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THESIS FOR THE DEGREEE OF DOCTOR OF PHILOSOPHY

FUNCTIONAL AND STRUCTURAL ALTERATIONS IN PEDIATRIC PATIENTS WITH TOURETTE AND OBSESSIVE-COMPULSIVE DISORDER

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Dedicato a mio padre e mia madre e mia sorella

Our weaknesses sometimes serve us better than our strengths

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AIM OF THE THESIS

Tourette syndrome (TS) is a frequent neuropsychiatric disorder characterized by multiple motor or phonic tics persistent for a year or more (American Psychiatric Association, 2013a). TS is accompanied by several comorbidities, predominantly obsessive-compulsive disorder (OCD) (Andrea Eugenio Cavanna et al., 2009; Hirschtritt et al., 2015). Independently from the co-occurrence in the context of TS, OCD may manifest alone as a disorder characterized by recurrent intrusive thoughts/urges and by compulsions, i.e., repetitive acts associated with the attempt by the individual to neutralize obsessions (James F. Leckman et al., 2010; Robbins et al., 2019). Repetitive, situation-inappropriate and distressful movements or behaviors are the hallmark of both TS and OCD. Particularly, in the case of TS+OCD patients are characterized by overlapping clinical features of the two disorders wherein the labeling of repetitive behaviors into complex tics or compulsions might be challenging (Mansueto & Keuler, 2005; Mathews & Grados, 2011a). In this context, patients with TS+OCD may either represent an intermediate phenotype underpinned by shared pathophysiological abnormalities of both TS and OCD or reflect a different pathophysiology altogether (Kloft et al., 2018).

Addressing this issue our primary aim was to employ an exploratory/data-driven approach to directly compare resting-state functional connectivity patterns (rs-FC) in independent cohorts of TS without comorbidity (TSpure), TS with OCD comorbidity (TS+OCD), and pure OCD. This approach would further aid in clarifying whether TS+OCD patients are characterized by overlapping or independent FC changes when compared to TS pure or OCD patients. By examining functional connectivity (FC) patterns in seven resting-state networks of interest, we reported functional changes in the above cohorts in the basal ganglia, sensorimotor, default mode, frontoparietal and salience network. We also observed significant changes within the cerebellar network in all three patient cohorts. In particular, we reported that compared with Ctrls, all patient groups were characterized by increased cerebellar FC. While the rs-FC pattern was comparable in TSpure and TS+OCD, the OCD group had higher cerebellar connectivity than both the TS sub-cohorts. Moreover, the increased cerebellar connectivity correlated negatively with tic-severity in TS patients while a positive association was observed with compulsive scores in OCD. These correlations suggest a distinct functional role of cerebellum in the two neurodevelopmental disorders. In our sample the increased cerebellar FC changes in TS negatively correlated with tic severity indicating neuroplastic mechanisms involved in the modulation of tic expression. Contrastingly, in OCD the increased cerebellar FC positive correlated with compulsive scores reflecting maladaptive mechanism of neuroplasticity

possibly contributing to obsessive-compulsive symptom severity. These findings provided us with the necessary framework to fully investigate the involvement of cerebellum in the pathophysiology of TS and OCD. Cerebellum is involved in various motor functions and in several non-motor/emotion processing domains (Koziol et al., 2014; Van Overwalle et al., 2020) and only a handful of previous studies have postulated the involvement of cerebellum in TS and OCD (Sigurdsson et al., 2020; Tobe et al., 2010; Xu et al., 2019; H. Zhang et al., 2019). However, the precise role of the cerebellum in tics and compulsions has to be characterized in detail. Notably, to date direct comparisons contrasting cerebellar structural and functional changes in drug-naive children/adolescents with TSpure, TS+OCD, and pure OCD have not yet been explored. Therefore, to address this gap, and to better understand the potential contribution of the cerebellum and its afferent and efferent connections in the genesis of tics and compulsions we focused on exploring structural and functional connectivity of the cerebellum in our drug-naive pediatric cohorts. The structural analysis included the investigation of possible changes in cerebellar grey matter lobules as well as white matter (WM) fiber integrity of cerebellar peduncles. The functional analysis consisted of seed-based connectivity of deep cerebellar nuclei (i.e., dentate nucleus) with respect to whole brain (DN-FC). We specifically targeted the dentate nucleus in the cerebellum since it is the main cerebellar output pathway projecting its efferent fibers through the superior cerebellar peduncles (SCP) to the contralateral thalamus and various motor cortical and posterior associative areas. Hence the involvement of dentate in the neocerebellar functions is thought to subserve both motor and non-motor (cognitive) functions (Bernard et al., 2014; Bostan et al., 2013; Buckner, 2013). We anticipated to find alterations in the cerebellar grey matter lobules and white matter integrity of cerebellar peduncles. Additionally, we also hypothesized to find significant alterations in the cerebello-thalamo-cortical (CTC) circuit affecting both TS and OCD. Lastly, we expected to find possible correlations between significantly alerted cerebellar structural and functional connectivity and clinical severity scores. The pediatric nature of our cohorts enabled us to elucidate early pathophysiological changes in the cerebellum of children with TS and OCD. Also, the drug-free characteristic of our patients allowed us to demonstrate structural and functional cerebellar changes unrelated to chronic drug-treatments.

PREFACE

Chapter 1 is an overview of the clinical aspects such as age of onset, recurring symptoms, disease duration and other therapeutic interventions pertaining to Tourette syndrome (TS), obsessive-compulsive disorder (OCD) and Tourettic-OCD (TOCD).

Chapter 2 provides a brief introduction of the magnetic resonance imaging (MRI) principles and advanced neuroimaging methods employed to quantify structural and functional alterations in TS and OCD children. Additionally, a brief review of all the neuroimaging studies (both structural and functional) that have been conducted in the domain of TS and OCD has been summarized in this chapter.

Chapter 3 investigates the intrinsic functional connectivity in six predefined resting state networks between drug-naive patients with TS without any comorbidity (TS), TS with OCD comorbidity (TS+OCD), OCD and age matched controls. Significant changes in resting state-functional connectivity (rs-FC) in these six resting state networks were then correlated with clinical severity scale. We outlined that the OCD patients are characterize by a distinctive pattern of FC changes prominently involving the cerebellar network (CBN) and the frontoparietal network (FPN). Additionally, higher intrinsic rs-FC in these networks differentiates it from Tourette and its subtypes. The findings of this study have been outlined in the form of research article in the '*Journal of Psychiatric Research, published in July 2020'*.

Chapter 4 evaluates the cerebellar structural and dentate nucleus functional connectivity in drug-naive children with TS, TS+OCD, OCD and controls. In this study we focused on examining the role of cerebellum in the pathophysiology of TS and OCD. To accomplish this, we examined the differences in cerebellar grey matter lobules, white matter integrity of the cerebellar peduncles and cerebellar functional connectivity using deep cerebellar Dentate nucleus as the region of interest. Lastly, we correlated all the significant findings with the clinical measures.

Chapter 5 summarizes the functional and structural findings of Chapter 3 and 4 and provides an overall general conclusion of the thesis.

CHAPTER 1: INTRODUCTION

1.1 TOURETTE SYNDROME

Tourette syndrome (TS) is a neurodevelopmental disorder which is defined by the occurrence of multiple motor/phonic tics. Tics are defined as quick, sudden, non-rhythmic, recurrent, involuntary movements or phonic productions that have a waxing and waning course. TS affects about 0.5-0.8% of children with a male to female ratio of 3-4:1 (Khalifa & von Knorring, 2003; Robertson, 2015; Scharf et al., 2015). TS is frequently associated with obsessive-compulsive and attention deficit hyperactivity symptoms (Robertson et al., 2017). Previous studies have advocated the dysfunction of cortico-striatal-thalamo-cortical (CSTC) circuitry as the main cause of repetitive motor/phonic tics **(Fig. 1)**. In order to be diagnosed with TS an individual should have either multiple motor or at least one vocal tic, for a duration of a year or more during which the tic free period cannot last longer than 3 months (Association, 2013; Knight et al., 2012; Kurlan et al., 2001; Martino et al., 2013). Individuals with TS who have motor/vocal tics for more than a year are labelled as chronic while the others with tic history less than a year are deemed as provisional. Simple tics include blinking of the eye, frowning, flicking of head, shoulder shrugs, brisk arm or leg movements, and throat clearing whereas complex tics consist of isolated motor routines which involves different muscle groups, such as flexing or bending the torso or limbs, complex head movements, or enunciating syllables, words, or phrases (Martino et al., 2013).

The onset is commonly at the age of 4 to 6 years and the syndrome shows a waxing and waning course, a peak in severity in the pre-pubertal phase and a successive trend towards remission or symptom reduction during late adolescence and adulthood (Bloch & Leckman, 2009; Groth et al., 2017). Stress, anxiety and fatigue usually aggravates the tics especially in adolescents and adults. On the other hand, tics may improve when individuals are engaged in attention-demanding activities (e.g., playing videogames, practicing complex physical activities, etc.) or

when they are involved in practicing general physical exercise or relaxation. Tics also disappear during deep sleep (Augustine & Singer, 2019; Martino et al., 2013).

Some studies have documented that the tic TS patients also experience unpleasant somatic sensations termed as Premonitory urges (PUs) which build up immediately before tics and are momentarily relieved by tic release (Martino et al., 2013). Additionally (Cohen & Leckman, 1992) suggested that the positive reinforcement deriving from the temporary relief of PUs after the release of tics contributes to maintain the production of tics as automatic routines over time. PUs usually increases with age during child development (between 8-19 years) where the documented cases of PUs have been reportedly increased from 24% to 57%. It is still ambiguous whether this linear relationship of PUs with age is the result of a developmental progression of the urge phenomenon itself or rather the result of the progressive increase in children to verbalize the nature of their urges (Banaschewski et al., 2003).

As there is no pharmacological cure for TS, both symptomatic and behavioral therapy is recommended to patients suffering from psychosocial difficulties, physical discomfort, or other lifestyle disruptions due to tics. Behavioral therapy is usually effective (Piacentini et al., 2010) but many individuals with chronic tics require tic-suppressing pharmacotherapy. Habit reversal therapy (HRT) is the most common behavioral treatment given to patients who are affected by tics. HRT includes 9 different techniques within the realm of 4 discrete domains: i) awareness training: which aids patients to detect early warning signs related to disruptive tic behavior. ii) response technique: where the patients are instructed to perform a movement that is contradictory with the tic using the antagonistic muscles. iii) motivation techniques that pivots on social repercussions of tics and lastly iv) rehearsal of the HRT technique and its transference to everyday life (Fründt et al., 2017). HRT is a main component of comprehensive behavioral intervention (CBIT) which includes psychoeducation, relaxation training and functional intervention which eventually helps TS patients to identify and manage events and situations that worsen tic severity (Capriotti et al., 2014; Fründt et al., 2017; Piacentini et al., 2010).

Other therapeutical approaches include cognitive-behavioral treatment (CBT), contingency management (CM) and function-based interventions (FBI), relaxation training (RT), followed by self-monitoring (SM). All of the above therapies are designed to promote tic awareness by teaching patients to recognize and systematically manage their tics. Amongst all these therapeutical measures both HRT and CBIT are the pragmatic treatment recommendations for chronic TS patients (Steeves et al., 2012; Verdellen et al., 2011).

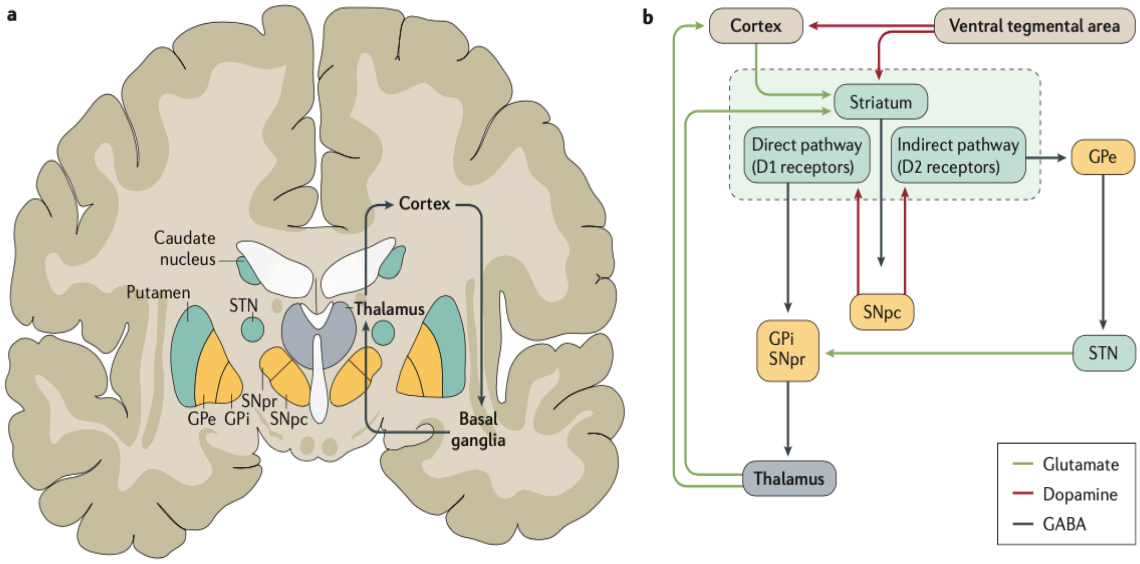


Fig 1. CSTC circuit. **a)** The **cortico–striato–thalamo–cortical** (CSTC) circuit is a complex interconnection between the cortex, basal ganglia and thalamus, which regulates complex behaviors and involves many neurotransmitters (including dopamine, glutamate and γ-aminobutyric acid (GABA)). An imbalance in one or more of these neurotransmitters might explain some of the characteristics of Gilles de la Tourette syndrome (GTS). **b**) A simplified CSTC circuit includes projections from excitatory glutamatergic pyramidal neurons located in the frontal cortex to GABAergic medium spiny neurons (MSNs) in the striatum. Striatal output pathways include a direct pathway that transmits striatal information monosynaptically to the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNpr) and an indirect pathway that conveys information to these same regions via a disynaptic relay from the globus pallidus express dopamine D1 receptors, muscarinic M1 and M4 acetylcholine receptors and the neuropeptide substance P. Indirect pathway MSNs express dopamine D2 receptors, muscarinic M1 receptors, adenosine A2A receptors and enkephalin. Each pathway has an opposing effect on GABAergic GPi and SNpr output neurons: the direct pathway inhibits and the indirect pathway stimulates. Consequently, these pathways have a reverse effect on excitatory projections from thalamic neurons to the frontal cortex and striatum, and, in turn, the facilitation of motor activity. Specifically, activation of the direct pathway facilitates motor activity, whereas activation of the indirect pathway reduces motor activity. The dopaminergic pathway, which is likely to be involved in GTS, is also indicated. SNpc, substantia nigra pars compacta. *(Robertson et al 2017) published in Nature reviews disease primers*.

1.2 OBSESSIVE COMPULSIVE DISORDER

Obsessive compulsive disorder (OCD) is a highly prevalent psychiatric condition which has a lifetime prevalence of 1-3% in general population. The principal symptoms of OCD are obsessions and compulsions which are now classified together in the together in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Association, 2013). Obsessions are basically repetitive invasive thoughts, urges, or impulses that the affected individual is unable to suppress. Compulsions are predominantly repetitive behaviors or mental rituals that arises in response to an obsession with the purpose of curbing down the distress caused by the obsessions.

Quotidian forms of obsessions and compulsions in OCD patients include concerns regarding contamination together with cleaning and washing, harm to others and self jointly with checking, hostile sexual thoughts together with mental rituals, and lastly concern about symmetry in conjunction with ordering or counting (Bloch et al., 2008; Mataix-Cols et al., 2005). A bimodal pattern with respect to age of onset has been observed in OCD patients where the symptoms start to appear during childhood/adolescence more frequently in males and in early adulthood in females. In the National Comorbidity Survey Replication (NCS-R) study, majority of males had onset before the age of 10 years whereas in females the onset occurred during adolescence or even transpired during peripartum/postpartum period(Ruscio et al., 2010; Russell et al., 2013). Like TS, OCD is characterized by substantial comorbidity with other disorders such as anxiety/mood disorders, impulse-control disorders, substance use disorder and other "Obsessive-Compulsive and Related Disorders," (OCRDs) such as (such as hoarding, body dysmorphic disorder or Tourette syndrome) (Stein et al., 2019). Although all the above-mentioned disorders share a clinical similarity it is crucial to distinguish them from one another because of a difference in treatment procedures. Previous studies have shown that only 14-56% of OCD patients seek medical treatment because the recognition and diagnosis of OCD is typically difficult due to the variability of OCD symptoms (Dell'Osso et al., 2013, 2016).

The present hypothesis of cortico-striato-thalamo-cortical loop (CSTC) dysfunction as the pathophysiological cause for the obsessions and compulsions has been derived from various neuroimaging, neuropharmacological and neuropsychological research suggesting the disparity between the glutamatergically mediated excitatory and γ-aminobutyric acid-mediated (GABA-ergic) inhibitory control mechanism (Brooks & Stein, 2015; Saxena & Rauch, 2000).

Fig.2 summarizes the neurocircuitry of normal individuals and OCD affected patients. According to this model OCD symptoms are not pertained to the dysfunction or lesion of a particular brain region but are caused by the disparity in the interactions of different brain structures which are a part of CSTC loop along with links to the amygdala region which plays a crucial role in the modulation of OCD behaviors (Brooks & Stein, 2015; Richter & Ramos, 2018; Rus et al., 2016; Simon et al., 2014). Besides the uneven interactions within the CSTC loop, a handful of studies have postulated the involvement of other brain structures such as fronto-limbic, frontoparietal and cerebellar networks in the pathogenesis of OCD (O. A. van den Heuvel et al., 2016; van Velzen et al., 2014).

Rudimentary treatment options for OCD patients include pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT). CBT is the most effectual treatment in OCD and the only form of psychotherapy for which robust evidence of success exists. CBT consists of two main components: behavioral intervention and cognitive reappraisal. Behavioral intervention comprises of 'exposure and response prevention' (ERP) which revolves around providing gradual and prolonged exposure to fear-provoking triggers combined with a set of instructions to abstain from the compulsive behavior. Additionally, by the integration of ERP with cognitive components OCD patients can identify and learn to modulate internally recurrent thoughts/beliefs. Nowadays ERP with cognitive reappraisal, either delivered in person or by internet-based protocols where the OCD patient carries out ERP exercises in the home environment is the most effective treatment for OCD (Stein et al., 2019; Wootton, 2016).

