33.89	-40.5	-38.3	2.47
	Left inferior fronto-occipital fasciculus	15	10	-41.5	-21.0	-44.5	2.32
	Right posterior thalamic radiation	20	40	27.4	-69.1	-45.4	3.47
	Left posterior thalamic radiation	30	35	-24.3	-64.3	-45.4	2.69

TS>OCD

ATR	Right anterior limb of internal capsule	21	15	12.26	-0.13	-28.3	2.48
CC	Splenium	7	5	-2.96	-41	-26.4	3.26
	Body	17	15	-2.01	-3.96	-18.8	4.10
CST	Right corticospinal tract	5	2	12.9	-21.0	-50.6	3.42
	Left corticospinal tract	15	10	-16	-17.7	-37.3	2.98
	Right cerebral peduncle	10	8	5.82	-25.3	-60.1	2.94
	Left cerebral peduncle	5	5	-7.94	-22	-62	3.60
ILF	Right inferior fronto-occipital fasciculus	5	7	35	-40.1	-41.1	3.18
	Left inferior fronto-occipital fasciculus	5	10	-34.9	-34.8	-41.1	2.96

4.3   Clinical-neuroradiological correlations

In Figures 5a/b the correlations between FA alterations with clinical scores are displayed for TS and OCD

groups. For both TS and OCD, the maps of MD, AD, RD alterations and correlation with clinical severity are shown as Supplementary Figure 4.

Concerning the severity of tics scored by the YGTSS, in the TS group, there was a negative correlation between FA and YGTSS within ATR (i.e., anterior limb of internal capsule), CC (i.e., body, splenium, genu), CST (i.e., cerebral peduncles) and ILF (i.e., posterior thalamic radiation, and inferior fronto-occipital fasciculus) (Figure 6a). Accordingly, within the same tracts, a positive correlation was found between the other diffusivity parameters, i.e., MD, AD, RD, and YGTSS. No significant correlation was observed between DTI parameters and YGTSS in any of the five selected WM tracts when TS-pure and TS+OCD were analyzed separately.

Concerning the severity of OCD symptoms as tested by the CY-BOCS, in the TS+OCD, there was no significant correlation between DTI parameters and CY-BOCS scores. In OCD, CYBOCS negatively correlated with FA and positively with MD, AD, and RD within ATR (i.e., anterior limb of internal capsule), CC (i.e., body, splenium, genu), CST (i.e., cerebral peduncles), and ILF (i.e., posterior

thalamic radiation, and inferior frontooccipital fasciculus) (Figure 6b). Correlational analyses of FA

with clinical scales are reported in Table 8.
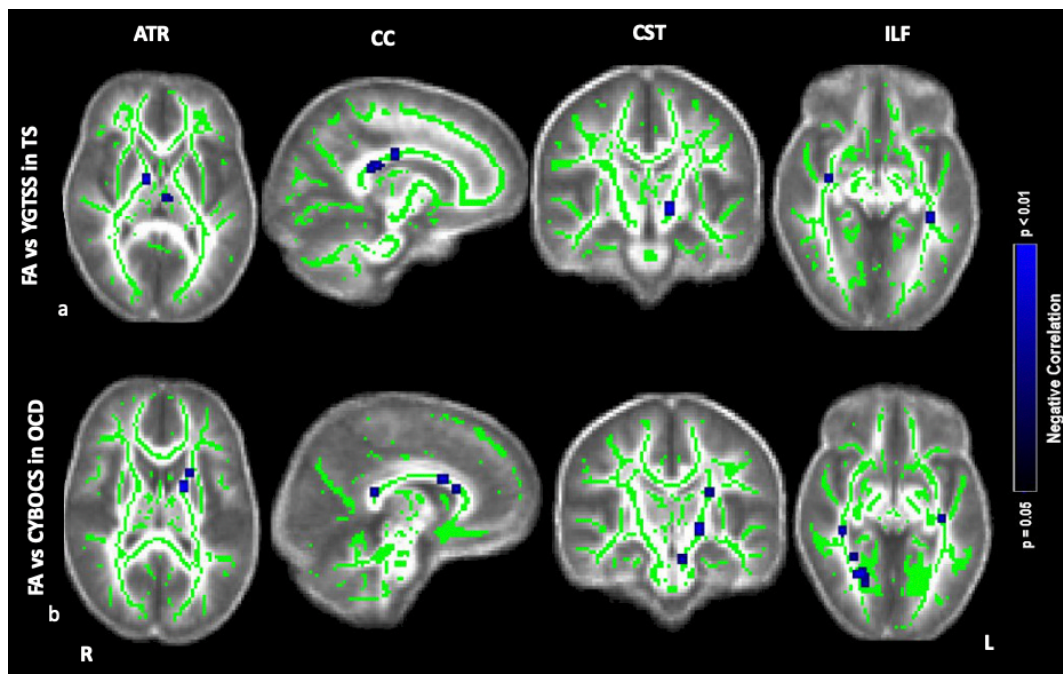
Figure 6. Correlations of fractional anisotropy (FA) abnormalities in (a) TS with YGTSS, (b) OCD with CYBOCS at the anterior thalamic radiation (ATR), corpus callosum (CC), corticospinal tract (CST), inferior longitudinal fasciculus (ILF). Results were obtained within the mask of ATR, CC, CST, and ILF. Results were presented in the whole brain FA skeleton mask derived from the complete set of participants. Results were corrected for multiple comparisons at the false discovery rate (FDR) of $p < 0.05$. Blue: Negative correlation, TS: participants with pure Tourette and comorbid condition [TS+(TS+OCD)]. OCD: participants with obsessive compulsive disorder, YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale Brown Obsessive-Compulsive Scale.