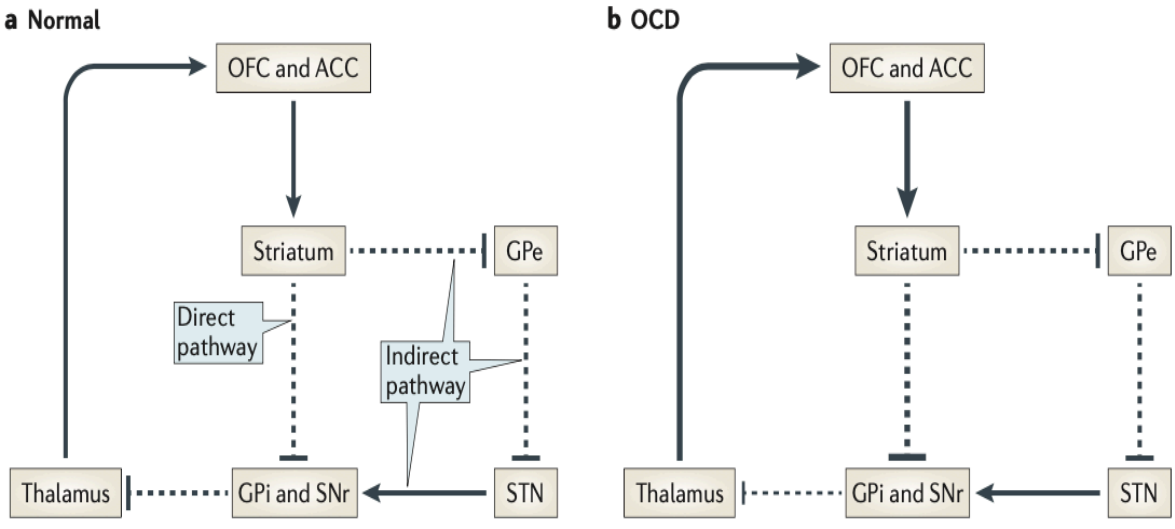


Fig2. The cortico-striato-thalamo-cortical circuitry. Solid arrows depict glutamate (excitatory) pathways and dashed lines depict GABAergic (inhibitory) pathways. **a** | In the normally functioning cortico–striato–thalamo–cortical circuit, glutamatergic signals from the frontal cortex (specifically, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC)) lead to excitation in the striatum. Through the so-called direct pathway, striatal activation increases inhibitory GABA signals to the globus pallidus interna (GPi) and the substantia nigra (SNr). This decreases the inhibitory GABA output from the GPi and SNr to the thalamus, resulting in excitatory glutamatergic output from the thalamus to the frontal cortex. This direct pathway is a positive-feedback loop. In an indirect, external loop, the striatum inhibits the globus pallidus externa (GPe), which decreases its inhibition of the subthalamic nucleus (STN). The STN is then free to excite the GPi and SNr and thereby inhibit the thalamus. **b** | In patients with obsessive– compulsive disorder (OCD), an imbalance between the direct and indirect pathways results in excess tone in the former over the latter. *(Pauls et al., 2014) Published in Nature reviews neuroscience*

1.3 TOURETTIC OCD (TOCD)

Both tics and compulsions share a number of clinical attributes, thus they both can have similar aggravating (anxiety, excitement) and alleviating (concentration) factors, that are followed by a degree of suppressibility although the suppressibility factor is usually shorter in case (few seconds) of tics (Martino et al., 2013). In order to apprehend the overlap between TS and OCD symptoms, a tic-related specifier has been introduced in the DSM-V in order to classify OCD patients with current or past comorbid TS. This tic related subtype is termed as as 'Tourettic-OCD' (TOCD), it is a distinct from the purer forms of OCD as it is strongly influenced by the attributes usually associated with TS. In case of OCD, compulsions typically consist of just-right or just-so requirements with a particular emphasis on symmetry, ordering, touching, arrangement. Moreover, compulsions are relatively minor symptoms compared to the obsessions which are anxiety driven where the patients suffer from fear that something catastrophic might happen if a ritual is not performed in the right order or the set number of times for e.g., cleaning of hands for a certain number of times to protect against AIDS. Contrarily compulsions in TOCD are not associated with anxiety but rather with sensory phenomenon such as physical discomfort/tension and diffused psychological distress (where a person has feelings of incompleteness)(Conelea et al., 2014; Mansueto & Keuler, 2005; Olatunji et al., 2007). Historical indicators for TOCD may involve the following: early

manifestations may include sensory hypersensitivity (excessive vexation with clothing tags, scratchy fabrics and uneven shoe laces), personal or family history of motor/phonic tics followed by the diagnosis of multiple comorbidities such as ADHD, learning disorder, and impulse control. Lastly, weak response to SSRI therapy and a non-response/weak or abnormal feedback to ERP(Mansueto & Keuler, 2005; Olatunji et al., 2007). In summary, we need to delve further to find measures/markers that can aid in the diagnostic classification of TOCD from OCD and TD.

1.4 Cerebellar involvement in TS and OCD

The interactions between the basal ganglia and cerebellum are thought to sub-serve not only motor functions but putatively also non-motor (cognitive) functions (Bostan et al., 2010; Strick et al., 2009). Both sub-cortical structures receive input from and send output to the cerebral cortex forming a multisynaptic loop. Prior studies have shown that the main output nuclei of the cerebellum, i.e., the dentate nucleus has its efferent projections travelling through the superior cerebellar peduncles to the cerebral cortex via the basal ganglia (GPi and SNr) thus influencing the action selection criteria of basal ganglia further inhibiting/exciting the cerebral cortex (Fig. 3). Thus the cerebellum plays an integral role in modulating motor/non-motor functions (Bernard et al., 2014; Bostan et al., 2013; Milardi et al., 2019; Strick et al., 2009). A handful of neuroimaging studies have started to indicate the potential role of cerebellum in the pathophysiology of TS and OCD. In particular, prior structural studies have reported reduced cerebellar grey matter (GM) volume in TS patients than controls (Sigurdsson et al., 2020; Tobe et al., 2010). Other studies have reported either decreased (Kim et al., 2001; Koprivová et al., 2009) or increased (Pujol et al., 2004) cerebellar GM volume in OCD patients compared to controls. In the context of white matter structural connectivity, former studies have demonstrated increased fractional anisotropy (FA) in TS (Thomalla et al., 2009) whereas decreased FA has been reported in OCD patients (Zhong et al., 2019). Lastly, in terms of cerebellar FC connectivity prior studies have reported either decreased cerebellar-frontal connectivity in TS (Ramkiran et al., 2019) or increased prefrontal/ orbitofrontal excitability in OCD (Apergis-Schoute et al., 2018; J. Hou et al., 2012; Ping et al., 2013). Differently from what has been speculated earlier, i.e., the fact that cortico-striato-thalamo-cortical circuit

dysfunction is the core pathophysiology of TS and OCD, the integral role of the cerebellum in the pathophysiology of TS and OCD cannot be denied. Hence further studies are warranted to characterize in detail the potential involvement of cerebellum in modulating tics and compulsions.

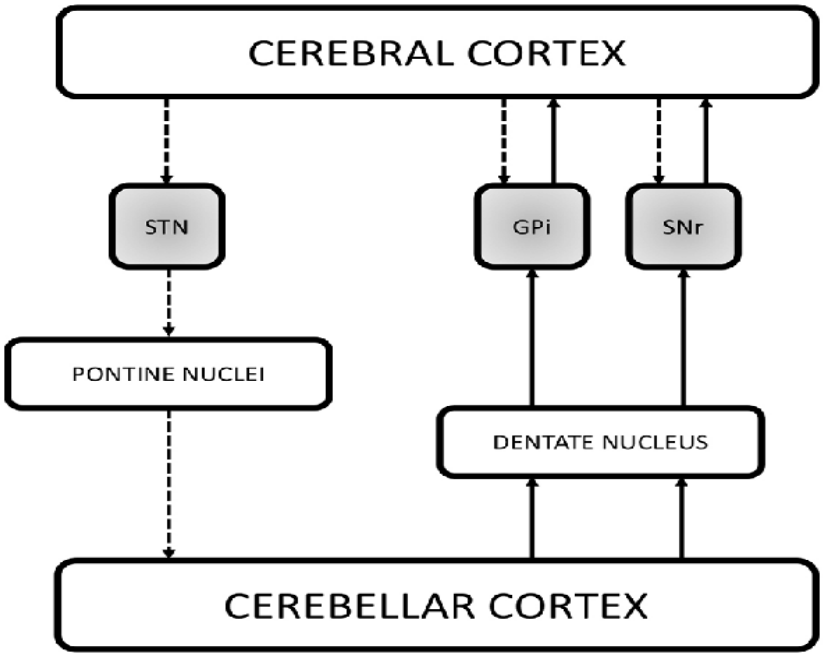


Fig3. Schematic illustration of the recently demonstrated anatomical connections in the basal ganglia network. The figure reports the three direct systems running between the cerebral cortex and the basal ganglia (STN, GPi and SNr, shaded gray boxes), providing a fast route of connection by passing the striatum and the thalamus. The dashed lines represent the cerebral cortex output on the basal ganglia and the information flow from the basal ganglia to the cerebellum. The solid lines instead represent the cerebellar output on the output nuclei of the basal ganglia which in turn communicates with the cerebral cortex. STN, subthalamic nucleus; GPi, internal segment of the globus pallidus; SNr, pars reticulata of the substantia nigra. (Milardi et al., 2019)

CHAPTER 2: MRI in Tourette and Obsessive-compulsive disorder

2.1 MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging (MRI) is a promising non-invasive imaging modality that provides detailed information on brain anatomy, function and metabolism. The evolution of MRI for utilization in medical investigation has provided a huge forward leap in the field of clinical decision making. With the reduction in costs, better availability and non-invasive nature, the MRI is becoming widely used throughout clinical practice (Grover et al., 2015; Yousaf et al., 2018).

MRI is a non-invasive imaging modality that generates cross-sectional images of the internal structures of the human body via non-ionizing electromagnetic radiation. The basic principle of MRI (Magnetic Resonance Imaging) is based on the spin property of the atomic nuclei present in our body. Spin is a vector quantity with magnitude and direction. In biological systems, proton nuclei are abundant in biological tissues in the form of hydrogen ($_1H^1$) in water molecules. MRI uses a powerful magnet which produces a strong static magnetic field (B_0) forcing the protons in the body to align with the magnetic field direction. A radiofrequency (RF) current is pulsed through a coil winding the object, that produces a magnetization in body protons and forces their spin direction away from the direction of B_0. The angular frequency that is characteristic of proton procession around the B_0 is termed as Larmor frequency (ω_0) and is directly proportional to the applied magnetic field B_0 by the gyromagnetic ratio (γ), which is a nuclei specific constant.

$$\omega_0 = \gamma B_0$$

where, (ω_0) = Larmor frequency, B_0 = static magnetic field and γ = gyromagnetic ratio which is a nuclei specific constatnt.

On stopping the RF field, the protons realign back with B_0 releasing electromagnetic energy along the way, that is detected by the coil as free-induction decay (FID) response signal. The process of reaching equilibrium is called as relaxation. The FID is measured by a conductive field coil placed around the object being acquired and is further constructed to get a 3-dim grey

scalar images (Grover et al., 2015; Yousaf et al., 2018). The MRI system is then able to differentiate various tissues on the basis of how quickly they release energy after the pulse is turned off.

2.2. T1- AND T2-WEIGHTED MR IMAGING:

The most common MRI-sequences are T1-weighted and T2-weighted images. T1 weighted images are built on MRI acquisition sequences that exploit the difference in 'spin-lattice' relaxation times that are exhibited by tissues. Water and cerebrospinal fluids have long T1 values (3000–5000 ms), and they appear dark on T1-weighted images, whereas fat has a short T1 value (260ms) and they appear white (Fig1a). On the contrary, T2-weighted images exploit the difference in tissues' 'spin-spin' relaxation time. They are produced by using longer TE (90ms) and TR (4000ms). The contrast and brightness are particularly determined by the T2 properties of tissue(Grover et al., 2015).

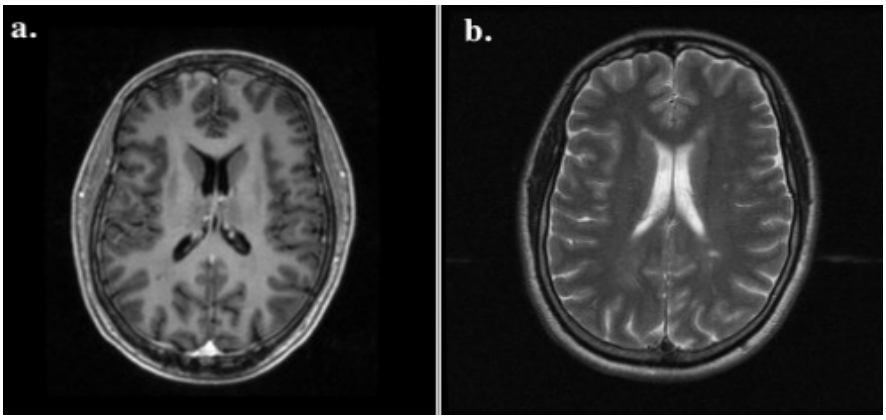


Fig 1. depicts T1 weighted image (a); T2 weighted image (b).

2.3 DIFFUSION WEIGHTED IMAGING (DWI):

The Diffusion-weighted imaging (DWI) technique allows for the quantification of water molecules movement. 60%-70% of the human body is made of water. The diffusion of water molecules follows the principle of Brownian motion. Thus, in a perfect homogenous medium diffusion is said to be random and isotropic i.e., equal in all directions. In structured

environments the motion of water molecules is restricted due to their physical surroundings for e.g in the brain the microstructure within the grey and white matter restricts the flow of water molecules. Usually, water molecules move parallel to white matter tracts rather than perpendicular because the axon membranes limit the molecular movement perpendicular to the fibers. This particular motion is termed as 'anisotropic' given that it is not equal in all directions. 'Diffusion tensor' is the mathematical term used to define the motion of molecules in x, y, z planes and the correlation between these directions. Mathematically speaking a tensor defines the properties of a 3-dim ellipsoid (**Fig2**). So, in order to calculate the diffusion tensor, diffusion data in a minimum of 6 non-collinear directions is required. This is termed as Diffusion tensor imaging (DTI). DTI gives the micro-architectural detail of the white matter tracts and produces information regarding white matter integrity (Alexander et al., 2007; Baliyan et al., 2016; P J Basser et al., 1994; Peter J. Basser & Jones, 2002; Chenevert et al., 1990; Doran et al., 1990; Grover et al., 2015).

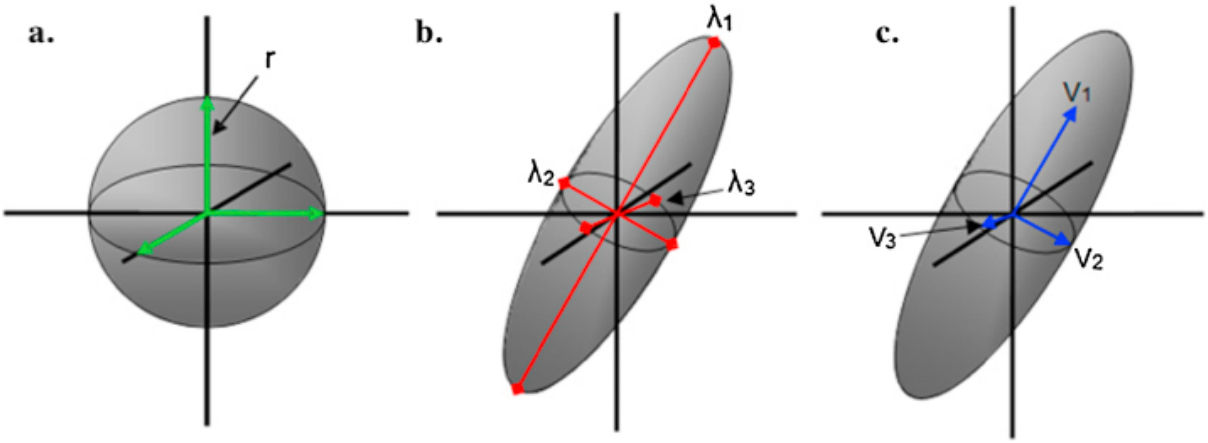


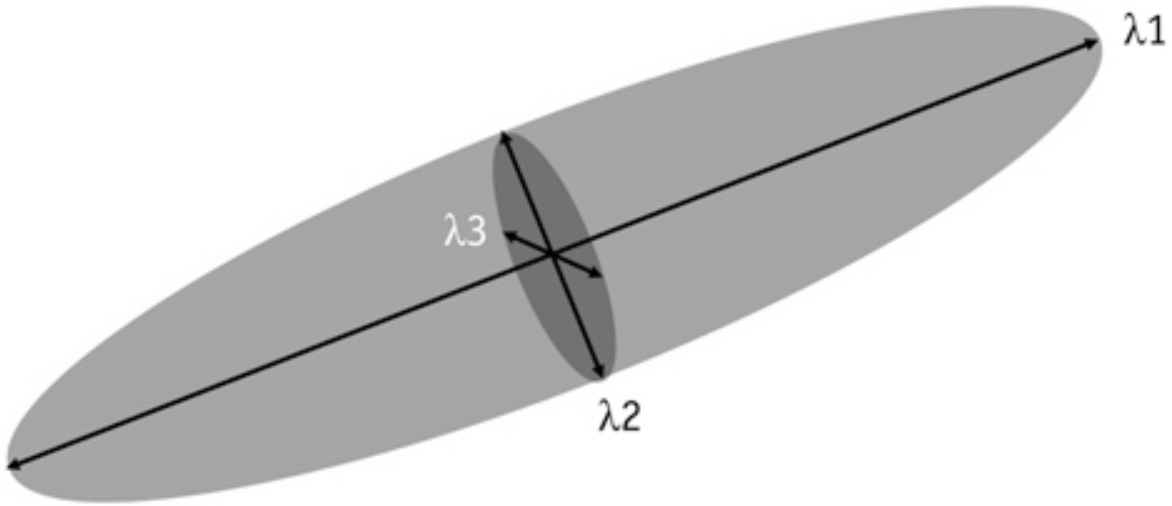
Fig 2. Depicts the graphical representation of a diffusion tensor, a three-dimensional ellipsoid; the long axis represents the primary direction of motion. Figure (a) exhibits isotopic diffusion while figure (b) and (c) exhibits restricted diffusion.