Table 8. Brain areas within white matter tracts showing significant correlations between fractional anisotropy (FA) and clinical data

Clinical Parameters	Brain Areas within the tract	No of clusters	Clusters Voxels	Coordinates			Peak – t stat
				X	Y	Z	
FA vs YGTSS in Tourette (TS)							
ATR	Right anterior limb of internal capsule	26	10	8.45	-6.31	-38.3	1.20
CC	Splenium	26	12	3.22	-29.1	-23.1	1.15
	Body	12	10	3.22	-13.4	17.4	1.30
CST	Left cerebral peduncle	20	10	-8.89	-26.2	-56.8	1.07
ILF	Right posterior thalamic radiation	11	9	30.8	-10.1	-46.8	1.16
	Left inferior fronto-occipital fasciculus	13	15	-36.7	-37.2	-46.8	1.05
FA vs CYBOCS in obsessive compulsive disorder (OCD)							
ATR	Left anterior limb of internal capsule	15	10	-15.3	-3.9	-28.3	1.20
CC	Splenium	5	10	-8.19	-41.9	-25.9	1.23
	Body	10	5	-8.19	-2.5	-15.0	1.05
	Genu	5	10	-8.19	16.4	-25.5	1.69
CST	Left Corticospinal Tract	13	9	-23.1	-19.1	-15.5	1.25
	Left cerebral peduncle	15	10	-16.1	-19.1	-42.5	1.89
		10	7	-7.94	-19.1	-59.6	1.30
ILF	Left inferior fronto-occipital fasciculus	17	15	36.4	-30.1	-38.8	1.99
		13	10	31.7	-46.2	-38.8	1.56
		25	40	27.9	-68.1	-38.8	1.85
	Right posterior thalamic radiation	10	9	-33.3	-44.8	-38.8	1.23

After having registered the pediatric template, that we used for the second level analysis, on MNI space, coordinates were extracted from MNI 152 space.

FA vs YGTSS in Tourette (TS) represents negative correlations between FA values and YGTSS in TS patients at ATR, CC, CST, ILF.

FA vs CYBOCS in Obsessive compulsive disorder (OCD) represents negative correlations between FA values and CYBOCS in OCD patients at ATR, CC, CST, ILF.

FA: fractional anisotropy; YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale Brown Obsessive-Compulsive Scale; ATR: Anterior thalamic radiation CC: Corpus Callosum; CST: Corticospinal tract; ILF: Inferior longitudinal fasciculus.

Results were corrected for false discovery rate (FDR) at p <0.05

*Peak-t stat denotes the maximum statistical value (t-stat) for the peak activity

5. DISCUSSION

The present study extends prior observations (Tikoo et al., 2020, 2021) demonstrating abnormalities in several WM tracts in drug-naïve TS, TS+OCD, and OCD. Such WM microstructural changes represent early-stage correlates, which are not affected by long disease duration, medication, or any other comorbidity.

5.1 WM microstructural alterations in TS

TS and TS+OCD showed common DTI changes with respect to controls, i.e., increased FA in the corpus callosum, anterior thalamic radiations, corticospinal tract, and inferior longitudinal fasciculus. Previous studies in children with TS reported variable DTI findings, i.e., increased FA (Bruce et al., 2021), reduced FA (Jackson et al., 2011b; Plessen et al., 2006a), or no variation at all (Jeppesen et al., 2014; Wolff et al., 2016b). Despite such inconsistencies, evidence from prior works in children are in agreement with our results converging on early structural abnormalities in three major regions, i.e., interhemispheric bundles (Bruce et al., 2021; Govindan et al., 2010; Jackson et al., 2011b; Plessen et al., 2006a; Sigurdsson et al., 2018a; Wolff et al., 2016b), main motor pathways (Bruce et al., 2021; Govindan et al., 2010; Liu et al., 2013b; Sigurdsson et al., 2018a) and prefrontal and fronto-striatal pathways (Debes et al., 2015; Makki et al., 2009). In adult TS studies, results on DTI changes are also heterogeneous, showing either an increased (Neuner et al., 2010; Thomalla, Siebner, Jonas, Baumer, et al., 2009) and a decreased FA (Cavanna et al., 2010; Draganski et al., 2010) of the interhemispheric bundles and WM tracts of sensorimotor regions. The factor age is critical to explain such inconsistencies. The WM undergoes age-dependent changes throughout the lifespan (Lebel & Deoni, 2018), making comparisons between pediatric and adult cohorts hardly affordable. Moreover, given that less than 25% of individuals with TS encounter a significant persistence of tics into adulthood

(Groth et al., 2017), adults may be conceived as a peculiar subpopulation with different or more pronounced neural abnormalities. Comorbidities – which were poorly controlled in former pediatric investigations – represent another relevant aspect contributing to heterogeneous findings. To control for this aspect, we have carefully selected participants based on comorbid conditions and included only treatment-naïve children. To our knowledge, the only previous pediatric study with a similar design is that of Wolff et al. (Wolff et al., 2016), which did not show FA difference in the CC of boys with pure TS compared to controls. Differences in DTI analyses procedure, in particular the selection of a definite TOI, which was further partitioned into five segments (or sub-TOIs), might explain the discrepancy with our results.