Diffusion Indices

Mean Diffusivity (MD): The average of the tensor's eigenvalues is referred to as mean diffusivity. MD describes the rotationally invariant magnitude of water diffusion within the brain tissues.

$$MD = (\lambda_1 + \lambda_2 + \lambda_3)/ 3$$

Fractional Anisotropy (FA): FA is used to describe the degree of anisotropy. FA is often considered as the measure of 'White matter integrity' though FA can be modulated by several other factors. We can measure the degree of diffusion anisotropy by using a measurement of difference among the three eigenvalues: $(\lambda1 - \lambda2)^2 + (\lambda1 - \lambda3)^2 + (\lambda2 - \lambda3)^2$. If diffusion is isotropic ($\lambda1 = \lambda2 = \lambda3$), this measure becomes 0 (Grover et al., 2015; O'Donnell & Westin, 2011; Soares et al., 2013). FA can be measured as follows (**Fig 3**).



$$FA = \sqrt{\frac{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}{2(\lambda_1{}^2+\lambda_2{}^2+\lambda_3{}^2)}}$$

Fig 3. The above figure depicts the calculation of Fractional anisotropy: Largest vector of diffusion ellipsoid is eigenvector 1 and its value is λ1. Shortest one is λ3 and remainder is λ2. Fractional anisotropy is calculated by each of eigenvalues. Fractional anisotropy varies from 0 (infinite isotropy) to 1 (infinite anisotropy) (Ahn & Lee, 2011).

2.4 FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI):

Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) allows the exploration of neural response to a particular stimuli. It utilizes the differences in the paramagnetic properties of oxyhemoglobin and deoxyhemoglobin, also referred to as

BOLD contrast to produce images of cerebral brain activity (Ogawa & Lee, 1990). Since its inception in 1990 BOLD-fMRI has been widely used in numerous studies of cognition for clinical applications such as surgical planning, inspecting treatment outcome and as a functional biomarker in pharmacological studies (Glover, 2011). BOLD contrast differentiates tissues based on the intrinsic magnetic properties of oxyhemoglobin and deoxyhemoglobin. Oxyhemoglobin is diamagnetic and is repelled by a magnetic field whereas deoxyhemoglobin is paramagnetic and tends to align with the magnetic field generated by the MRI magnet. This property is exploited by the MRI scanner and leads to the detection of magnetic signal variation (J. E. Chen & Glover, 2015; Glover, 2011; Ogawa et al., 1990).

Accurate estimation of the BOLD hemodynamic response function (HRF) is important for the analysis and interpretation of the fMRI data. HRF is basically a regional BOLD response generated from a brief stimulus. The HRF typically exhibits a small initial dip, followed by a tall peak, and then a variable post-stimulus undershoots (Buxton, 2013) (**Fig 4**).

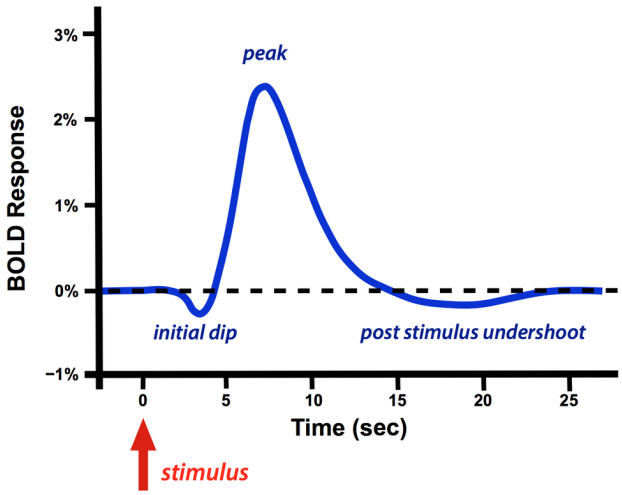


Fig 4. Depicts a BOLD Hemodynamic Response Function (HRF) following a single brief stimulus

Types of functional MRI (fMRI)

Task-based fMRI: As the name suggests, in task-based fMRI the acquisition is performed while the subject is performing a cognitive task (**Fig 5**). The time series data are compared against a hypothesized model of neural function based on the task being performed and a map of brain regions that respond to the cognitive task is constructed. In the task-based fMRI a sensory/auditory stimulus cues the subject to perform a behavioral task while the BOLD images are acquired for a fixed duration of the task (J. E. Chen & Glover, 2015).

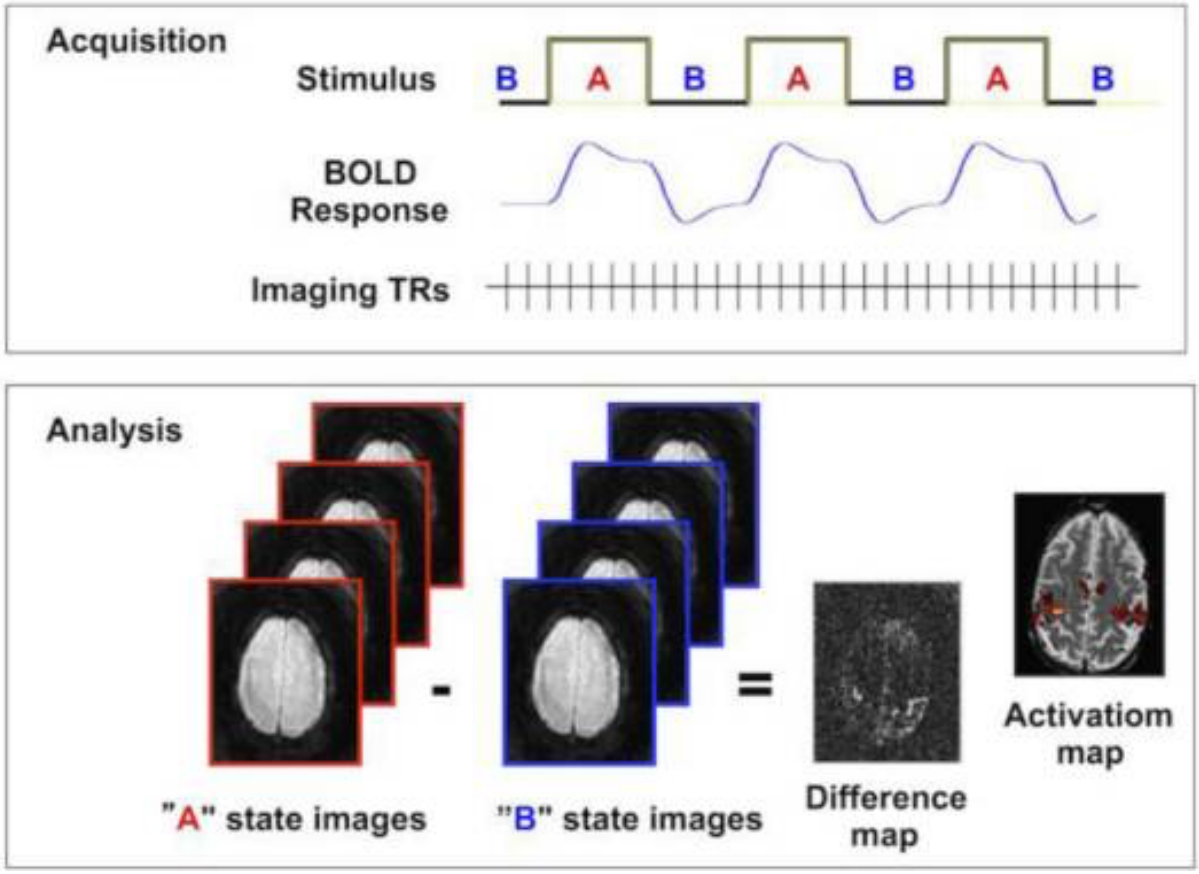


Fig 5. Task-based fMRI experiment acquires a time series of images while participant performs cognitive manipulation that causes a change between brain states A and B. The functional map depicts those regions that were more metabolically activated in state A than B, using a statistical test to demonstrate significant signal differences in each voxel (J. E. Chen & Glover, 2015).

Resting-state functional MRI: Since its first finding of temporal correlations between spontaneous BOLD signals in the bilateral motor cortices (Biswal et al., 1995) 'resting-state' fMRI(rs-fMRI) has been widely used in both healthy subjects and patients with various neurological and psychiatric disorders to investigate functionally connected networks throughout the brain (J. E. Chen & Glover, 2015; Lv et al., 2018). Resting-state fMRI measures the low frequency fluctuations (<0.1 Hz) in the BOLD signal (Lee et al., 2013). As opposed to task-based fMRI, rs-fMRI is acquired in the absence of any stimulus or any cognitive task.

2.5 METHODS EMPLOYED TO QUANTIFY STRUCTURAL AND FUNCTIONAL CHANGES:

2.5.1 Voxel-based Morphometry (VBM):

Voxel-based Morphometry (VBM) is an automated technique that analyzes the structural changes in the brain by looking for localized differences in gray matter density, between group of subjects (Ashburner & Friston, 2000a). VBM gives a detailed assessment of anatomical differences in the brain. Pathological changes in the brain due to loss of brain tissue/atrophy can be detected by structural MRI. Traditional techniques to detect atrophy includes visual assessment by experienced radiologists. However automated techniques like VBM have been developed which allows the assessment of atrophy over large group of subjects. VBM typically uses a T1-weighted image and performs statistical voxel-wise comparison of all voxels in the T1-weighted scan in order to find the volumetric differences between groups (Whitwell, 2009). VBM consists of the following steps that are undertaken in order to assess the volumetric differences between any group of subjects. The first step is the 'spatial normalization' that involves transforming all the subject's data to the same stereotactic space or the MNI 152 space. In case of specialized cases where we have to deal with pediatric data, a customized template is developed to which all the structural data of the subjects is registered to using linear and non-linear affine registration technique. Spatial normalization corrects for global brain shape differences rather than matching every cortical feature exactly. If this was the case, we wouldn't find any volumetric differences. VBM tries to find differences in the regional concentration of grey matter at a local scale after having corrected for global shape differences. The next step includes the partitioning of the spatially normalized images into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Now the GM images are smoothened by convolving with an isotropic gaussian kernel to produce an image which represents a local 'grey matter density'. Typically, between 8mm-12mm of smoothing kernel is applied. The smoothing step also aids in compensating for the effects of misalignment during spatial normalization. The final step requires the statistical analysis of the smoothed grey matter images using a general linear model (GLM) to identify the regions of grey matter concentration after accounting for the multiple comparison correction. GLM is a flexible framework that allows many group comparisons tests to be applied accounting for age, gender and total intracranial volume as nuisance covariates (Ashburner & Friston, 2000b; Whitwell, 2009).

2.5.2 Tract-Based Spatial Statistics (TBSS):

DTI provides information regarding the microstructural alterations in the white matter tracts by quantifying the anisotropic diffusion of water in the white matter tracts. Tract-Based spatial statistics (TBSS) a part of FSL diffusion toolbox (FDT) is utilized for voxelwise statistical analysis of the FA data (Smith et al., 2006). First, the DTI data is visually checked for any outliers or eddy motion. Second an eddy correction is used to correct for any eddy-induced distortions or subject movements. It also performs outlier detection and identifies the slices where signal has been lost due to subject movement. These slices are then replaced by the non-parametric predictions by the gaussian process. After eddy correction dti-fit is used that fits a diffusion tensor model at each voxel. Next a non-linear registration is run that aligns all the FA images to a standard 1*1*1 space. For specialized cases such as dealing with children's data, all the FA images area aligned to every other one, thus identifying a specific 'target image' which is affined aligned to the MNI152 standard space. Next, the mean FA image created is thinned to form a mean FA skeleton **(Fig7)** representing all the white matter tracts containing all subject's aligned FA data. Finally, the skeletonized FA data is fed into voxel wise statistics to identify which FA skeleton voxels are significantly different between group of subjects (Smith et al., 2006).

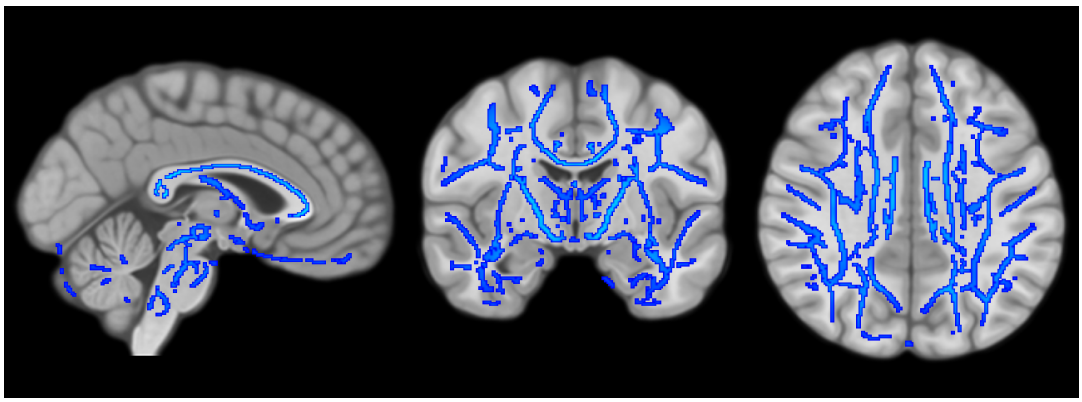


Fig 7. Depicts microstructural mean FA skeleton tracts superimposed on a MNI152 template.

2.5.3 Independent Component Analysis (ICA):

Independent component analysis (ICA) splits the 4D functional data into a set of statistically independent spatial maps each associated with a specific time course (Beckmann & Smith, 2004). It is a hypothesis free exploratory approach where the between network functional connectivity is assessed within the pre-defined resting state networks (RSNs). The result of ICA is usually independent components some of which are related to activation while others to physiological noise such as (heartbeat and respiration) or to imaging artefacts (ghosting, signal dropout, motion etc). Some of these imaging artefacts such as motion artefacts can be removed with various artefact removal techniques such as ICA-AROMA to get a clean motion free independent component. After generating the group ICA components dual-regression is implemented that proceeds in two stages: In 1st stage subject-specific time course for each template network is extracted via multivariate spatial regression. In the second stage, the subject specific time courses from the stage 1 are used in second multivariate regression against the subject's fMRI data to identify subject specific spatial maps which can be further fed for statistical analysis (Nickerson et al., 2017) (**Fig8**).

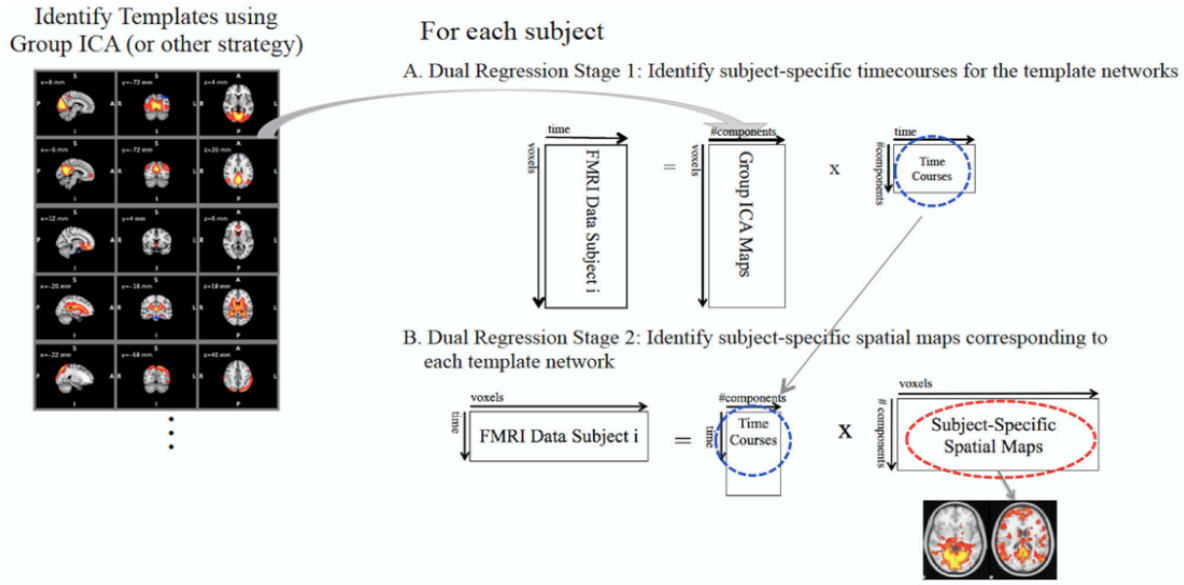


Fig 8. The dual regression proceeds in two stages. (A) In the first stage, subject-specific timecourses (blue circle) for each template network are extracted. (B) In the second stage, the subject-specific timecourses from stage 1 are used in a second multivariate regression against the subjects' FMRI data to identify the subject-specific spatial maps (red circle) (Published in (Nickerson et al., 2017).

2.5.4 Seed based correlation analysis (SCA):

This SCA method was first used by (Biswal et al., 1995) to identify the resting state networks. Seed based correlation analysis (SCA) is a model-based method in which we define a region or seed of interest based on a priori hypothesis and find the linear correlation of this region of interest with all the voxels in the entire brain yielding a seed based functional connectivity map. (Smitha et al., 2017). The primary advantage of SCA is that it shows the network of regions most strongly functionally connected with the seed/region of interest (Cole et al., 2010).

2.6 REVIEW OF NEUROIMAGING STUDIES IN TS AND OCD

2.6.1 Neuroimaging studies in TS

Over the past few years, a significant number of neuroimaging studies have been published in the domain of TS mainly in adult cohorts than children. Several new methodological approaches have been applied in addition to the more conventional neuroimaging methods to study the neural underpinnings of TS patients. Prior volumetric studies in TS patients have yielded conflicting results. For instance, previous studies have reported decreased grey matter volume in basal ganglia and left hippocampal gyrus as well as in orbitofrontal, anterior cingulate, post central gyrus and ventrolateral prefrontal areas (Bloch et al., 2005; Draganski et al., 2010; Liu et al., 2013; B. S. Peterson et al., 2001; Bradley S. Peterson et al., 2003). In contrast grey matter volumes in dorsolateral prefrontal regions and bilateral putamen and posterior thalamus have been found to be increased in TS patients (Greene et al., 2017; Kassubek et al., 2006; Liu et al., 2013; Ludolph et al., 2006; B. S. Peterson et al., 2001). Other regions associated with TS such as insula has yielded mixed results where some studies have exhibited lower grey matter volume in insula in both children and adults with TS (Draper et al., 2016) while some have reported increased volumes in insular cortices (Liu et al., 2013). All in all, some of these regions with alterations in grey matter are associated with the CSTC circuit implicated in TS (Liu et al., 2013).