The increased FA in the CC of children with TS, that we found, may be indicative of stronger structural connectivity due to increased axonal density, thicker axons, greater myelination, or a combination of these processes. In normal neurodevelopment, there is a linear relationship between interhemispheric connectivity and motor learning/control (Ciechanski et al., 2017; Sisti et al., 2012; Takeuchi et al., 2012). The observed increased connectivity in callosal fibers, which was negatively correlated to tic severity, raises the intriguing possibility of enhanced interhemispheric communication between areas involved in motor control and tic inhibition in children with TS. Moreover, the presence of atypical WM structure in the ATR, which is the major fiber bundle connecting the prefrontal cortex with the thalamus through the anterior limb of the internal capsule, greatly supports the cortico-striatal-thalamic circuitry model of TS, which is considered the leading pathophysiological account of the disorder (Albin & Mink, 2006; Mink, 2006). Lastly, increased FA was also identified in the ILF of TS children. ILF is a large associative bundle connecting the occipital with the temporal lobe, and it is critically involved in visually-guided behaviors and object recognition (Ashtari, 2012; Latini et al., 2017; Ortibus et al., 2012; Zemmoura et al., 2021). Our finding of increased FA in ILF might explain the enhanced abilities in visuomotor integration and learning in patients with TS, which have been

described on both behavioral (Kim et al., 2018; Takács et al., 2018) and neurophysiological levels (Kleimaker et al., 2020).

Overall, the observation that lower FA was associated with greater tic severity, strongly suggest an inverse relationship between WM organization in TS and disorder expression. Thus, by detecting common structural correlates, in line with our previous findings (Tikoo et al., 2020, 2021), our data support the conceptualization of TS+OCD as a specific subtype of TS, in which obsessive-compulsive symptoms may be conceived as heterotypic manifestations of a spectrum rather than the expression of a distinct disorder.

5.2   WM microstructural alterations in OCD

Children with pure OCD manifested opposite FA changes compared to the TS group, suggesting different WM changes sustain two disorders. To date, several DTI meta-analyses have been conducted in OCD, albeit they have many inconsistencies. In a meta-analysis combining data from pediatric and adult cohorts (Hu et al., 2020), the most prominent and replicable result was a decreased FA in the genu of CC and left orbito-frontal WM. Conversely, another metanalytic investigation analyzing pediatric and adult studies separately (Li et al., 2020) showed no FA alterations in children but decreased FA in the genu and anterior body of CC in adults. In sum, this latter study suggested the existence of different pathophysiological processes in early onset compared to adult OCD. Similarly, no FA changes were detected in a large cohort of children and adolescents in a study from the ENIGMA OCD working group (Piras et al., 2021b). However, a previous study by Fitzgerald et al. (Fitzgerald et al., 2014) specifically addressed the effects of age on FA in children and adolescents with OCD. The authors showed an FA reduction of the CC in children aged 8-11 years and an FA increase in adolescents aged 16-19 years. Thus, WM organization likely undergoes different developmental phases in OCD, which are sustained by differing patterns of pruning and myelination

according to age. Therefore, inconsistencies across DTI findings, as well as the null results from metanalyses, might be explained according to neurodevelopmental features, especially when pediatric broad-aged cohorts are considered.

In our study, FA changes in the anterior CC and ATR agrees with previously reported evidence of abnormal function and structure in the cortico-striatal-thalamic circuitry in OCD (Lochner et al., 2012; Menzies et al., 2008; Posner et al., 2014). The anterior CC contains WM fibers projecting to the prefrontal regions and connecting the right and left prefrontal, premotor and supplementary motor cortex, all areas repeatedly shown to have aberrant function and volume in OCD (e.g., (Robbins et al., 2019)). The ATR contains WM pathways connecting the frontal lobe and thalamus. Thus, anterior CC and ATR collectively represent key traits of cortico-striatal-thalamic circuitry, on which pathophysiological models of OCD are built. Compared to controls, OCD children also exhibited decreased FA within the ILF. Such findings indirectly suggest abnormalities in WM areas relevant for visuo-spatial abilities, which have been repeatedly reported to be impaired in OCD patients (Shin et al. 2014) and have been associated with the persistence of OCD in adult age (Bloch et al., 2011).

Overall, the observed negative correlation of obsessive-compulsive symptoms with FA values in the CST, ATR, CC, and ILF indicate that more severe clinical phenotypes are underpinned by less organized WM tracts in OCD children.

5.3   Differences in WM microstructural alterations in TS and OCD

When looking at the specific difference between clinical groups, a dichotomic pattern of WM abnormalities within ATR, CST, and ILF emerged in TS versus OCD, i.e., increased FA in TS as opposed to decreased FA in OCD. This further supports the hypothesis that pure OCD represents a different entity from OCD in the context of TS, reflecting independent neuroadaptive processes. Interestingly, the TS group showed a negative correlation between FA and YGTSS, pointing to the

idea that an early increase in axons, fiber density bundles and/or myelination in TS may be indicative of a compensatory reorganization in response to the disease pathophysiology. In the OCD group, the clinical-neuroradiological correlations suggest opposite considerations, as reduced fiber myelination and organization are associated with the overall disease burden.

A final comment concerns the DTI indexes other than FA such as MD, AD, and RD, collected in the TS and OCD cohorts. It is known that FA reflects myelination and organization of axon fibers (Johansen-Berg & Rushworth, 2009; Toga et al., 2006). Decreased FA would point to less myelinated and less compact WM tracts and vice versa (Beaulieu, 2002; Mori et al., 2005). However, given that the interpretation of FA changes is not univocal (Alexander et al., 2007), additional DTI parameters such as MD, RD, and AD might help characterize WM microstructural abnormalities. RD and AD provide measures of myelin and axonal integrity, respectively (Song et al., 2002, 2005). In the present study, MD, RD, and AD scaled in the same direction within each clinical cohort, i.e., they all resulted decreased in TS and increased in OCD. Overall, these results further support our hypothesis of a differential organization and maturation of WM fibers rather than selective damage to axons or myelin in both TS and OCD.

5.4 Clinical course of TS and OCD at long-term follow-up

Although our sample was too small to allow for estimation of long-term outcomes by WM changes discovered at T_1, the results of the follow-up study provide further data to define the clinical course of TS and early-onset OCD. This study is also the first to systematically gather time course data regarding TS+OCD evolution.