Diffusion Tensor Imaging (DTI) when coupled with Tract Based Spatial Statistics (TBSS) is becoming widely popular in detecting microstructural alterations in the white matter tracts of the diseased brain (P J Basser et al., 1994; Smith et al., 2006). There exists a large pool of DTI

studies that investigates structural alterations in TS patients (Andrea E. Cavanna et al., 2010; Jackson et al., 2011; Liu et al., 2013; Makki et al., 2008; Neuner et al., 2010; Plessen et al., 2006; Wolff et al., 2016). Several studies on TS cohorts have found decreased FA in the corpus collosum (Andrea E. Cavanna et al., 2010; Draganski et al., 2010; Jackson et al., 2011; Liu et al., 2013; Neuner et al., 2010; Plessen et al., 2006) which has been interpreted as the compensatory dampening of inter-hemispheric communication (neuroplastic adaptation) to reduce unwanted behaviors. Beyond the corpus callosum, few studies reported increased FA and MD in pre- and post-central gyrus and corticostriatial pathways in TS adults (Draganski et al., 2010; Govindan et al., 2010; Thomalla et al., 2009) other whole-brain studies have exhibited decreased FA in frontal, parietal, occipital and cingulate regions (Müller-Vahl et al., 2014). Collectively, these findings are in accordance with the hypothesis of abnormal structural connectivity of the CSTC circuit along with reduced inter-hemispheric transfer of information that might hinder cortical inhibition in TS.

Resting-state functional connectivity examines the spontaneous fluctuations of the BOLD signal obtained when the subjects are lying in the scanner without any explicit task. This technique has become immensely popular for examining patient population who are unable to perform a specific task. A growing number of neuroimaging studies investigated abnormalities in TS over the last years and reported contrasting results (Church et al., 2009; Y. Cui et al., 2014a; Liu et al., 2017a; Ramkiran et al., 2019; Tikoo, Cardona, et al., 2020; Tinaz et al., 2014; Worbe et al., 2012) likely due to differences in the clinical samples, especially in terms of the comorbidity burden. Studies focusing on TS population showed alterations in the basal ganglia circuitry consistent with the long-standing hypothesis of a primary cortical-striato-thalamo-cortical (CSTC) circuitry disruption in TS ((Caligiore et al., 2017b; Ji et al., 2016; Liu et al., 2017a; Tikoo, Cardona, et al., 2020). Besides the CSTC circuit other brain regions like cingulate and insular cortices that are said to be implicated in the TS have been reported to have decreased intrinsic brain activity in TS patients than controls (Y. Cui et al., 2014a; Liu et al., 2017a). On the whole, finding a convergence among these studies remains a challenge. This heterogeneity in the structural and functional findings in TS patients might be attributed to the differences in sample size or presence of comorbidities, and exposure to pharmacological treatments etc. Hence an investigative study is required which is not confounded by these factors to better understand the neural underpinnings of TS patients during the early life onset.

2.6.2 Neuroimaging studies in OCD:

Several studies have utilized voxel-based morphometry (VBM) as a technique to find regional differences in grey matter volume between OCD patients and age matched controls (M. P. van den Heuvel et al., 2009; Kim et al., 2001; Kwon et al., 2003; Pujol et al., 2004; Szeszko et al., 1999; Togao et al., 2010; Zarei et al., 2011). Findings from these studies have been consistent with the traditional neurobiological model where OCD is characterized by alterations in the CSTC circuit which includes orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), basal ganglia and thalamus. Decrease in the grey matter volume have been uniformly reported in the ACC while increase in the grey matter volume has been reported in the Thalamus, striatum and putamen (Kim et al., 2001; Pujol et al., 2004; Valente et al., 2005; So Young Yoo et al., 2008). Other brain areas such as superior temporal gyrus and parahippocampal gyrus have yielded mixed results where some volumetric studies have demonstrated increased superior temporal grey matter volume in OCD patients (Kim et al., 2001) while others have reported decreased (So Young Yoo et al., 2008). Additionally, increased grey matter volume in parahippocampal gyrus extending to amygdala has been reported in prior volumetric studies as well (Valente et al., 2005). Lastly, other areas such as the insula and cerebellum have exhibited altered structural volumes in OCD cohorts (Kim et al., 2001; Pujol et al., 2004; Valente et al., 2005; So Young Yoo et al., 2008). OCD itself is a heterogenous disorder with complex pathophysiological underpinnings with overlapping comorbidities. Hence structural volumetric assessment is required in a more homogenous sample from an early-stage onset.

As discussed before Diffusion tensor imaging (DTI) allows the quantification of diffusion characteristics of water molecules within the white matter tracts. So, for most of the studies investigating microstructural alterations in OCD patients have reported decreased white matter connectivity in OCD patients than controls (Admon et al., 2012; Benedetti et al., 2013; Bora et al., 2011; Fontenelle et al., 2011; Garibotto et al., 2010; Gonçalves et al., 2017) while there are few that have exhibited increased connectivity both in adults (Nakamae et al., 2011; S. Y. Yoo et al., 2007) and adolescent patients (Gruner et al., 2012; Zarei et al., 2011). Corpus callosum and cingulate are the ones most frequently affected by white matter aberrations with studies reporting decreased and increased FA within the corpus callosum and cingulate tracts (Admon et al., 2012; Benedetti et al., 2013; Bora et al., 2011; Garibotto et al., 2010; Nakamae et al., 2011). Apart from alterations in FA, some studies have also reported altered MD, RD, ADC (Benedetti et al., 2013; Bora et al., 2011; S. Fan et al., 2016; Garibotto et al., 2010). Whilst the

exact neurobiological underpinnings of these white matter indices are still a matter of debate but usually, decreased FA has been associated with alterations in fiber structure, increased ADC might be associated with increased extracellular water diffusion and increased RD has been related to deficits in myelination (Schwartzman et al., 2005; Song et al., 2002; Syková, 2004). However, the exact nature of white matter alterations in the domain of OCD still needs to be unmasked and hence further investigations are needed in a more homogenous sample.

Resting state fMRI, an immensely popular technique is used to investigate brain activity while the subject is at rest. Prior resting fMRI studies have highlighted that alterations within the CSTC loop have been the most consistent findings in the pathophysiology of OCD (Anticevic et al., 2014b; Armstrong et al., 2016; Bernstein et al., 2016; Haber & Calzavara, 2009; Harrison et al., 2009; Sakai et al., 2011) along with aberrations within the cerebellum and parietal cortices (J. Hou et al., 2012; Jang et al., 2010; Li et al., 2012; Stern et al., 2012; Tikoo, Cardona, et al., 2020). (T. Yang et al., 2010) reported that medication naïve OCD patients had higher regional homogeneity than controls in the anterior cingulate cortex while lower regional homogeneity in the left inferior temporal gyrus speculating the dysfunction of action monitoring system in OCD. Similarly, (J. Hou et al., 2012) demonstrated that adult OCD patients had higher amplitude of spontaneous low frequency fluctuation (ALFF) in the anterior cingulate gyrus, orbitofrontal gyrus followed by lower ALFF in the cerebellum and parietal cortex. All in all, the above studies suggest that OCD is not caused by disruption in a single brain network but is rather accompanied by disruptions in multiple brain circuits. Additionally, alterations have also been observed in the brain regions that are not classically associated to OCD such as the cerebellum and hence further studies are warranted to investigate the pathophysiological role of brain regions beyond the CSTC circuit in the OCD patients.

2.6.3 Neuroimaging studies in TS and OCD:

A growing number of neuroimaging studies investigated abnormalities in TS and OCD over the last years and reported contrasting/mixed results (Bastian Cheng et al., 2014; Jackson et al., 2011; Stern et al., 2012; Thomalla et al., 2009; Togao et al., 2010; Worbe et al., 2015; S. Y. Yoo et al., 2007), likely due to differences in the clinical samples, especially in terms of the comorbidity burden. Most of the studies focused on adult TS patients, who may be theorized

as a “residual” category. Furthermore, research findings in adult TS and OCD may be biased by long disease durations reflecting adaptation and compensation and variability in treatments. Structural studies focusing on TS population showed alterations in the basal ganglia circuitry consistent with the long-standing hypothesis of a primary cortical-striato-thalamo-cortical (CSTC) circuitry disruption in TS (Bloch et al., 2005; Draper et al., 2016; Thomalla et al., 2009). Moreover, studies pivoting on OCD patients have exhibited similar structural abnormalities in the CSTC loops specifically in the putamen regions along with variations in the cingulate, orbitofrontal cortex and insular regions (Bochao Cheng et al., 2016; Christian et al., 2008; Matsumoto et al., 2010). Resting state studies focusing on the fractional amplitude of low frequency fluctuations (fALFF), have reported increased intrinsic brain activity in the thalamus bilaterally and left putamen, followed by a decrease in the cingulate cortex and insular regions in pediatric TS patients with respect to controls (Y. Cui et al., 2014a). A similar study by (Liu et al., 2017a) demonstrated decreased intrinsic brain activity in the left insular cortex of TS patients in comparison with HC. On the contrary a pediatric OCD study reported higher expression scores in the middle frontal/dorsal anterior cingulate and anterior/posterior cingulate networks when compared to controls indicating abnormalities within the cingulate cortex(Gruner et al., 2014a) with further studies indicating that anterior cingulate cortex and the insular cortex show increased connectivity in adult OCD patients(Fitzgerald et al., 2011).
Despite the ubiquitous use of rs-fMRI studies in TS and OCD the overall functional connectivity patterns of pediatric TS and OCD are still poorly understood and, and further studies are warranted to explore the possible differences in brain functional and structural connectivity in pediatric patients with TS (with or without OCD comorbidity) and pure OCD.

CHAPTER 3

Resting-State Functional Connectivity in Drug-naive Pediatric Patients with Tourette Syndrome and Obsessive-Compulsive Disorder

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ABSTRACT

Previous studies in cohorts of Tourette syndrome (TS) or obsessive-compulsive disorder (OCD) patients have not clarified whether these two disorders represent two clinical conditions or they are distinct clinical phenotypes of a common disease spectrum. The study aimed to compare functional connectivity (FC) patterns in a pediatric drug-naive cohort of 16 TS patients without any comorbidity (TS), 14 TS patients with OCD (TS+OCD), and 10 pure OCD patients as well as 11 matched controls that underwent resting state fMRI. Via independent component analysis, we examined FC in the basal ganglia (BGN), sensorimotor (SMN), cerebellum (CBN), frontoparietal (FPN), default-mode (DMN), orbitofrontal (OBFN), and salience (SAN) networks among the above cohorts and their association with clinical measures. Compared to controls, TS and TS+OCD patients showed higher FC in the BGN, SMN, CBN and DMN and lower FC in the FPN and SAN. The TS and TS+OCD groups showed comparable FC in all networks. In contrast to controls, OCD patients exhibited increased FC in the BGN, SMN, CBN, DMN, FPN, and SAN. OCD patients also showed higher FC in CBN and FPN when compared with TS and TS+OCD patients both separately and as one group. Tic severity negatively correlated with FC in CBN and FPN in the TS group, while the compulsiveness scores positively correlated with the same two networks in OCD patients. Our

findings suggest common FC changes in TS and TS+OCD patients. In contrast, OCD is characterized by a distinctive pattern of FC changes prominently involving the CBN and FPN.

3.1 INTRODUCTION

Tourette syndrome (TS) is a neurodevelopmental disorder defined by the occurrence of multiple motor and phonic tics (American Psychiatric Association, 2013b). Tics affect about 0.5-0.8% of children and have a typical onset at 4-6 years (Robertson et al., 2017; Scharf et al., 2015). Although the current diagnostic definition for TS does not include obsessive-compulsive disorder (OCD), TS and OCD tend to display a phenomenological overlap. First, TS is frequently associated with obsessive-compulsive symptoms (Robertson et al., 2017). Second, TS and OCD patients are known to share a common genetic susceptibility (Mathews & Grados, 2011b). Third, both TS and OCD patients exhibit repetitive behaviors, whose labelling into complex tics or compulsions may be clinically challenging at times (Mansueto & Keuler, 2005). Accordingly, TS and OCD may share similar pathophysiological features, including common patterns of brain activity responsible for repetitive behaviors. In keeping with this hypothesis, patients manifesting TS with OCD may reflect an intermediate clinical phenotype characterized by overlapping pathophysiological features. Alternatively, TS and OCD may reflect independent disorders arising from different pathophysiological mechanisms (Mancini et al., 2018; Miguel et al., 1995; Mirabella et al., 2020). As a result, the frequently observed obsessive-compulsive symptoms in TS patients may reflect pathophysiological mechanisms that differ from those underlying pure OCD. To address this issue, an appropriate methodological approach would be to compare possible brain functional changes in patients with TS without comorbidity (TS), TS with OCD symptoms (TS+OCD), and pure OCD (OCD).

Brain functional changes may be investigated by means of resting-state functional magnetic resonance imaging (rs-fMRI), which, by monitoring oscillations in the blood oxygen level dependent (BOLD) signal across time, allows the identification of specific brain resting-state networks (RSNs) (Fox & Raichle, 2007) which are visualized as spatial maps representing the brain's resting-state functional connectivity (FC).

Previous rs-fMRI studies in TS have focused on adult cohorts with or without different types of psychiatric comorbidities and with variable exposure to chronic pharmacological treatments.

Additional confounders (e.g. differences in sample size or the presence of comorbidities) have further contributed to the heterogeneous findings insofar reported. Therefore, it is still unclear whether FC abnormalities previously demonstrated in adult TS patients reflect neural adaptation processes or instead depend on primary pathophysiological abnormalities (Bohlhalter, 2006; Neuner et al., 2014; B. S. Peterson et al., 1998). Given the neurodevelopmental nature of TS and early-onset OCD (Huyser et al., 2009) studies on pediatric patients could be particularly valuable in elucidating the primary FC disruptions in both disorders.

A handful of rs-fMRI studies examining FC in pediatric drug naive patients with TS without comorbidities have shown increased brain activity within the basal ganglia network (BGN) (Y. Cui et al., 2014a) and in vision-related areas (Liu et al., 2017a) as compared to healthy controls. In contrast, decreased FC has been found in the frontal, parietal and cingulate cortices, as well as in insular regions (Y. Cui et al., 2014a; Liu et al., 2017a; Wen et al., 2018). Other pediatric studies in TS exploring functional network topology have reported widespread abnormalities within the sensorimotor, default mode and frontoparietal networks (Church et al., 2009; Openneer et al., 2020). However, those studies are hindered by the inclusion of both medicated/unmedicated patients with varying profiles of comorbidities and wide age ranges. Furthermore, none of the previous studies have ever looked at differences between pediatric drug-naive TS patients with and without OCD, making it impossible to infer which abnormalities relate to TS, OCD, or both. Another brain region has been recently gained attention in TS, i.e., the cerebellum. More recently, several studies have hinted about the salient role of the cerebellum in the tic disorder (Caligiore et al., 2017b; McCairn et al., 2013; Neuner et al., 2014). Previous functional studies in drug-naive pediatric and adult TS cohorts have demonstrated decreased cerebellar activity and reduced cortico-cerebellar connectivity in TS patients with respect to controls (Liu et al., 2017a; Ramkiran et al., 2019). Additionally, a recent seed-based rs-fMRI study using the caudate nucleus as the region of interest has shown that adult TS patients exhibit weaker connectivity between caudate and cerebellum compared to healthy persons (Bhikram et al., 2020). All in all, these findings highlight the involvement of highly complex networks in tic pathophysiology as opposed to models of single-network dysfunction and advocate the need to further inspect the involvement of the cerebellum in TS.

Regarding OCD, previous rs-fMRI studies have mainly examined adult patients and have reported FC changes in the orbitofronto-striato-thalamic circuitry, cingulate cortex (Anticevic

et al., 2014b; Calzà et al., 2019; J. Fan, Zhong, Gan, et al., 2017; Ping et al., 2013; T. Yang et al., 2010; Zhu et al., 2016), and cerebellum (Anticevic et al., 2014a; Ping et al., 2013; H. Zhang et al., 2019). However, only a few studies have focused on pediatric patients with OCD, and these studies have been limited by relatively small sample sizes and medication exposure((Bernstein et al., 2016; Weber et al., 2014a). A resting fMRI study using region-of-interest analysis approach (via seeds placed in the thalamus and striatum) in an OCD cohort of both children and adults, first demonstrated that fronto-striato-thalamic loops showed decreased FC at an early disease stage, whereas the entire cohort exhibited increased FC between the dorsal striatum and medial frontal cortex. However, the cohort investigated was rather heterogeneous in that it included both medicated and unmedicated patients (Fitzgerald et al., 2011). In addition, two resting-state FC studies in pediatric drug-naïve OCD patients have also highlighted the presence of cingulate cortex FC alterations in this disorder (Gruner et al., 2014a; Weber et al., 2014a).

To date, no previous rs-fMRI study has directly compared FC changes in drug-naive pediatric patients with TS, TS+OCD, and OCD. The current study therefore aimed to investigate FC patterns in the above patient cohorts along with age-matched controls using an automated hypothesis-free approach, i.e. independent component analysis (ICA). This approach has the potential to add new relevant insights into the pathophysiology of TS and OCD by clarifying: i) whether drug-naive pediatric patients with TS, TS+OCD, and OCD differ in terms of FC in specific RSNs; ii) whether TS+OCD patients are characterized by overlapping or independent FC changes when compared to TS or OCD patients; and iii) whether FC changes correlate with clinical measures in each patient cohort. The developmental approach of our study might provide clinicians and researchers with relevant information. First, it may help to differentiate primary neural correlates of different symptom dimensions, thereby detailing the pathophysiological relationship between two highly comorbid disorders. Second, it may pave the way for longitudinal studies to further analyze FC changes over time, in order to evaluate the modulations related to disease course severity and treatment.

3.2 METHODS

3.2.1 Participants

From a consecutive series of 70 children, a group of 51 subjects were included in this study: 16 patients with TS (15 males, mean age: 9.7 ± 2.1), 14 with TS+OCD (10 males, mean age: 10.2 ± 2.1), 10 with OCD (7 males, mean age: 10.9 ± 2.5), and 11 children with episodic tension headache who were headache-free during the MRI scan (controls) (2 males, mean age: 9.9 ± 1.3 years). A total of 19 children were excluded due to head movement during the scan (n=10) or inability to complete the MRI exam (n=9). Of note, the total YGTSS scores of the excluded participants did not significantly differ from that of the included participants. All subjects were recruited from the child and adolescent neuropsychiatry outpatient clinic at the Department of Human Neurosciences, Sapienza University of Rome, Italy.