The observed age of onset of OC symptoms in the OCD group (9.8 years) follows the bimodal distribution of this disorder, with the first mean age of onset around 9–10 years (SD ± 2.5 years)(Geller

et al., 2001; Taylor, 2011). Similarly, mean age at tic onset (6.2 years) in the TS group falls within previously reported ranges (Bloch & Leckman, 2009; Freeman et al., 2000; Khalifa & von Knorring, 2003). In contrast to TS alone, TS+OCD had statistically significant later onset of tics (9.3 ± 2.5 years), suggesting a possible delayed presentation of tics in the context of OCD.

On average, age of peak tic severity is around 10-12, followed by gradual improvement through adolescence. Tic remission rate in our sample (58.3%) replicates data from available longitudinal studies on children with clinically problematic tics using similar assessment methods to define remission (Groth et al., 2017; Stárková, 1990). Analogous remission rates were found for OC symptoms in TS+OCD, and OCD. Comparing such findings to past studies is challenging, given the differences in study methodology and sampling issues. Our results regarding OCD remission are fairly comparable with those reporting up to 75% remission rate at 13-year follow-up (Angst et al., 2004; Reddy et al., 2005), offering a better outcome of what is generally assumed for this disorder (Fineberg et al., 2013).

Overall, our data point out that about 30-40% of patients with TS and early-onset OCD still have relevant clinical symptoms during late adolescence or young adult age. Furthermore, our results highlight that children with tics/OCD are at increased risk of developing additional disorders in young adult age such as anxiety or depression, which further impede social, emotional, and academic development (Bloch et al., 2006).

5.5   Limitations

Some limitations of the current study should be stressed. First, differences in sex distribution between patients and controls may have influenced the results. However, the effects of sex on our DTI findings have been minimized by including this variable as a nuisance covariate in the analysis. Thus, we believe that sex distribution has unlikely influenced our results. Second, the relatively small number

of participants precludes the immediate generalization of our findings to all children with TS and OCD. Moreover, the small sample size at follow-up further limits the investigation of the predictive value of early WM changes on long-term clinical outcomes and global functioning. Being retrospective, recall biases may have arisen due to inaccurate reconstruction of clinical history by the participants. To limit this potential confound, participant responses were verified with information in any available medical record and compared to what reported by parents or family members invited to the T_2 visit. Since we did not retain data about the patients who declined to participate, it is not possible to rule out some degree of selection bias.

Nevertheless, given the specific participants' age range and their careful selection, we believe that our results offer new insight on WM microstructural organization in the early stages of TS and OCD, uninfluenced by other comorbidities, long disease duration and pharmacological treatment.

6. CONCLUSIONS

This is the first study to characterize and compare WM microstructure in drug-naïve TS and OCD children. We highlight a shared pattern of WM microstructural changes in pure TS and combined TS+OCD as opposed to pure OCD, pointing to the conceptualization of TS+OCD as a peculiar subtype of TS. Our current understanding of TS+OCD therefore supports an endophenotype that shares commonalities with TS in the brain CSTC circuitry. Compared to the normative population, the overall TS group showed a unique pattern of increased FA in callosal WM and in tracts linking the frontal, occipital and temporal cortices with each other and with the thalamus. The increased WM connectivity - which inversely correlated to tic severity - may represent an adaptive reorganization to aberrant or overactive sensory-motor processing in TS, possibly allowing partial compensation of tics.

Conversely, children with OCD showed widespread reduced WM connectivity of callosal, temporo-occipital, and fronto-thalamic bundles, which were all related to greater disease severity and appear to play a role in the disease pathophysiology since an early stage.

Confirmation of these possibilities awaits longitudinal studies. The observation of shared DTI correlates of TS and TS+OCD strengthens the concept that at least some forms of OCD are etiologically related to TS and might therefore be a variant expression of the same etiologic factors that are important for the expression of tics (i.e., TS+OCD as a peculiar subtype of TS). By characterizing and differentiating early-stage neural underpinnings of OCD and TS, future targeted and neuroimaging-informed interventions may be developed.