Inclusion criteria were as follows: a) drug naivety; b) not having received any behavioral treatment; c) right-handed (as assessed by the Edinburgh Handedness Inventory, Bryden, 1977); and d) having a normal cognitive profile (IQ≥70). Exclusion criteria were as follows: a) comorbidity with attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, schizophrenia, or developmental disabilities; or b) contraindications to MRI.

All subjects underwent a cognitive evaluation by means of the Wechsler Intelligence Scale for Children III (WISC-III) full scale. TS and OCD diagnoses were made according to DSM-5 criteria by a child neuropsychiatrist experienced in TS, OCD, and related comorbidities. The severity of tics and OCD symptoms was assessed using the Yale Global Tic Severity Scale (YGTSS) (symptom severity scale: max. 50, without impairment score) (J. F. Leckman et al., 1989) and Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) (Goodman et al., 1989) respectively. Patients with YGTSS scores above 14 typically seek medical treatment and this is also figures as a common inclusion criterion for clinical studies including, for instance, the ongoing clinical trial assessing the efficacy and of online delivered behavioral treatment for children and adolescents with tic disorders (ORBIT trial) (Hall et al., 2019).

The presence of other developmental disorders including ADHD or psychiatric disorders other than OCD was ruled out by means of the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL) parental interview administered to both parents. The anamnestic interview of all participants included items on family history. The parents or guardians of participants provided written informed consent. The study was approved by the institutional review board and conformed to the Declaration of Helsinki.

3.2.2 MRI acquisition

All subjects underwent a 3T MRI scan at Sapienza University of Rome, Italy. MRI was performed with the 3.0T MR scanner (Verio, Siemens AG, Erlangen, Germany) with a 12-channel head coil designed for parallel imaging (GRAPPA). A multiplanar T1-weighted localizer image with section orientation parallel to the subcallosal line was acquired at the start of each MRI examination. Noise reduction headphones were used for attenuation of scanner noise. MRI protocol included the following sequences: a) high-resolution 3D, T1-weighted (3DT1) MPRAGE: TR = 1900 ms; TE = 2.93 ms; flip angle = 9°; field of view [FOV] = 260 mm2; matrix = 256 × 256; 176 sagittal slices 1 mm thick; no gap; b) dual-turbo spin-echo, proton density (PD) and T2-weighted images: TR = 3320 ms; TE = 10/103 ms; FOV = 220 mm; matrix = 384 × 384; 25 axial slices 4 mm thick; 30% gap; c) rs-fMRI: repetition time [TR] = 3000 ms; echo time [TE] = 30 ms; flip angle = 89°, 64 × 64 matrix; 50 contiguous axial slices 3 mm thick; 140 volumes; acquisition time = 7 min. Before being positioned in the scanner, participants were instructed to lie down relaxed, awake, and with the eyes closed.

3.2.3 MRI data analysis

Images were analyzed using FMRIB Software Library (FSL) tools (http://www.fmrib.ox.ac.uk/fsl/fslwiki/FSL). Brain Extraction Toolbox (BET) FSL was used to skull strip three-dimensional T1-weighted structural images. Cortico-spinal fluid (CSF), grey matter (GM), and white matter (WM) segmentation masks were created via FAST (FMRIB's Automated Segmentation Tool). In order to minimize potential confounders introduced by the differences in cortical thickness, surface area, and folding between children and adult brains, an age-specific template was generated via the CerebroMatic toolbox (Wilke et al., 2017), including age and gender as nuisance covariates.

The following pre-processing steps were administered via FSL FEAT (FMRI-Expert Analysis Tool) after discarding the first three volumes to maintain a steady-state rs-fMRI signal: a) head motion correction using MCFLIRT; b) slice time correction; c) spatial smoothing using a Gaussian kernel of 8 mm full width at half maximum (FWHM); e) high-pass filter with a threshold of 100 s. Furthermore, movements and artefacts were removed using ICA-AROMA (Automatic Removal of Motion Artifacts), which recognizes and removes motion-related independent components from rs-fMRI data (Pruim et al., 2015), out-regressing WM and CSF

time series, and filtering the resultant functional images, band-pass at [0.01-0.09] Hz. Individual denoised functional images were spatially registered with their respective 3D T1 images and then finally normalized into the customized T1 template space using FSL FLIRT (FMRIB's Linear Image Registration Tool, FLIRT) and FNIRT (FMRIB's Non-Linear Image Registration Tool), respectively. A multisession temporal concatenation approach in FSL-MELODIC (Beckmann et al., 2005) was implemented, which decomposed the data into 30 independent components.

Statistical analysis

Kruskal-Wallis test and post-hoc Mann Whitney U test were performed to investigate between-group differences with respect to age. Chi-square test was also used to check for gender distribution between groups. Differences between TS, TS+OCD, and OCD with respect to clinical scores were analyzed with Mann-Whitney U test. Analyses were performed with SPSS (Statistical Package for the Social Sciences).

Using FSL Randomise (5000 permutations), non-parametric statistics were performed to investigate FC differences between pairs of groups (unpaired two-sample t-test two-tailed, alpha = 0.05) and to compute correlations between FC and clinical scores in patients. Randomise is a non-parametric permutation algorithm which enables modelling and inference using a standard GLM design setup (Winkler et al., 2014). Age and gender were included as nuisance variables. In each RSN, correlation analysis was performed between FC and clinical scores via a general linear model compensating for age and gender. Statistical significance was set at $p<0.05$, FDR corrected for multiple comparisons. Demographic and clinical data of participants are summarized in Table 1.

3.3 RESULTS

Kruskal-Wallis test revealed that, TS, TS+OCD, OCD, and controls did not statistically differ in terms of age ($H(3) = 2.575$, $p= 0.46$). Chi-square test revealed uneven gender distribution between TS patients and controls ($\chi2 [1, N = 27] = 15.9$, $p <0.001$) and between OCD patients and controls ($\chi2 [1, N = 21] = 48.9$, $p<0.001$). There were significant differences in clinical measures between the TS, TS+OCD, and OCD groups. Post-hoc Mann-Whitney U test

revealed that YGTSS scores were higher in the TS (U =1.0, p <0.001) and TS+OCD (U =1.0, p <0.001) groups than the OCD group. In addition, as expected, OCD patients had higher CYBOCS scores than TS patients (U =0, p <0.001). Moreover, we found significant differences in the CYBOCS scores of TS and TS+OCD patients (U = 0, p < 0.001) **(Table 1).**

Table 1: Demographic variables and clinical characteristics.

Variables	**TS** (n = 16)	**TS+OCD** (n = 14)	**OCD** (n = 10)	**Ctrl** (n = 11)	**TS vs Ctrl**	**TS vs OCD**	**TS+OCD vs Ctrl**	**TS+OCD vs OCD**	**TS vs TS+OCD**	**OCD vs Ctrl**
*Age (years)	9.7 ± 2.1	10.2 ± 2.1	10.9 2.5	9.9 1.3	p = 0.30	p = 0.18	p= 0.43	p =0.46	p =0.44	p =0.31
**Male /Female	15/1	10/4	7/3	2/9	p < **0.001**	p=0.10	**p = .008**	p= 0.94	p= 0.10	p< **0.001**
***YGTSS score (0-50)	17.5 6.7	18.1 10.8	0.8 1.7	-	-	p **<0.001**	-	p**< 0.001**	p = 0.72	-
***CYBOCS score (0-40)	0.25 0.7	16.4 6.1	18.6 7.5	-	-	p **<0 .001**	-	p = 0.62	p **< 0.001**	-

Data are expressed as mean (*M*); standard deviation (*SD*),

YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale-Brown Obsessive-Compulsive Scale
OCD: Obsessive Compulsive Disorder
TS: Tourette syndrome without Obsessive Compulsive Disorder symptoms.
TS+OCD: Tourette syndrome with Obsessive Compulsive Disorder symptoms.
Ctrl: controls.
*Age difference were assessed via Mann Whitney (*U*) test.
** Gender differences were assessed via chi square ($\chi 2$) test.
*** Mann Whitney (*U*) test was used to evaluate differences in patient cohort with respect to clinical scores.
Tic severity was evaluated by summing the motor and phonetic tics (without impairment scores) as per the YGTSS guidelines.
Significant *p* values are highlighted in bold font ($p<0.05$)

Functional connectivity changes

ICA decomposed the data into 30 spatial components. The neuroanatomically-relevant RSNs (i.e. representing brain activity after the removal of physiological and non-physiological noise,

e.g. respiratory, vascular, and motion artefacts) were identified by visually matching them against a previously published dataset of 20 canonical RSNs (Smith et al., 2009). Seven RSNs that were found to be impaired either in TS or in OCD in previous studies(Y. Cui et al., 2014b; Gruner et al., 2014b; Liu et al., 2017b; Weber et al., 2014a) were selected for further analysis. These RSNs included the basal ganglia (BGN), cerebellum (CBN), frontoparietal (FPN), default-mode (DMN), orbitofrontal (OBF), salience (SAN), and sensorimotor (SMN) networks. Dual regression was applied to regress the group ICA maps to subject-specific spatial maps.TS patients exhibited higher FC than controls in four RSNs: the BGN (right thalamus and left putamen), SMN (bilateral precentral gyrus), CBN (right Crus I), and DMN (right precuneus and left frontal medial cortex). They also showed lower FC than controls in two RSNs: the FPN (right middle frontal and superior parietal gyrus) and SAN (right insula, right superior temporal gyrus) **(Fig. 1)**. TS+OCD patients exhibited an FC pattern very similar to TS patients **(Fig. 2).** Therefore, we merged the two subgroups of TS patients into a single group (TS/TS+OCD) for further analyses **(Fig. 3).** When considering TS and TS+OCD as one group (TS/TS+OCD), FC was still higher in the aforementioned four RSNs and lower in the remaining two RSNs than controls.

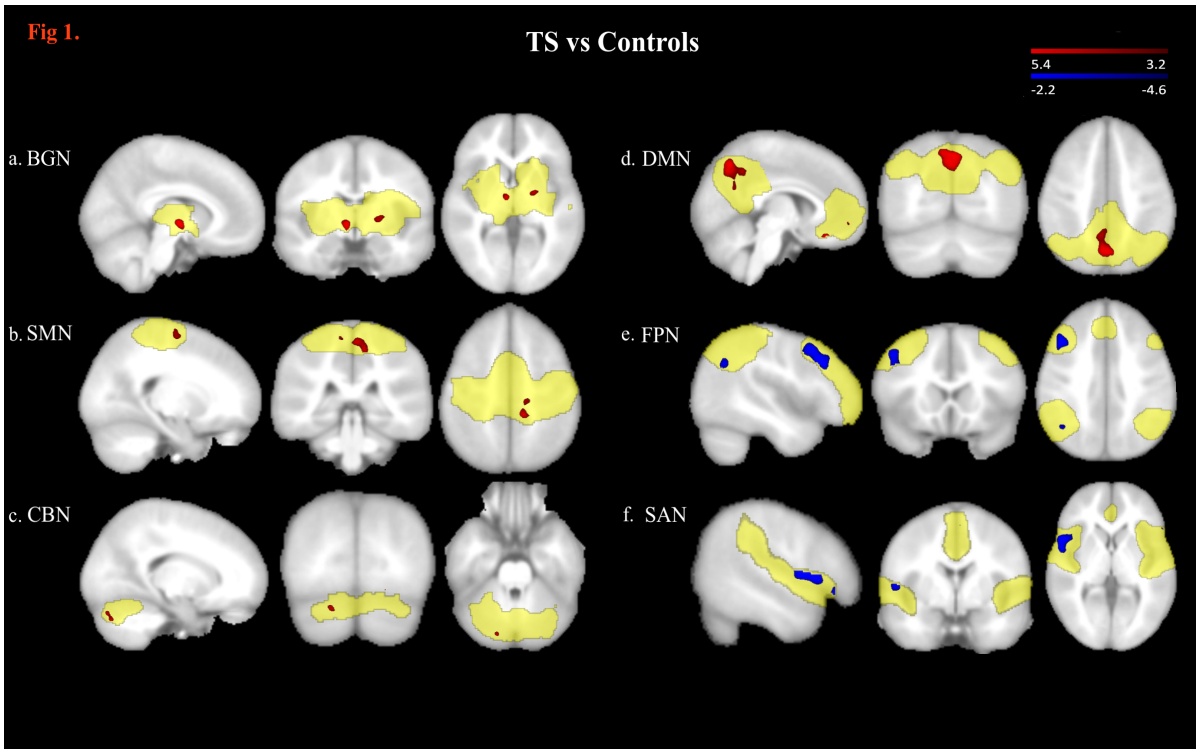


Fig 1. Significant differences in functional connectivity (FC) in six resting state net- works (RSNs) between patients with Tour- ette syndrome without any comorbidity (TS) and controls:

Within each RSN, areas of increased FC are shown in red, areas of decreased FC in blue. Red and blue bars represent t values. The binarized masks in yellow represent the six RSNs. Compared with controls, TS patients showed increased FC in four RSNs: a) BGN (Basal ganglia network): right thalamus, left putamen. b) SMN (Sensorimotor network): bilateral precentral gyrus c) CBN (Cerebellar network): right Crus I and d) DMN (Default mode network): right precuneus and left medial frontal cortex), and decreased FC in two RSNs e) FPN (Frontoparietal network): right middle frontal gyrus, and right superior parietal gyrus and f) SAN (Salience network): right insula (right superior tem- poral gyrus). Results were FDR corrected ($p < 0.05$) for multiple comparisons.

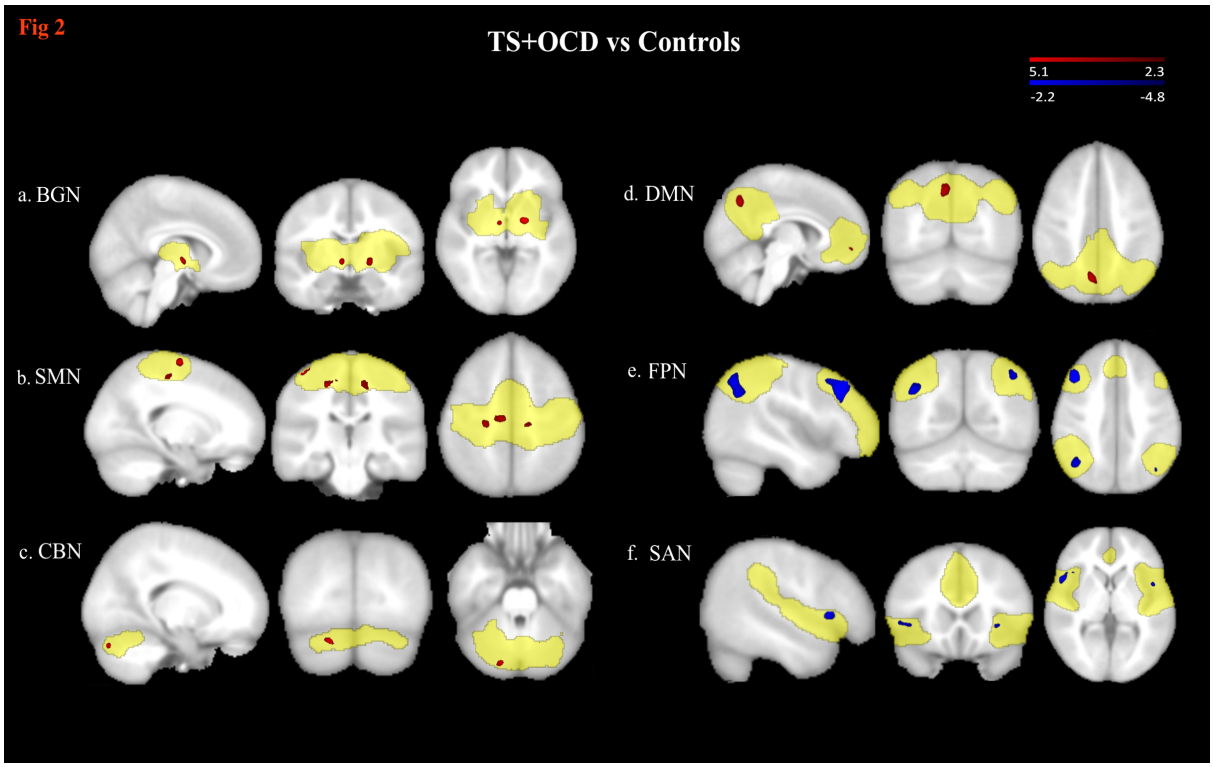


Fig 2. Significant differences in functional connectivity (FC) in six resting state net- works (RSNs) between patients with Tour- ette syndrome with comorbidity (TSþOCD) and controls:

Within each RSN, areas of increased FC are shown in red, areas of decreased FC in blue. Red and blue bars represent t values. The binarized masks in yellow represent the six RSNs. Compared with controls, TSþOCD patients showed increased FC in four RSNs: a) BGN (Basal ganglia network**):** right thal- amus, left putamen. b) SMN (Sensorimotor network): right supplementary motor area and bilateral precentral gyrus c) CBN (Cerebellar network): right Crus I and d) DMN (Default mode network): right pre- cuneus and left medial frontal cortex, while decreased functional connectivity was observed in two RSNs e) FPN (Frontoparietal network): right superior parietal lobule, left angular gyrus and right middle frontal gyrus f) SAN (Salience network): bilateral insula (left planum polare and right superior tem- poral gyrus). Results were FDR corrected ($p < 0.05$) for multiple comparisons.