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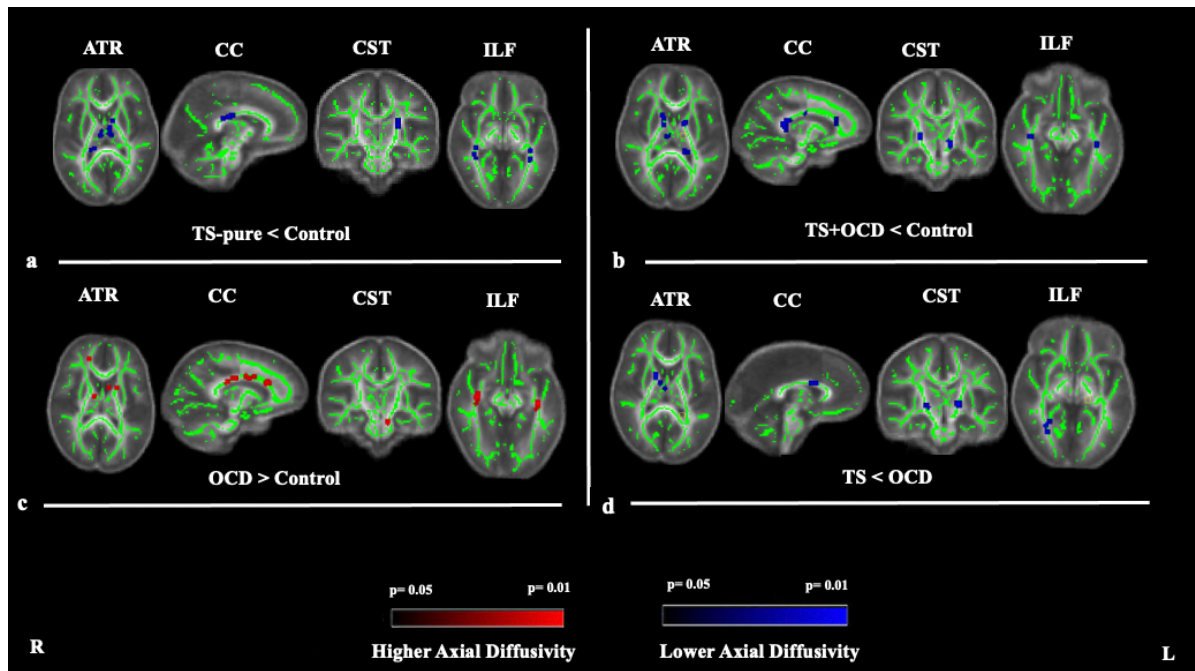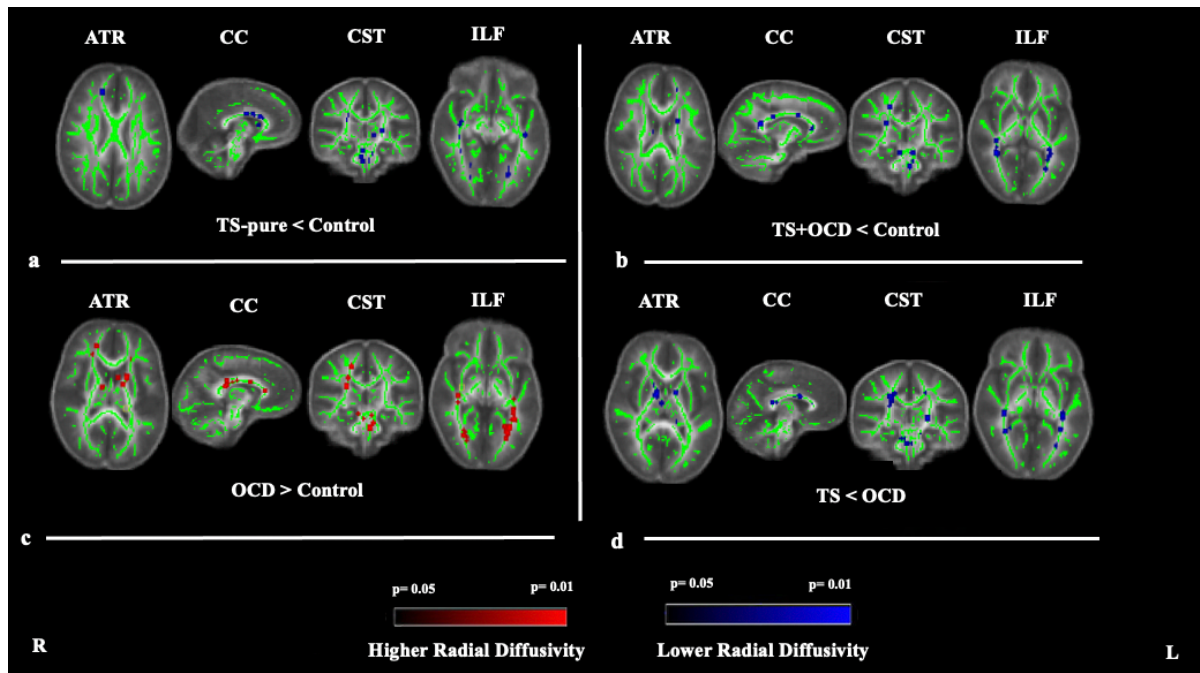
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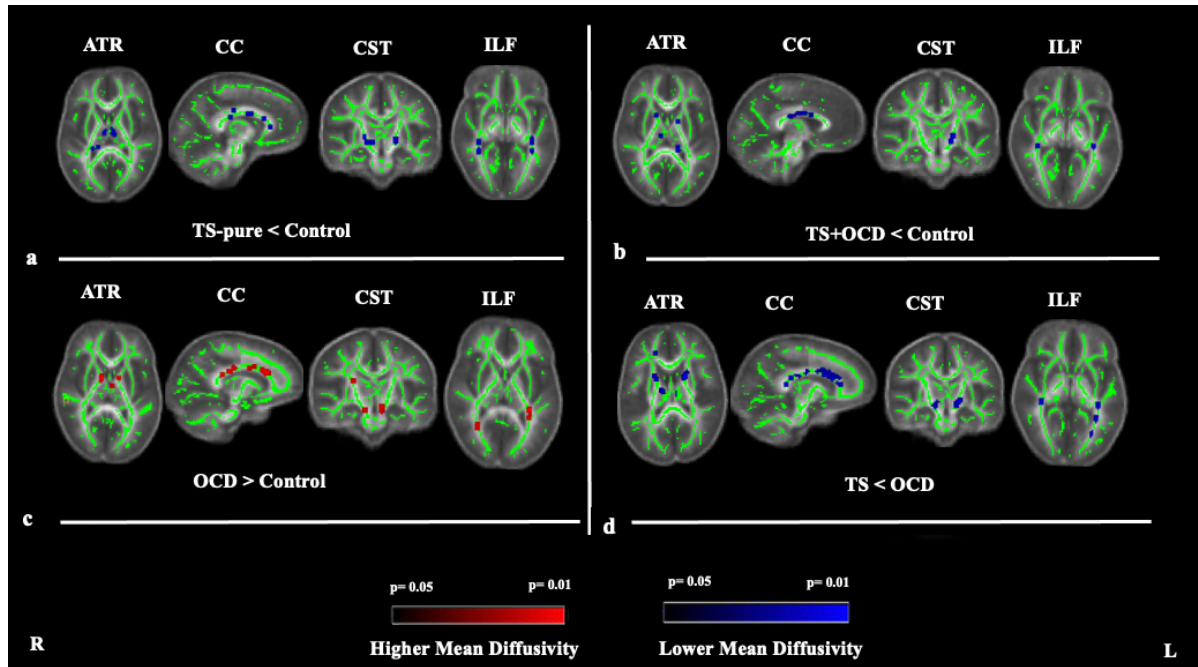
Supplementary Figure 1: Mean diffusivity (MD) differences between (a) TS-pure and controls, (b) TS+OCD and controls, (c) OCD and controls (d) TS and OCD at anterior thalamic radiation (ATR), corpus callosum (CC), corticospinal tract (CST), inferior longitudinal fasciculus (ILF). a: lower MD in TS-pure than in controls, b: lower MD in TS+OCD than in controls, c: higher MD in OCD than in controls, d: lower MD in TS than in OCD. Results were obtained within the mask of ATR, CC, CST, and ILF. Results were presented in the whole brain FA skeleton mask derived from the complete set of participants. MD results were corrected for multiple comparisons at the false discovery rate (FDR) of p < 0.05. Red: Higher MD differences, Blue: Lower MD differences, TS-pure: participants with pure Tourette syndrome (TS), OCD: participants with obsessive compulsive disorder, TS+OCD: TS participants with comorbid condition, TS: participants with TS-pure and TS+OCD.