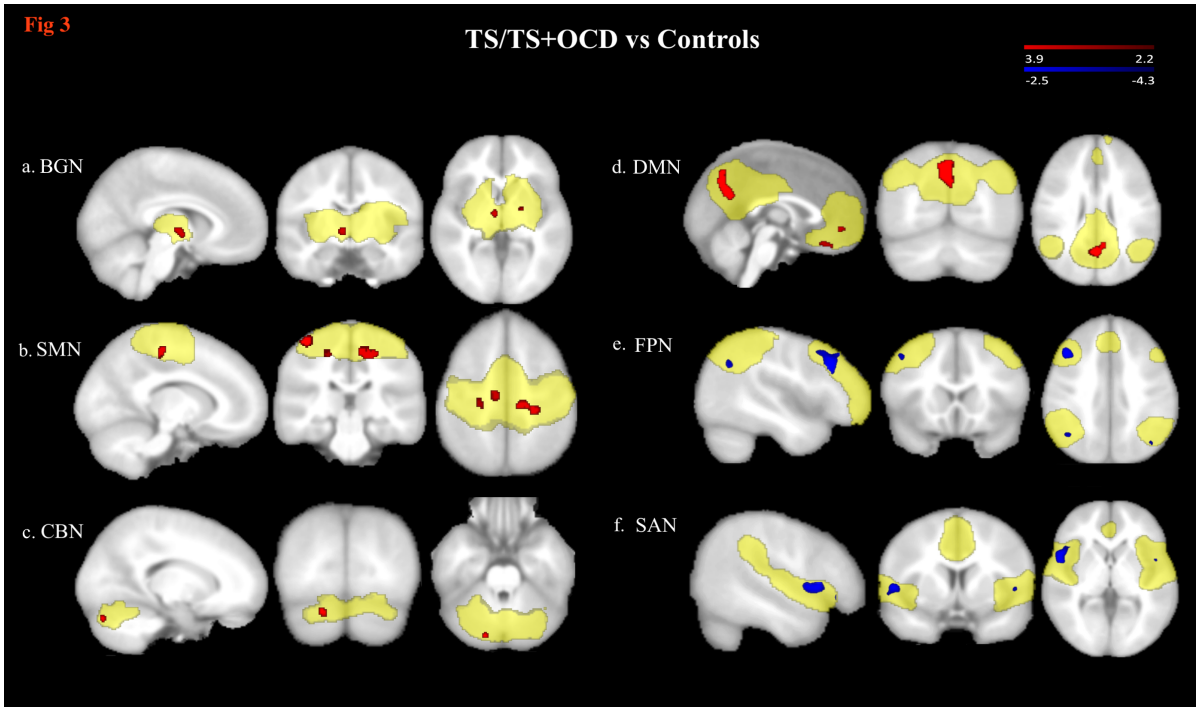


Fig 3. Significant differences in functional connectivity (FC) in six resting state net- works (RSNs) between Tourette syndrome with and without comorbidity (TS/ TSþOCD) and controls:

Within each RSN, areas of increased FC are shown in red, areas of decreased FC in blue. Red and blue bars represent t values. The binarized masks in yellow represent the six RSNs. Compared with controls, (TS/ TSþOCD) showed increased functional con- nectivity in four RSNs: a) BGN (Basal ganglia network): right thalamus, left putamen. b) SMN (Sensorimotor network): right supple- mentary motor area and bilateral precentral gyrus c) CBN (Cerebellar network): right Crus I and d) DMN (Default mode network): right precuneus and left medial frontal cor- tex, while decreased functional connectivity was observed in two RSN e) FPN (Fronto- parietal network): right middle frontal gyrus, and right superior parietal and left angular gyrus and f) SAN (Salience network): bilateral insula(left planum polare and right superior temporal gyrus). Results were FDR corrected ($p < 0.05$) for multiple comparisons.

OCD patients showed functional abnormalities in the same six RSNs, but in contrast to both TS and TS+OCD patients, all RSNs showed higher FC than controls. Higher FC was observed in the BGN (bilateral thalamus and left palladium), SMN (right SMA and left precentral gyrus), CBN (bilateral Crus I and left lobule VI), DMN (right precuneus and left frontal medial cortex), FPN (right middle frontal gyrus, bilateral superior parietal lobule), and SAN (anterior cingulate gyrus and left insula-planum polare) **(Fig.4).** One of the seven RSNs considered, the OFN,

showed no FC differences between groups. Brain regions exhibiting altered FC between TS, TS+OCD, TS/TS+OCD and OCD with respect to controls are depicted in **(Table 2).**

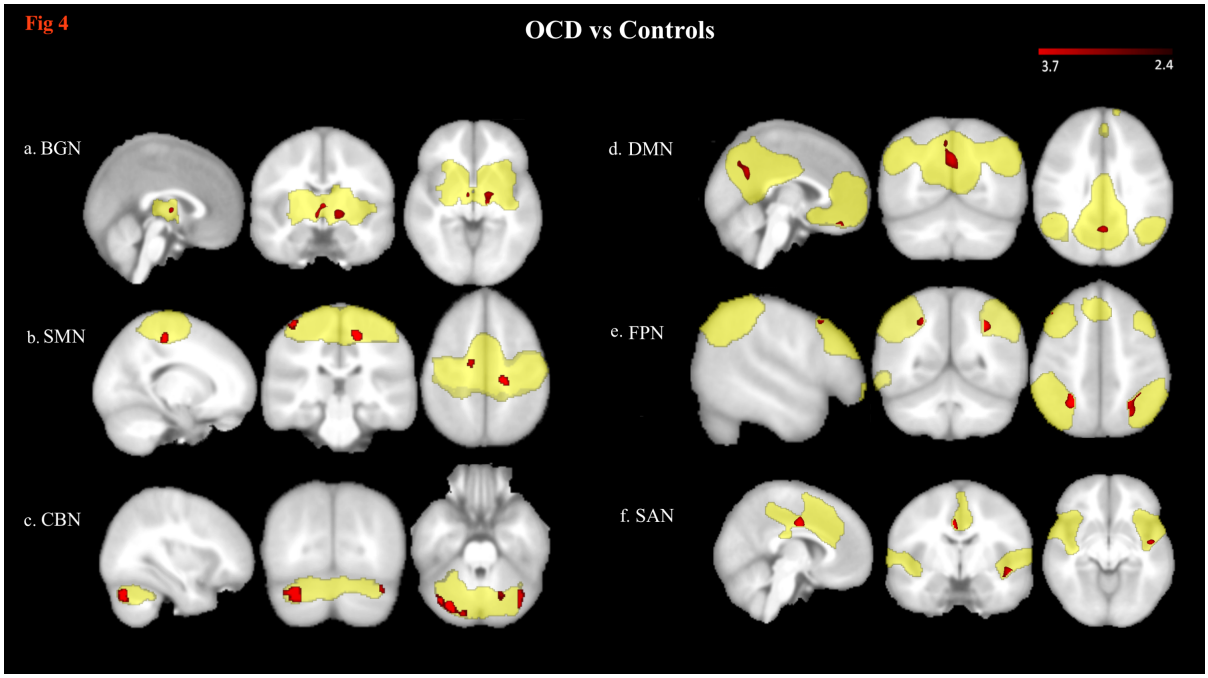


Fig 4. Significant differences in functional connectivity (FC) in six resting state net- works (RSNs) between Obsessive compulsive disorder patients (OCD) and controls: Within each RSN, areas of increased FC are shown in red, areas of decreased FC in blue. Red and blue bars represent t values. The binarized masks in yellow represent the six RSNs. Compared with controls, OCD patients showed increased functional connectivity in five RSNs: a) BGN (Basal ganglia network)**:** bilateral thalamus, left putamen. b) SMN (Sensorimotor network): right supplemen- tary motor area and left precentral gyrus c) CBN (Cerebellar network): bilateral Crus I and left lobule VI), d) DMN (Default mode network): right precuneus and left medial frontal cortex, and e) FPN (Frontoparietal network) : right middle frontal gyrus, bilat- eral superior parietal cortex, f) SAN (Salience network): Anterior cingulate gyrus and left insula(Planum polare). Results were FDR corrected ($p < 0.05$) for multiple comparisons.

Table 2: Altered resting state functional connectivity (rs-FC) between all groups.

Networks	F/(p-value)	Two sample t-test						
		TS vs Ctrl	**TS+OCD vs Ctrl**	**TS/TS+OCD vs Ctrl**	**OCD vs Ctrl**	**OCD vs TS**	**OCD vs TS+OCD**	**OCD vs TS/TS+OCD**
		Brain area Cluster size MNI coord T/p-value	Brain area Cluster size MNI coord T/p-value	Brain area Cluster size MNI coord T/p-value	Brain area Cluster size MNI coord T/p-value	Brain area Cluster size MNI coord T/p-value	Brain area Cluster size MNI coord T/p-value	Brain area Cluster size MNI coord T/p-value
BGN	**2.74 /(0.003)**	**TS > Ctrl**	**TS+OCD > Ctrl**	**TS/TS+OCD vs Ctrl**	**OCD > Ctrl**	**OCD > TS**	**OCD > TS+OCD**	**OCD > TS/TS+OCD**
		R. thalamus 161 55 78 47 2.51/0.001 L. putamen 73 74 81 51 2.45/0.006	R. thalamus 34 55 79 47 2.36/0.008 L. putamen 194 73 82 47 2.28/0.003	R. thalamus 84 54 78 59 2.20/0.005 L. putamen 37 73 81 50 2.19/0.013	Bilateral thalamus 106 60 79 53 2.29/0.007 L. putamen 254 70 74 48 2.30/0.007			
SMN	**2.34/0.009**	**TS > Ctrl**	**TS+OCD > Ctrl**	**TS/TS+OCD > Ctrl**	**OCD > Ctrl**	**OCD > TS**	**OCD > TS+OCD**	**OCD > TS/TS+OCD**
		R. precentral gyrus 165 67 60 84 2.05/0.013	R. precentral gyrus 97 48 76 94 2.09/0.008	R. precentral gyrus 42 45 67 83 2.33/0.007	R. supplementary motor 570 58 80 79 2.14/< 0.001			
		L. precentral gyrus 60 47 77 92 2.03/0.026	L. precentral gyrus 27 71 67 81 2.08/0.027 R. supplementary motor 652 59 82 75 2.04/0.002	L. precentral gyrus 208 75 65 82 2.36/0.003 R. supplementary motor 74 53 72 86 2.34/0.006	L. precentral gyrus 492 65 58 84 2.12/0.001			
CBN	**1.95/0.003**	**TS > Ctrl**	**TS+OCD > Ctrl**	**TS/TS+OCD > Ctrl**	**OCD > Ctrl**	**OCD > TS**	**OCD > TS+OCD**	**OCD > TS/TS+OCD**
		R. crus I 54 32 42 27 1.97/0.001	R. crus I 39 48 32 29 1.95/0.016	R. crus I 37 48 31 30 2.32/0.005	R. crus I 195 43 33 26 2.27/0.009 L. crus I 115 85 39 30 2.26/< 0.001 L. lobule VI 165 82 44 31 2.27/< 0.001	R. crus I 340 36 34 41 2.70/< 0.001 L. crus II 312 63 31 32 2.72/< 0.001 L. lobule VI 26 74 41 29 2.68/0.005	R. crus I 427 39 35 25 2.60/0.001 L. lobule VI 205 81 45 30 2.62/< 0.001	R. crus I 490 36 36 26 2.81/< 0.001 L. crus I 46 83 45 31 2.71/0.002 L. crus II 137 60 31 34 2.74/0.006 R. lobule VI 79 56 44 33 2.72/0.007
DMN	**2.47/0.005**	**TS > Ctrl**	**TS+OCD > Ctrl**	**TS/TS+OCD > Ctrl**	**OCD > Ctrl**	**OCD > TS**	**OCD > TS+OCD**	**OCD > TS/TS+OCD**
		R. precuneus 1418 61 40 81 2.44/0.001 L. medial frontal cortex 41 63 111 34 2.43/0.009	R. precuneus 128 55 40 77 2.27/0.014 L. medial frontal cortex 63 52 118 44 2.22/0.008	R. precuneus 820 66 48 62 2.29/0.003 L. medial frontal cortex 104 63 115 44 2.35/0.002	R. precuneus 622 60 45 68 2.34/0.003 L. medial frontal cortex 80 66 109 35 2.47/0.003			
FPN	**2.84/0.003**	**TS < Ctrl**	**TS+OCD < Ctrl**	**TS/TS+OCD < Ctrl**	**OCD > Ctrl**	**OCD > TS**	**OCD > TS+OCD**	**OCD > TS/TS+OCD**
		R. middle frontal gyrus 459 30 101 70 -2.64/< 0.001 R. superior parietal 60 31 43 70 -2.57/0.004	R. middle frontal gyrus 609 31 101 72 -2.63/< 0.001 R. superior parietal 434 29 41 77 -2.48/0.004 L. angular gyrus 436 90 38 82 -2.49/< 0.001	R. middle frontal gyrus 594 30 100 70 -2.51/< 0.001 R. superior parietal 83 31 43 72 -2.32/0.011 L. angular gyrus 57 87 38 74 -2.30/0.021	R. middle frontal gyrus 26 23 95 76 2.93/0.001 R. superior parietal 195 43 52 77 3.15/< 0.001 L. superior parietal 178 78 47 75 3.07/< 0.001	R. middle frontal gyrus 412 28 91 75 2.27/< 0.001 R. superior parietal 54 43 52 79 2.14/0.008 L. superior parietal 51 77 47 79 2.13/0.006	R. middle frontal gyrus 38 31 89 76 2.19/0.015 R. superior parietal 390 43 52 78 2.20/< 0.001 L. angular gyrus 421 90 37 76 2.12/0.004	R. middle frontal gyrus 274 28 103 78 2.24/0.001 R. superior parietal 265 42 53 80 2.23/0.001 L. angular gyrus 61 91 47 80 2.20/0.017
SAN	**2.96/< 0.001**	**TS < Ctrl**	**TS+OCD < Ctrl**	**TS/TS+OCD < Ctrl**	**OCD > Ctrl**	**OCD > TS**	**OCD > TS+OCD**	**OCD > TS/TS+OCD**

R. insula	R. insula	R. insula	Anterior cingulate gyrus
675	259	820	126
23 86 51	24 93 50	24 90 49	55 77 75
-2.81/< 0.001	-2.26/0.002	-2.32/0.001	2.84/< 0.001
	L. insula	L. insula	L. insula
	175	51	94
	85 106 48	92 88 49	91 81 42
	-2.23/0.003	-2.20/0.008	2.81/0.005

Table 2: The above table shows brain regions with abnormal rs-FC between all 4 groups: TS: Tourette syndrome patients without comorbidity, TS+OCD: Tourette syndrome patients with Obsessive compulsive disorder comorbidity, TS/TS+OCD: Tourette syndrome patients with and without comorbidity, OCD: Obsessive compulsive disorder patients and controls (FDR corrected for multiple comparisons, $p < 0.05$). Cluster size and coordinates are extracted from Harvard-Oxford cortical, sub-cortical structural Atlas and Cerebellar Atlas in MNI152 space along with T and p values.

The direct comparison between OCD and TS subgroups showed significant and consistent differences in two RSNs, the CBN and FPN. OCD patients exhibited higher FC in the CBN (right Crus I, left Crus II, and left lobule VI) and FPN (right middle frontal gyrus and bilateral superior parietal lobule) than TS patients **(Fig. 5a).** Similarly, OCD patients exhibited higher FC in the CBN and FPN than TS+OCD patients **(Fig. 5b).** Lastly, when directly comparing OCD patients with the TS/TS+OCD group, FC was higher in those RSNs **(Fig. 5c).** Brain regions exhibiting altered FC between patient groups i.e., TS, TS+OCD, TS/TS+OCD with respect to OCD patients are depicted in **(Table 2).**

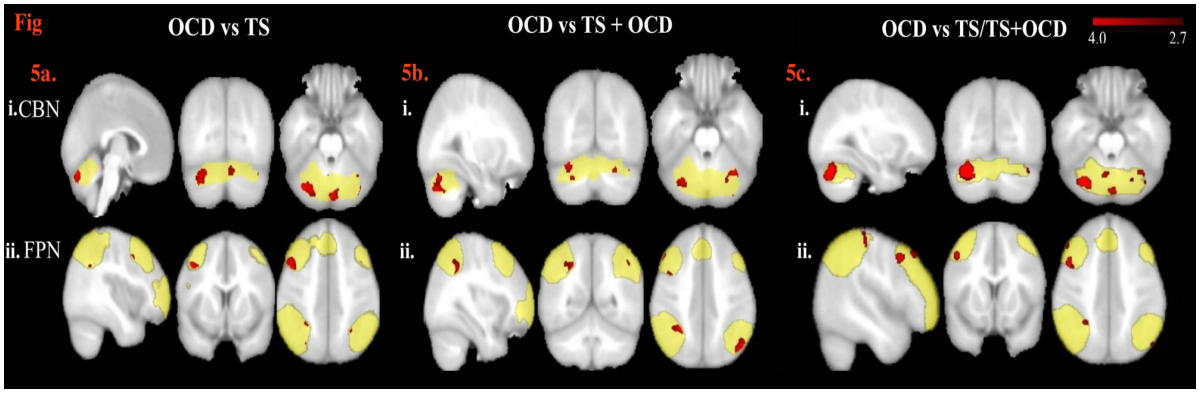


Fig 5. Significant differences in functional connectivity (FC) among patient cohorts: a. Obsessive compulsive disorder (OCD) vs Tourette syndrome without any comorbidity (TS): Compared with TS, OCD patients showed increased FC in two RSNs: i) CBN (Cerebellar network): right Crus I, left Crus II and left Crus VI and ii) FPN (Frontoparietal network): right middle frontal gyrus, and bilateral superior parietal. b**.** Obsessive compulsive disorder (OCD) vs Tourette syn- drome with comorbidity (TSþOCD): Compared with TSþOCD, OCD patients showed increased FC in two RSNs: i) CBN (Cerebellar network): right Crus I and left Crus VI

and ii) FPN (Frontoparietal network): right middle frontal gyrus, right superior parietal lobule and left angular gyrus. c**.** Obsessive compulsive disorder (OCD) vs Tourette syndrome with and without co- morbidity (TS/TSþOCD): Compared with whole TS group(TS/TSþOCD), OCD patients showed increased FC in two RSNs: i) CBN (Cerebellar network): bilateral Crus I, left Crus II and right Crus VI and ii) FPN (Fron- toparietal network): right middle frontal gyrus, right superior parietal lobule and left angular gyrus). Within each RSNs illustrated in yellow, areas of increased FC are shown in red. Positive t values are represented by red bars and the results are FDR corrected ($p < 0.05$) for multiple comparisons.

Table 3. Correlation between altered rs-FC in (TS/TS+OCD) and OCD patients with respect to clinical scores

Brain regions (TS/TS+OCD) vs YGTSS	Cluster size (voxels)	MNI coordinates			t value
		x	y	z	
Right Crus I	31	40	37	34	-1.80
Right middle frontal gyrus	352	37	90	82	-2.13

Brain regions OCD vs CYBOCS	Cluster size (voxels)	MNI coordinates			t value
		x	y	z	
Right Crus I	36	39	39	22	2.07
Right middle frontal gyrus	49	27	111	56	1.36

The above table shows brain regions with abnormal resting state functional connectivity (rs-FC) in patients with (TS/TS+OCD) and OCD when correlated with YGTSS and CYBOCS scores respectively. (FDR corrected, $p < 0.005$) for multiple comparisons. Cluster size and coordinates are extracted from Harvard-Oxford cortical, sub-cortical structural Atlas and Cerebellar Atlas in MNI152 space along with T and p values.

TS/TS+OCD: Tourette syndrome patients without comorbidity + Tourette syndrome patients with OCD comorbidity, OCD: Obsessive compulsive disorder, YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale-Brown Obsessive-Compulsive Scale.

Correlations between FC and clinical scores

FC within two RSNs, the CBN and FPN, negatively correlated with YGTSS scores in the TS/TS+OCD group, whereas FC positively correlated with CYBOCS in OCD patients **(Fig. 6)**. In addition, the TS/TS+OCD group showed a positive correlation of BGN and DMN FC

with YGTSS **(Supplementary material 1 and 2).** When TS and TS+OCD patients were analyzed separately, the positive correlation between BGN FC and YGTSS remained significant in both groups, whereas the negative correlation between CBN FC and YGTSS remained significant only in TS patients and the negative correlation between FPN FC and YGTSS remained significant only in TS+OCD patients. Of note, no significant correlation was observed between FC within any RSN and CYBOCS scores in TS+OCD patients. FC correlations with TS, TS+OCD, and OCD patient's clinical scores are reported in **Table 4**.

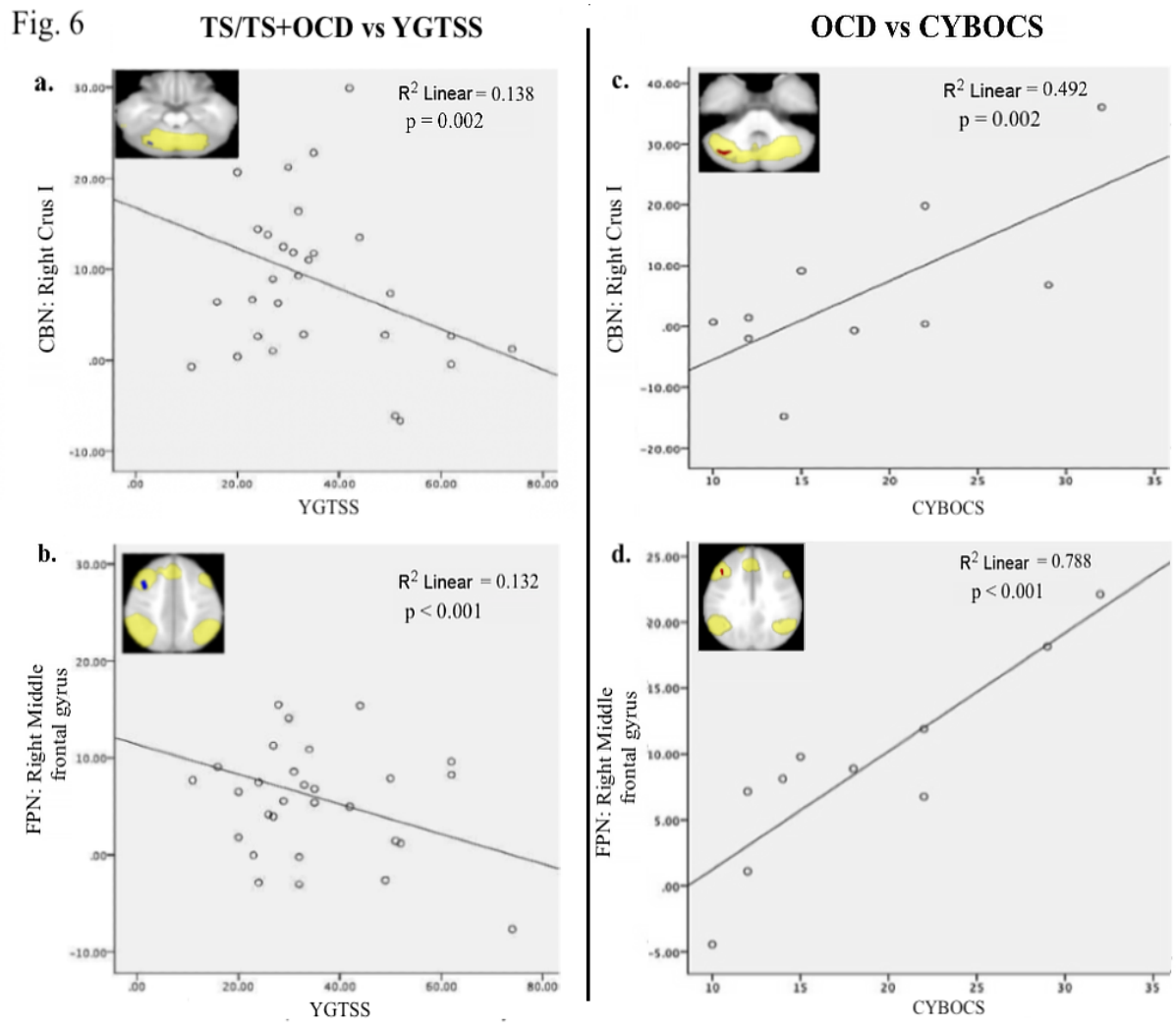
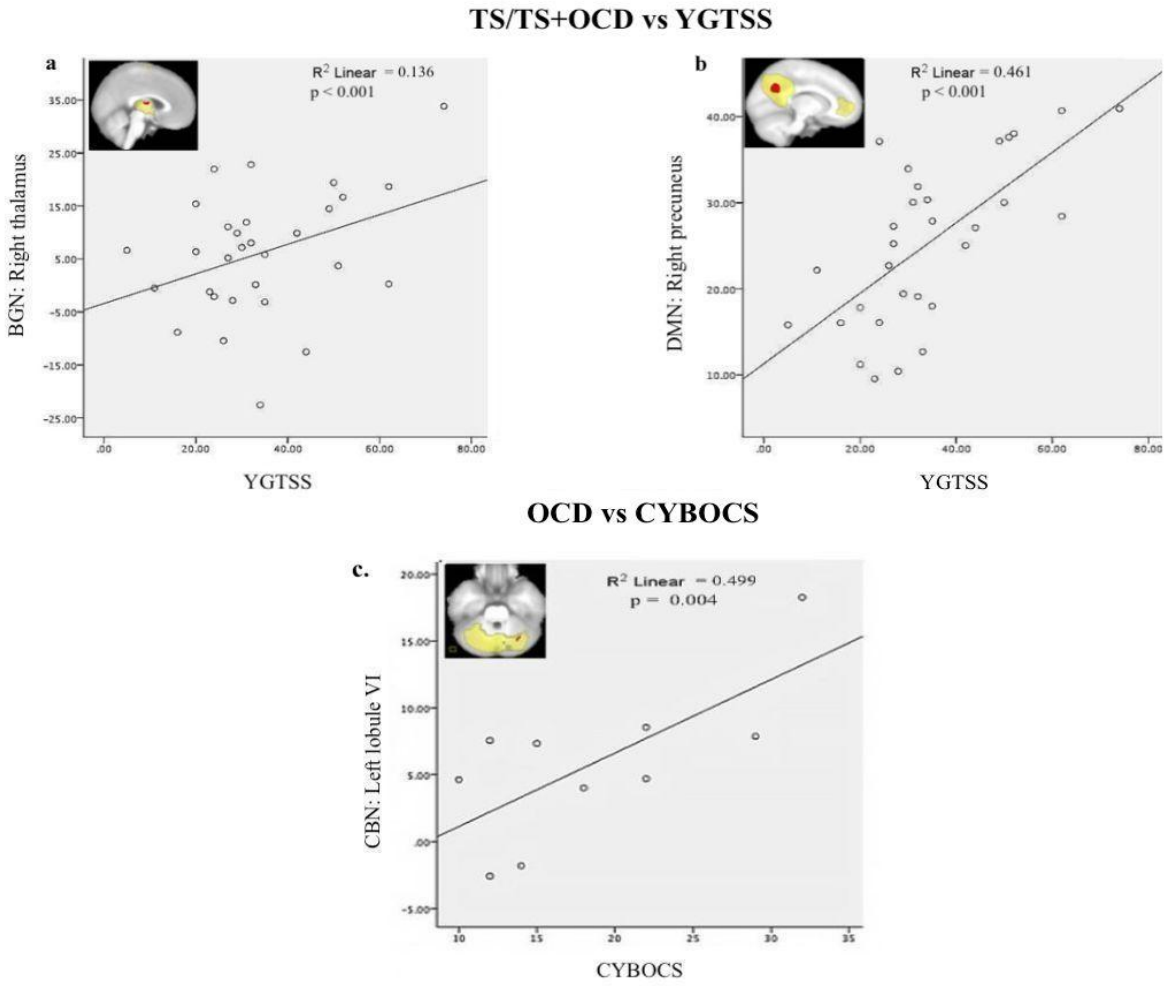


Fig 6. Scatterplots show correlations between altered functional connectivity (FC) and clinical scores: YGTSS (Yale global tic severity scale) and CYBOCS (Children's Yale-Brown Obsessive-Compulsive Scale). In Tourette syndrome with and without comorbidity (TS/TSþOCD), a negative correlation was found between FC in the cerebellar network (CBN, right crus I) (a) and frontoparietal network (FPN, right middle frontal gyrus) (b) and tic severity(YGTSS). In OCD patients, a positive correlation was found between FC in the cerebellar network (CBN, right crus I) (c) and frontoparietal network (FPN, right middle frontal

gyrus) (d) and severity of obsessive-compulsive symptoms, as indicated by CYBOCS scores. Correlation analysis was performed between significant FC differences and clinical scores using a non-parametric test (FSL randomise, 5000 permutations) via a general linear model compensating for age and gender. Results were FDR corrected ($p < 0.05$) for multiple comparisons.

Supplement 1: Correlation b/w altered rs-FC and clinical scores



Scatterplots show correlations between altered functional connectivity (FC) and clinical scores: YGTSS (Yale global tic severity scale) and CYBOCS (Children's Yale-Brown Obsessive-Compulsive Scale). In Tourette syndrome with and without comorbidity (TS/TS+OCD), a positive correlation was found between FC in the basal ganglia network (BGN, right thalamus) (a) and default mode network (DMN, right precuneus) (b) and tic severity, as indicated by YGTSS scores. In OCD patients, a positive correlation was found between FC in the cerebellar network (CBN, left lobule VI) (c) and severity of obsessive-compulsive symptoms, as indicated by CYBOCS scores. Correlation analysis was performed between significant FC differences and clinical scores using a non-parametric test (FSL randomise, 5000 permutations) via a general linear model compensating for age and gender. Results were FDR corrected ($p < 0.05$) for multiple comparisons.

Supplement 2: Correlation between altered within-network rsFC in (TS/TS+OCD) and OCD patients with respect to their clinical measures.

Brain regions	Cluster size (voxels)	MNI coordinates			T/p- value
(TS/TS+OCD) vs YGTSS		x	y	z	
Right Thalamus	258	59	77	55	2.61/<0.001
Right Precuneus	512	51	43	68	1.16/<0.001

Brain regions	Cluster size (voxels)	MNI coordinates			T/p- value
OCD vs CYBOCS		x	y	z	
Left VI	29	78	38	29	1.35/0.004

The above table shows brain regions with abnormal resting state functional connectivity (rsFC) in patients with (TS/TS+OCD) and OCD when correlated with YGTSS and CYBOCS scores respectively. (FDR corrected, $p < 0.005$) for multiple comparisons. Cluster size and coordinates are extracted from Harvard-Oxford cortical, sub-cortical structural Atlas and Cerebellar Atlas in MNI152 space.

TS/TS+OCD: Tourette syndrome patients without comorbidity + Tourette syndrome patients with

OCD comorbidity, OCD: Obsessive compulsive disorder, YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale-Brown Obsessive-Compulsive Scale.

3.4 DISCUSSION

To the best of our knowledge, this is the first study comparing FC alterations between drug-naïve children with TS, TS+OCD, OCD, and matched controls. To overcome possible confounding, we carefully selected a cohort of children without any comorbid disorders known to be associated with these conditions, e.g., ADHD. Moreover, the pediatric and drug-naïve nature of our cohort allowed us to minimize confounding factors such as age, disease duration, and chronic pharmacological treatment.

In the present study, children with TS and TS+OCD exhibited the same pattern of increased FC in four RSNs (the BGN, SMN, CBN, and DMN) and decreased FC in two RSNs (the FPN

and SAN), when compared to controls. With respect to controls, OCD patients showed FC alterations in the same six RSNs as TS and TS+OCD patients, though they had higher FC in all six RSNs. OCD patients had higher FC in two RSNs, CBN and FPN, as compared to TS and TS+OCD patients both separately and as one TS/TS+OCD group. When exploring the relationship between CBN and FPN FC and clinical scores, we found that FC in both the CBN and FPN negatively correlated with YGTSS scores in TS and positively correlated with CYBOCS scores in OCD.

FC changes in TS, TS+OCD, and OCD

BGN and SMN. FC within the BGN and SMN was increased in the TS, TS+OCD, and OCD groups with respect to age-matched controls. Increased FC in the thalamus, lentiform nucleus, SMA, and primary motor cortex supports the traditional model of cortico-striato-thalamo-cortical (CSTC) motor loop disruption in TS, which is considered a hallmark of TS pathophysiology (Albin & Mink, 2006; James F. Leckman, 2002; Suppa et al., 2011, 2014). These findings are consistent with previous rs-fMRI studies in TS that have reported a central involvement of the BGN in tic pathophysiology, both in children (Y. Cui et al., 2014a) and adults (Ramkiran et al., 2019; Wang et al., 2011). In keeping with this evidence, the positive correlation of the right thalamus with YGTSS scores indicates that higher BGN connectivity is associated with greater tic severity. Also, our findings strengthen the role of basal ganglia and sensorimotor cortical dysfunction in OCD, in that increased FC in the BGN and SMN was observed in this cohort. This is consistent with previous studies (Armstrong et al., 2016; Calzà et al., 2019; Fitzgerald et al., 2011; Sakai et al., 2011) and has been linked to processes of altered action monitoring and error detection in OCD (Bonini et al., 2014; Maltby et al., 2005; Stern et al., 2011a).

CBN. We found increased FC in the right Crus I in TS. Cerebellar involvement in TS has been reported in clinical, neurophysiological, and neuroimaging studies (Bohlhalter, 2006; Ramkiran et al., 2019; Sigurdsson et al., 2020; Tobe et al., 2010). One such rs-fMRI study in children with TS reported decreased regional homogeneity within the right cerebellum (Liu et al., 2017a), while another study investigating whole brain functional network topology in TS reported reduced cerebellar-cortical connectivity (Ramkiran et al., 2019). Differences in patient clinical features or in the methodological approach used (ICA vs. a regional homogeneity method or graph theory analysis) may account for inconsistencies between studies. Moreover,

while we did not find generalized cerebellar functional abnormality, we did find specific topographic involvement of Crus I, an area involved in higher cognitive functions and depending on connectivity with multimodal association cortices (Stoodley, 2012; Voogd, 2014), thereby suggesting the involvement of the cognitive cerebellum in TS and TS+OCD. Increased FC in the cognitive cerebellum (Crus I and lobule VI within the CBN) was also observed in OCD patients, consistent with previous rs-fMRI studies (Anticevic et al., 2014a; Ping et al., 2013). Overall, the present study provides evidence of the cerebellum's role in the pathophysiology of both TS and OCD. Cerebellar involvement, however, differs between the two disorders in terms of both synchronization level and its relationship with clinical severity, as discussed below.

DMN. Within the DMN, we found increased FC in the precuneus and left medial prefrontal cortex (mPFC) both in TS and OCD. The DMN has been found to be disrupted in a wide range of neuropsychiatric disorders and has been implicated in processes related to mind-wandering or task-independent thoughts (Mason et al., 2007). Within this network, rs-fMRI abnormalities have been reported in both TS (S. Fan, Heuvel, et al., 2018) and OCD patients (J. Fan, Zhong, Gan, et al., 2017; Jang et al., 2010) with equivocal results. Of note, former studies in TS and OCD have particularly focused on between-network connectivity and pointed out increased connectivity between the DMN and other networks, particularly the FPN (J. Fan, Zhong, Gan, et al., 2017; Stern et al., 2012). The altered coupling between DMN and FPN has been variably interpreted either as a sign of the inability in OCD to disengage from internal thoughts when performing everyday tasks requiring attention to the outer environment (Stern et al., 2012) or as the attempt in TS to enhance monitoring of the outer world due to long-term struggling and coping with inappropriate acts (S. Fan, Heuvel, et al., 2018).

FPN. In the FPN, TS and OCD patients exhibited FC changes in opposite directions with decreased FC in TS and increased in OCD within the middle frontal gyrus and superior parietal cortex. In TS patients, decreased FC in the frontal and parietal cortices has already been reported in pediatric drug-naive patients (Buse et al., 2016; Church et al., 2009; Y. Cui et al., 2014b). The FPN is considered a core system underlining attention control (Ptak, 2012; Scolari et al., 2015) and sub-serving attentional gating, shifting and information retaining to perform rapid adaptive control tasks (Dosenbach et al., 2008). Given the involvement of such structures in adaptive action control (Zanto & Gazzaley, 2013), this finding may explain defective control over volitional actions observed in TS (Andrea E. Cavanna & Nani, 2013a)whereas in OCD it

may reflect an overactive cognitive control over behavior, as occurs in obsession-compulsion pairing (de Vries et al., 2019; Viard et al., 2005).

SAN. Similar to the FPN, brain areas in the SAN also showed opposite FC changes in TS and OCD, with decreased insular FC in TS and increased insular FC in OCD. The insula has been associated with social cognitive fitness, and decreased FC in TS consistent with previous studies (Liu et al., 2017a) may be in tune with evidence of an impairment in social cognition in these patients (Vicario & Martino, 2018). Moreover, the pathological role of the insula is supported by previous MRI studies showing structural and functional abnormalities in the insula related to premonitory urges (Jackson et al., 2020; Tinaz et al., 2015). Conversely, in OCD some areas of the SAN, namely the anterior cingulate gyrus and left insula, displayed increased FC, which is consistent with previous reports (J. Hou et al., 2012; Ping et al., 2013; T. Yang et al., 2010; T. Zhang et al., 2011). The functional involvement of the limbic system in OCD may underpin the heightened emotional processing linked to arousal and negative emotional states experienced by these patients (Stern et al., 2011b).

Resting-state fMRI differences between TS and OCD

Comparison between the three groups of patients showed that: i) children with TS and TS+OCD did not show any significant FC differences; ii) children with TS and TS+OCD significantly differed from those with OCD in two RSNs, the CBN and FPN.