Supplementary Figure 2: Axial diffusivity (AD) differences between (a) TS-pure and controls, (b) TS+OCD and controls, (c) OCD and controls (d) TS and OCD at anterior thalamic radiation (ATR), corpus callosum (CC), corticospinal tract (CST), inferior longitudinal fasciculus (ILF). a: lower AD in TS-pure than in controls, b: lower AD in TS+OCD than in controls, c: higher AD in OCD than in controls, d: lower AD in TS than in OCD. Results were obtained within the mask of ATR, CC, CST, and ILF. Results were presented in the whole brain FA skeleton mask derived from the complete set of participants. AD results were corrected for multiple comparisons at the false discovery rate (FDR) of p < 0.05. Red: Higher AD differences, Blue: Lower AD differences, TS-pure: participants with pure Tourette syndrome (TS), OCD: participants with obsessive compulsive disorder, TS+OCD: TS participants with comorbid condition, TS: participants with TS-pure and TS+OCD.

Supplementary Figure 3: Radial diffusivity (RD) differences between (a) TS-pure and controls, (b) TS+OCD and controls, (c) OCD and controls (d) TS and OCD at anterior thalamic radiation (ATR), corpus callosum (CC), corticospinal tract (CST), inferior longitudinal fasciculus (ILF). a: lower RD in TS-pure than in controls, b: lower RD in TS+OCD than in controls, c: higher RD in OCD than in controls, d: lower RD in TS than in OCD Results were obtained within the mask of ATR, CC, CST, and ILF. Results were presented in the whole brain FA skeleton mask derived from the complete set of participants. RD results were corrected for multiple comparisons at the false discovery rate (FDR) of p < 0.05. Red: Higher RD differences, Blue: Lower RD differences, TS-pure:
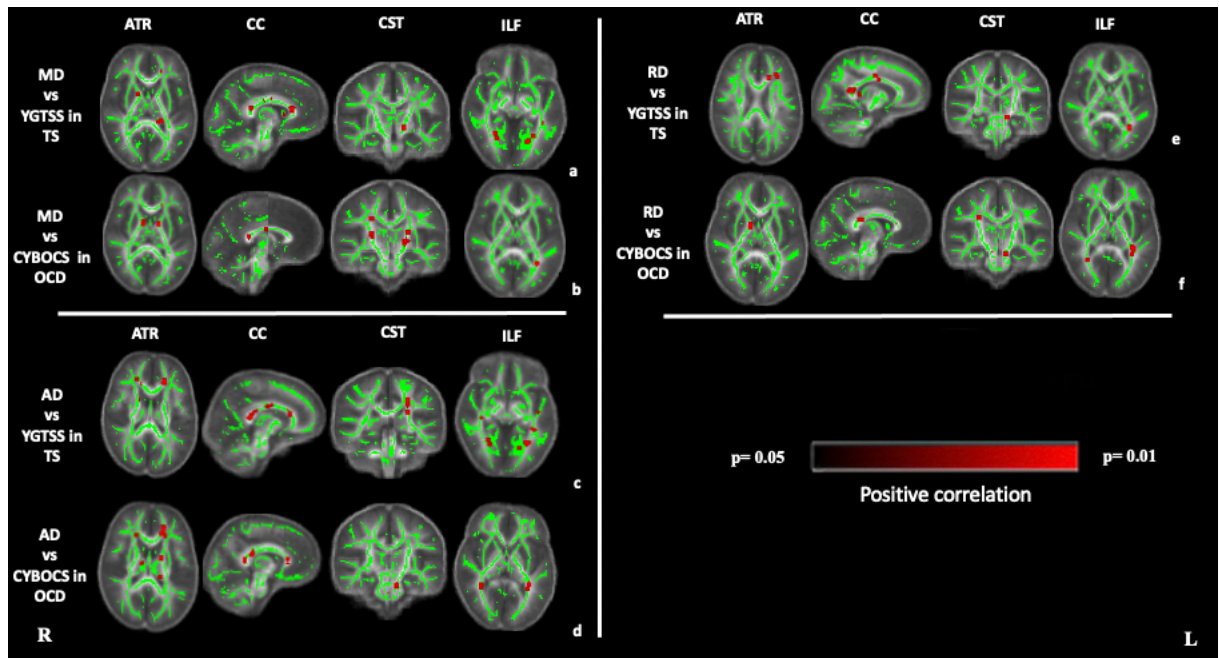
Supplementary Figure 4: Clinical correlations in TS and OCD with YGTSS and CYBOCS at the anterior thalamic radiation (ATR), corpus callosum (CC), corticospinal tract (CST), and inferior longitudinal fasciculus (ILF). a: positive correlation in TS between MD and YGTSS, b: positive correlation in OCD between MD and CYBOCS, c: positive correlation in TS between AD and YGTSS, d: positive correlation in OCD between AD and CYBOCS, e: positive correlation in TS between RD and YGTSS, f: positive correlation in OCD between RD and CYBOCS. Results were presented in the whole brain FA skeleton mask derived from the complete set of participants. Results were corrected for multiple comparisons at the false discovery rate (FDR) of $p < 0.05$. TS: participants with pure Tourette and comorbid condition [TS+(TS+OCD)]. OCD: participants with obsessive compulsive disorder, YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale Brown Obsessive-Compulsive Scale.

APPENDICES

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EDUCATION

| 2019-2022: | **PhD programme in Clinical-Experimental Neuroscience and Psychiatry** |
| | Department of Human Neuroscience, Sapienza University of Rome |

2019-2020:	**High-specialization course on Developmental Psychiatry: diagnosis, treatment, and trajectories into adulthood**
	Sapienza University of Rome, Rome, Italy
	Unit of child and adolescent neuropsychiatry - Umberto I Hospital,
	Via dei Sabelli 108, 00185 Rome, Italy
2019:	**Visiting Researcher at University of Lübeck for the project "TEC4Tic" (DFG - FOR 2698) on the pathophysiology of tic disorders**
	University of Lübeck, Universitätsklinikum Schleswig-Holstein
	Ratzeburger Allee 160, 23538 Lübeck, Germany
2015-2019:	**Residency postgraduate programme in child and adolescent Neuropsychiatry**
	Final evaluation 70/70 cum laude (top marks)
	Department of Clinical Neuroscience, Sapienza University of Rome.
	Unit of child and adolescent neuropsychiatry - Umberto I Hospital,
	Via dei Sabelli 108, 00185 Rome, Italy
2015-2012:	**General Practitioner Specialty Training**
	San Camillo-Forlanini Hospital
	Circonvallazione Gianicolense 87, 00152 Rome, Italy
2012:	**Medical Licensing examination**
	Catholic University of Sacred Heart
	Largo Francesco Vito 1, 00168 Rome, Italy
2010-2009:	**LLP ERASMUS programme student**
	Charité Universitätsmedizin Berlin
	Charitéplatz 1, 10117 Berlin, Germany
2011-2005:	**Medicine School and Graduation with honors (MD)**
	Final evaluation 100/100 cum laude (top marks)
	Catholic University of Sacred Heart
	Largo Francesco Vito 1, 00168 Rome, Italy

2005-2000:	**"Diploma" at senior High School specialized in scientific education**
	Final evaluation 100/100
	Liceo Scientifico Alessandro Volta
	Via Martiri di Via Fani 1, 71122 Foggia, Italy

CLINICAL ACTIVITIES

From December 2022:	**Consultant Neuropsychiatrist**
	Psychiatric outpatient service for adolescents
	Unit of child and adolescent neuropsychiatry - Umberto I Hospital,
	Via dei Sabelli 108, 00185 Rome, Italy
2020-2021:	**Consultant Neuropsychiatrist**
	"Villa Von Siebenthal" Psychiatric residential care facilities for adolescents
	Via della Madonnina 1, 00045 Genzano di Roma, RM, Italy
2019-2020:	**Consultant Neuropsychiatrist**
	"A.L.M." Rehabilitation Center for children with neurodevelopmental disorders and intellectual disabilities
	Km. 0.400 Via Maremmana Inferiore, 00019 Tivoli, RM, Italy

TEACHING ACTIVITIES

2021-2022:	**Rehabilitation in pediatric neurology for the Degree of Neurodevelopmental Disorders Therapy**
	Sapienza University or Rome
2022-2023:	**Rehabilitation in child neuropsychiatry for the Degree of Physiotherapy**
	Sapienza University or Rome
From 2021:	**Supervision of students and residents (Sapienza University or Rome):**
	- 2 master students in psychology
	- 12 residents in child and adolescent neuropsychiatry

SCIENTIFIC PRODUCTION

16 publications on international peer-reviewed journals

H-Index: 8 (Scopus)

Research funding

Finantial contribuition for young researcher's career development (euro 2.000) – year 2022
Regione Lazio, Italy

Starting research grant for PhD students (euro 1.500) – year 2021
Sapienza University or Rome

Prizes and Awards

Excellence Award for poster presentation (euro 500) – year 2022
European College of Neuropsychopharmacology, 35th international congress, Vienna, 15-18/10/2022

LIST OF PUBLICATIONS

1. **Conte, G.**, Bharti, K., Suppa, A., Tikoo, S., Giannì, C., Tommasin, S., Mirabella, G., Pantano, P., & Cardona, F. (2022). Differential white matter involvement in drug-naïve children with obsessive-compulsive disorder and Tourette syndrome. *Neuroscience Applied*, *1*, 100758. https://doi.org/10.1016/j.nsa.2022.100758

2. Bharti, K., **Conte, G.**, Tommasin, S., Giannì, C., Suppa, A., Mirabella, G., Cardona, F., & Pantano, P. (2022). White matter alterations in drug-naïve children with Tourette syndrome and obsessive-compulsive disorder. *Frontiers in Neurology*, *13*. https://www.frontiersin.org/articles/10.3389/fneur.2022.960979

3. Renzi, A., **Conte, G**., & Tambelli, R. (2022). Somatic, Emotional and Behavioral Symptomatology in Children during COVID-19 Pandemic: The Role of Children's and Parents' Alexithymia. *Healthcare*, *10*(11), Article 11. https://doi.org/10.3390/healthcare10112171

4. **Conte, G**., Arigliani, E., Martinelli, M., Di Noia, S., Chiarotti, F., & Cardona, F. (2022). Daydreaming and psychopathology in adolescence: An exploratory study. *Early Intervention in Psychiatry*, 1-9. https://doi.org/10.1111/eip.13323

5. **Conte, G**., Baglioni, V., Valente, F., Chiarotti, F., & Cardona, F. (2020). Adverse Mental Health Impact of the COVID-19 Lockdown in Individuals With Tourette Syndrome in Italy: An Online Survey. *Frontiers in Psychiatry*, *11*. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.583744

6. Tikoo, S., Suppa, A., Tommasin, S., Giannì, C., **Conte, G.**, Mirabella, G., Cardona, F., & Pantano, P. (2022). The Cerebellum in Drug-naive Children with Tourette Syndrome and Obsessive–Compulsive Disorder. *The Cerebellum*, *21*(6), 867–878. https://doi.org/10.1007/s12311-021-01327-7

7. Mielke, E., Takacs, A., Kleimaker, M., Schappert, R., **Conte, G.**, Onken, R., Künemund, T., Verrel, J., Bäumer, T., Beste, C., & Münchau, A. (2021). Tourette syndrome as a motor disorder revisited – Evidence from action coding. *NeuroImage: Clinical*, *30*, 102611. https://doi.org/10.1016/j.nicl.2021.102611

8. **Conte, G.**, Valente, F., Fioriello, F., & Cardona, F. (2020). Rage attacks in Tourette Syndrome and Chronic Tic Disorder: A systematic review. *Neuroscience & Biobehavioral Reviews*, *119*, 21–36. https://doi.org/10.1016/j.neubiorev.2020.09.019

9. Tikoo, S., Cardona, F., Tommasin, S., Giannì, C., **Conte, G.**, Upadhyay, N., Mirabella, G., Suppa, A., & Pantano, P. (2020). Resting-state functional connectivity in drug-naive pediatric patients with Tourette syndrome and obsessive-compulsive disorder. *Journal of Psychiatric Research*, *129*, 129–140. https://doi.org/10.1016/j.jpsychires.2020.06.021

10. Kleimaker, M., Takacs, A., **Conte, G**., Onken, R., Verrel, J., Bäumer, T., Münchau, A., & Beste, C. (2020). Increased perception-action binding in Tourette syndrome. *Brain*, *143*(6), 1934–1945. https://doi.org/10.1093/brain/awaa111

11. Resting state Functional Connectivity differences in Pediatric Patients with Tourette syndrome and Obsessive-compulsive disorder. (2019). *MDS Abstracts*. Retrieved January 29, 2023, from https://www.mdsabstracts.org/abstract/resting-state-functional-connectivity-differences-in-pediatric-patients-with-tourette-syndrome-and-obsessive-compulsive-disorder/

12. Robinson, S., Hedderly, T., **Conte, G.**, Malik, O., & Cardona, F. (2018). Misophonia in Children with Tic Disorders: A Case Series. *Journal of Developmental & Behavioral Pediatrics*, *39*(6), 516. https://doi.org/10.1097/DBP.0000000000000563

13. Quagliariello, A., Del Chierico, F., Russo, A., Reddel, S., **Conte, G**., Lopetuso, L. R., Ianiro, G., Dallapiccola, B., Cardona, F., Gasbarrini, A., & Putignani, L. (2018). Gut Microbiota Profiling and Gut–Brain Crosstalk in Children Affected by Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. *Frontiers in Microbiology*, *9*. https://www.frontiersin.org/articles/10.3389/fmicb.2018.00675

14. Masciullo, M., Iannaccone, E., Bianchi, M. L. E., Santoro, M., **Conte, G.**, Modoni, A., Monforte, M., Tasca, G., Laschena, F., Ricci, E., & Silvestri, G. (2013). Myotonic dystrophy type 1 and de novo FSHD mutation double trouble: A clinical and muscle MRI study. *Neuromuscular Disorders*, *23*(5), 427–431. https://doi.org/10.1016/j.nmd.2013.02.002

15. Bianchi, M. L. E., Losurdo, A., Di Blasi, C., Santoro, M., Masciullo, M., **Conte, G**., Valenza, V., Damiani, A., Della Marca, G., & Silvestri, G. (2014). Prevalence and clinical correlates of sleep disordered breathing in myotonic dystrophy types 1 and 2. *Sleep and Breathing*, *18*(3), 579–589. https://doi.org/10.1007/s11325-013-0921-5

16. Santoro, M., Masciullo, M., Pietrobono, R., **Conte, G.**, Modoni, A., Bianchi, M. L. E., Rizzo, V., Pomponi, M. G., Tasca, G., Neri, G., & Silvestri, G. (2013). Molecular, clinical, and muscle studies in myotonic dystrophy type 1 (DM1) associated with novel variant CCG expansions. *Journal of Neurology*, *260*(5), 1245–1257. https://doi.org/10.1007/s00415-012-6779-9

BOOKS AND CHAPTERS

1. **Conte, G.**, Gabaglio, C., Pacifici, S., Valente, F., De Filippis, S. (2021). Le droghe d'abuso e l'emergenza psicopatologica in adolescenza**.** *Bambini e adolescenti a «distanza». Il disagio psichico e l'emergenza psicopatologica durante la Pandemia da Covid-19.* Alpes edizioni. ISBN 9788865317570