Both TS and OCD patients showed increased FC in the CBN, though FC was significantly higher in OCD than in TS patients. Crucially, CBN FC changes were contrarily correlated to the clinical scales in the two disorders, i.e., negatively with YGTSS scores and positively with CY-BOCS scores. These correlations suggest a different functional role of FC changes in the two disorders. Since higher FC in the CBN was associated with lower tic severity in TS, CBN FC may reflect neuroplastic mechanisms seemingly involved in the modulation of tic expression. Conversely, the direct correlation between FC and OCD clinical severity suggests that increased cerebellar FC may represent an abnormal maladaptive mechanism of neuroplasticity possibly contributing to symptom severity. Thus, our findings point out the CBN as a relevant network in the pathophysiology of both TS and OCD, even if further research is needed to elucidate its precise interactions at a multi-network level and explain its role in the modulation of symptoms.

In addition, FPN FC showed opposite changes in that it decreased in TS patients and increased in OCD patients. In TS, decreased FPN connectivity may result in impaired cognitive control over volitional actions, provoking tics and tic-like compulsions. Conversely, in OCD increased FPN connectivity may reflect an overactive cognitive control over behavior, typically occurring in the obsession-compulsion pairing. Thus, the changes in FPN FC may be exploited as a neural marker to distinguish TS from OCD. Moreover, FPN FC negatively correlated with tic severity in TS, whereas it positively correlated with compulsive scores in OCD. Overall, correlation analysis suggests that FPN plays a different pathophysiological role in TS and OCD, i.e. physiological vs pathological as observed in the CBN. Although speculative at this stage, the different involvement of the FPN, thus of brain areas related to action monitoring and control, might provide an interesting argument to look at some phenomenological differences of the two disorders. Obsessive-compulsive symptoms in TS patients, as opposed to OCD patients, are mostly represented by non-cognitive repetitive phenomena, i.e. tic-like compulsions and other movement-related sensory events ("just right" and "just so" requirements). Conversely, in OCD compulsions are generally associated with underlying cognitive processes (i.e. an obsession) (Miguel et al., 1995, 2000), Moreover, some types of OC symptoms are more prevalent in patients with TS as compared to the broader OC phenomenology observed in OCD (Cath et al., 2001). It is possible to speculate that the decreased FPN connectivity observed in TS may result in impaired cognitive control over volitional actions, in that it is disrupted by tics and tic-like compulsions. Conversely, in OCD increased FPN connectivity may reflect an overactive cognitive control over behavior, typically occurring in the obsession-compulsion pairing.

3.5 LIMITATIONS

This study has few limitations that deserve emphasis. First, no online tic measurement was collected during rs-fMRI acquisition, thus possibly masking the exact neural underpinnings of TS. Second, gender distribution differences between patients and controls may have influenced results. However, since gender was included as a nuisance covariate in FC analysis, we assume that gender distribution likely did not influence our results. Third, our study cohorts consisted of only 51 patients and such a small sample size may make the study prone to Type II error in the findings. Moreover, previous pediatric studies (Y. Cui et al., 2014a; Liu et al., 2017b; Mirabella et al., 2020; Weber et al., 2014a) with small sample size were able to detect only

major effects and the studies might have succumbed to type-II error in the findings and hence the comprehensive interpretation of the results were affected. Fourth, we focused on FC changes by using the ICA approach, which allowed us to only investigate intrinsic activity within well-defined RSNs. Further investigation is needed to address these aspects.

3.6 CONCLUSION

The present study demonstrated FC differences between pediatric drug-naïve patients with TS and no comorbidity, TS+OCD, pure OCD, and matched controls. A novel finding of our study is that TS patients with and without OCD did not exhibit significant FC differences in any of the RSNs, suggesting common pathophysiological underpinnings of the two clinical subgroups. Conversely, FC alterations in brain areas associated with cognitive functions in the CBN and FPN differed between TS and OCD patients, suggesting distinct neural underpinnings of the two disorders. FC changes in these two networks could play a different role (adaptive vs. maladaptive), possibly leading to different effects on the severity of clinical expression. Given the pediatric and drug-naïve nature of study cohorts, this study offers a previously unavailable glimpse at which correlates emerge early in the course of TS, TS+OCD and OCD. Our findings support the evidence of TS and OCD as multinetwork disorders and differentiate the primary pathophysiological correlates of two highly comorbid and overlapping conditions. Longitudinal studies that capture FC modifications over time are greatly needed and would foster the identification of prognostic and outcome markers. Ultimately, this may pave the way for improved clinical care of patients with TS and OCD in the future.

CHAPTER 4

Cerebellar Involvement in Children with Tics and Compulsions: an evidence from a multimodal neuroimaging study

Abstract

Background: Tourette syndrome (TS) and Obsessive-compulsive disorder (OCD) appears as two intertwined disorders both exhibiting repetitive behaviors with TS+OCD being a possible intermediate clinical phenotype. Our recent exploratory study in drug naïve children with TS and OCD has provided novel evidence of a different pathophysiological role of the cerebellum in TS/TS+OCD and OCD.

Objectives: To evaluate cerebellar structural and functional connectivity in drug naïve children with TS, TS+OCD and OCD and the possible association with severity scores.

Methods: We examined 53 pediatric drug-naive patients with TS without comorbidity (TSpure, n = 16), TS with OCD comorbidity (TS+OCD, n = 14), and pure OCD (OCD, n = 11) along with controls (Ctrls, n = 12). All subjects underwent a multimodal 3T MRI study. Cerebellar lobular volumes and quantitative diffusion tensor imaging (DTI) parameters of cerebellar peduncles were employed as measures of structural integrity. Resting state functional connectivity (FC) of the dentate nuclei with the whole brain was assessed by seed-based analysis.

Results: OCD patients had lower volumes of Crus I and lobule VIIIb, bilaterally, than TSpure. DTI analysis revealed that both TSpure and TS+OCD patients had higher fractional anisotropy (FA) in cerebellar peduncles than Ctrls. Conversely, OCD patients were characterized by lower FA than both Ctrls and TS sub-cohorts. Lastly, cerebellar FC analysis revealed significant alterations in the cerebello-thalamo-cortical circuit in TSpure, TS+OCD and OCD.

Conclusions: Our study provides evidence of early pathophysiological changes in the cerebellum and its connections in drug naïve TS/TS+OCD and OCD children. We also advocate that TS+OCD share common pathophysiological features with TSpure but not with OCD.

4.1 INTRODUCTION

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by multiple motor or phonic tics persistent for a year or more (*APA - Diagnostic and Statistical Manual of Mental Disorders DSM-5 Fifth Edition*, n.d.). TS is accompanied by several comorbidities, predominantly obsessive-compulsive disorder (OCD)(Andrea Eugenio Cavanna et al., 2009; Hirschtritt et al., 2015; Robertson et al., 2017). Independently from the co-occurrence in the context of TS, OCD may manifest alone as a disorder characterized by recurrent intrusive thoughts/urges that are accompanied by compulsive actions rendering transient relief (Gillan et al., 2017; James F. Leckman et al., 2010; Robbins et al., 2019). TS and OCD appear as two intertwined disorders exhibiting repetitive behaviors, whose labeling into complex tics and compulsions might be challenging at times (Mansueto & Keuler, 2005; Mathews & Grados, 2011b; Robertson et al., 2017). In this context, patients with TS+OCD might be characterized by overlapping clinical features with TS and OCD (Mansueto & Keuler, 2005).

Addressing this issue, we have recently used a data-driven approach to directly compare resting-state functional connectivity patterns (rs-FC) in independent cohorts of TS without comorbidity (TSpure), TS with OCD comorbidity (TS+OCD), and pure OCD (Tikoo, Cardona, et al., 2020). Also, our previous study design minimized relevant and well-known confounding factors, such as the effect of heterogeneous disease duration and chronic drug treatments, by studying pediatric cohorts of medication-naive patients along with age-matched controls (Ctrls). By examining rs-FC patterns in seven resting-state networks of interest, we have highlighted functional changes in the above cohorts within the cerebellar network (Tikoo, Cardona, et al., 2020). More specifically, we demonstrated that compared with Ctrls, all patients' groups were characterized by increased cerebellar connectivity, and the specific pattern of rs-FC was comparable in TSpure and TS+OCD. By contrast, the OCD group had higher cerebellar connectivity than both TSpure and TS+OCD. Additionally, cerebellar FC changes were contrarily correlated to the clinical scales in the two disorders, i.e., negatively with YGTSS scores and positively with CY-BOCS scores. These correlations suggest a different functional role of FC changes in the two disorders. Since higher FC in the cerebellum was associated with lower tic severity in TS, cerebellar FC may reflect neuroplastic mechanisms seemingly involved in the modulation of tic expression. Conversely, in OCD the direct correlation between cerebellar FC and compulsive scores suggests that increased

cerebellar FC may represent an abnormal maladaptive mechanism of neuroplasticity possibly contributing to symptom severity. Overall, our observations led us to two conclusions: first, TSpure and TS+OCD share common patterns of rs-FC; second, the cerebellum plays an integral role in the pathophysiology of both TS and OCD. Hence, our findings outlined the pathophysiological role of the cerebellum in both TS and OCD in agreement with prior structural and functional findings (Sigurdsson et al., 2020; Tobe et al., 2010; Xu et al., 2019; H. Zhang et al., 2019). In hindsight, the findings from our previous study provided us with the necessary framework to further investigate the involvement of the cerebellum in patients with TSpure, TS+OCD, and OCD.

For this purpose, the current study aims to examine cerebellar structural and functional changes in medication-naive children with TSpure, TS+OCD, pure OCD, and age-matched Ctrls. The structural analysis included the investigation of possible changes in cerebellar GM lobules as well as white matter (WM) fiber integrity of cerebellar peduncles. The functional analysis consisted of seed-based connectivity of the dentate nucleus with respect to whole brain (DN-FC). The pediatric nature of our cohort enabled us to elucidate early pathophysiological changes in the cerebellum of children with TS and OCD. Also, the medication-naive trait of our patients allowed us to demonstrate cerebellar structural and functional changes prior to any intervention of drugs or behavioral therapy.

4.2 METHODS

4.2.1 Participants

From a consortium of 70 children, a group of 53 subjects were included in this study: 16 patients with TSpure (15 males, mean age: 9.7 ± 2.1 years), 14 with TS+OCD (10 males, mean age: 10.2 ± 2.1 years), 11 with OCD (7 males, mean age: 10.7 ± 2.5 years), and 12 children with episodic tension headache, who were headache-free during the MRI scan, as Ctrls (3 males, mean age: 10 ± 1.2 years). A subgroup of 17 children were excluded from this study due to either severe head movement during the scan (n=8) or inability to complete the MRI exam (n=9). All subjects were enlisted from the child and adolescent neuropsychiatry outpatient clinic at the Department of Human Neurosciences, Sapienza University of Rome, Italy. Inclusion criteria were defined as follows: a) drug-naivety; b) right-handedness c) normal

cognitive profile (IQ≥70). Exclusion criteria were defined as follows: a) attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, schizophrenia, and any other comorbidities, or developmental disabilities; b) previous behavioral treatment; b) contraindications to MRI. Diagnoses was made according to the clinical history and the results of a structured interview with both parents and children following the DSM-5 criteria, by a neuropsychiatrist with experience in the assessment of paediatric TS, OCD, and related comorbidities. The severity of tics and OCD symptoms was assessed using the Yale Global Tic Severity Scale (YGTSS) (symptom severity scale: max. 50, without impairment score) (J. F. Leckman et al., 1989) and Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) (Goodman et al., 1989), respectively. This study was approved by the institutional review board and written informed consent of all parents/guardians was obtained following the Helsinki declaration.

4.2.2 MRI acquisition

After clinical evaluation, all participants underwent a 3T MRI scan at Sapienza University of Rome, Italy. MRI examination was conducted on a 3T scanner (Magnetic Verio; Siemens, Erlangen, Germany) using a standardized protocol and a 12-channel head coil designed for parallel imaging (GRAPPA, Generalized Autocalibrating Partial Parallel Acquisition). Noise reduction headphones were used to attenuate the scanner noise. Subjects were scanned in a supine, head-first position with symmetrically placed cushions on both sides of the head to minimize motion. MRI protocol included the following sequences: a) high-resolution 3D, T1-weighted (3DT1) MPRAGE: repetition time [TR] = 1900 ms; echo time [TE]= 2.93 ms; flip angle= 9°; field of view [FOV] = 260 mm^2; matrix = 256 x 256; 176 sagittal slices 1 mm thick; no gap b) Diffusion-tensor imaging (DTI, single-shot echo-planar spin-echo sequence, with one b = 0 and 30 gradient directions, b = 0 and 1000 s/mm^2, TR = 12,200 ms, TE = 94 ms, FOV = 192 mm, matrix = 96 ×96, 72 axial 2-mm-thick slices, no gap); c) resting-state functional magnetic resonance imaging (rs-fMRI): TR = 3000 ms; TE = 30 ms; flip angle= 89°, 64 × 64 matrix; 50 contiguous axial slices 3 mm thick; 140 vol; acquisition time = 7 min. During the image acquisitions, the subjects were asked to lie down relaxed, with their eyes closed without falling asleep.

4.2.3 Structural MRI data analysis

Images were analyzed via FMRIB software library (FSL, (https://www.fmrib.ox.ac.uk/fsl), version 6.0.1. Structural images were brain extracted using the Brain extraction toolbox (BET) (Smith, 2002) and segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) after bias-field correction via FAST. Both WM and CSF images were thresholded at 98% tissue type probability and binarized to create WM and CSF masks. Furthermore, an age-specific template was created to minimize potential confounders introduced by the differences in cortical thickness, surface area, and folding between children and adult brains, via cerebromatic toolbox (Wilke et al., 2017), keeping age, sex, and scanner strength as covariates.

Cerebellar lobular analysis

Cerebellar lobular volumes were calculated using SUIT toolbox via SPM 12 (Diedrichsen et al., 2009). The procedure involved cropping and isolating the cerebellum from the 3DT1anatomical images for each subject, followed by normalizing each cropped image into SUIT space using non-linear DARTEL normalization. Lastly, the probabilistic cerebellar atlas was resliced into the individual subject space using the deformation parameters calculated for normalization. This process resulted in volumetric GM measurements containing 13 bilateral regions of the cerebellum (lobules I-IV, V, VI, Crus I and Crus II, VIIb, VIIIa, VIIIb, IX, X, dentate, interposed nucleus and fastigial nucleus) and vermis containing 8 regions. The values of the extracted cerebellar lobules volumes were normalized to the total intracranial volume to reduce the head-size variability.

Cerebellar peduncles white matter analysis

Tract-based spatial statistics (TBSS) version 6.0.1 (Smith et al., 2006) was used on DTI to evaluate WM integrity. Diffusion images were corrected for movement and eddy current distortions. The eddy-corrected images were fitted to the tensor model at each voxel to calculate fractional anisotropy (FA) and mean diffusivity (MD) and generate FA and MD maps using DTIFIT. The next step consisted of non-linear registration to align all the FA and MD images to the target image using the FLIRT function. Given the pediatric nature of the studied cohorts, the FMRIB58_FA_target image was unsuitable. Hence, across the four groups the most representative target image (i.e., the one that requires the least amount of warping to match every other subjects) was identified and all the subject-specific FA and MD maps were non-

linearly aligned to this target image. Both target and individual FA and MD maps were affine-transformed into standard MNI space. Lastly, a WM skeleton was generated from the mean FA image by thresholding at 0.2 to exclude GM or CSF. This mean FA skeleton represents the common center of all white matter tracts. Automatic tract-specific quantification using the JHU white matter tractography atlas was performed to identify the inferior cerebellar peduncles (ICP), middle cerebellar peduncles (MCP), and superior cerebellar peduncles (SCP) tracts which were further binarized (Hua et al., 2008) and used as masks to restrict DTI analysis. FA and MD values of cerebellar peduncles were then computed.

4.2.4 Functional MRI data analysis

The rs-fMRI data were brain extracted, slice-time and motion corrected followed by 8mm spatial smoothing. Additionally, they were spatially registered with their respective structural images and then normalized onto a customized T1 template space. For detailed pre-processing steps of the rs-FMRI data, please refer to our previous study (Tikoo, Cardona, et al., 2020).

For seed-based analysis a bilateral spherical seed of dentate nucleus (2mm radius) was created using the following coordinates of the left and right dentate, (-18, -58, -34) and (18, -56, -34) respectively, in MNI standard space, according to our prior studies (Sbardella et al., 2017; Tikoo, Pietracupa, et al., 2020),. The bilateral dentate seed was then affine-transformed to the native subject space of each patient and its anatomical correspondence was individually checked on functional images. Then, for each subject, the meantime series within the dentate seed were extracted and fed into a general linear model to generate seed-based correlation maps via FEAT toolbox.

4.2.5. Statistical analysis

Kruskal-Wallis test and post-hoc Mann Whitney U test were performed to assess between-group differences with respect to age. A Chi-square test was also used to check for differences in sex distribution between groups. Differences between patients concerning clinical scores were analyzed with the Mann-Whitney U test. Analyses were performed with SPSS (Statistical Package for the Social Sciences) version 25.0. Statistical significance was set at $p < 0.05$, FWE corrected for multiple comparisons.

Cerebellar lobular analysis

Differences in normalized cerebellar GM volumes were calculated among the study cohorts using MANCOVA followed by post-hoc two-sample t-test implemented via SPSS. Results were corrected for age and sex, and defined as significant at $p < 0.05$ family-wise error (FWE) corrected for multiple comparisons. Lastly, a Pearson correlation was computed between the cerebellar lobules that significantly differed from Ctrls and the clinical scores keeping age and gender as covariates.

Cerebellar peduncles white matter analysis

To compute differences in FA and MD in the three cerebellar peduncles among our study cohorts a general linear model (GLM) keeping age and gender as covariates, were constructed. A two-sample t-test was run to investigate inter-group differences via a non-parametric approach (randomise, $n = 5000$). The statistical significance threshold was set at $p < 0.05$, and corrected for multiple comparisons with false discovery rate (FDR). Additionally, for the correlation analysis, the mean values of the significantly altered FA and MD between patients and controls were extracted within the mask of the three cerebellar peduncles for each subject. Pearson correlation was computed between the mean FA and MD values and the clinical severity measures and FWE corrected ($p < 0.05$) for multiple comparisons.

Dentate nucleus functional connectivity (DNFC)

To evaluate inter-group differences in terms of DNFC, an ANOVA test was performed non-parametrically via randomise ($n = 5000$), keeping age and sex as covariates in a GLM. The statistical group difference map derived from ANOVA was binarized to build a mask of differences, at $p<0.05$ after false discovery rate (FDR) correction for multiple comparisons. Within this mask of differences, two-sample t-tests were computed via randomise to evaluate between-group differences, controlling for age and sex. Differences were considered significant if $p < 0.05$, (FDR) corrected for multiple comparisons. The mean z scores of the significantly altered DNFC between the patients and controls were extracted for each subject and Pearson correlation was computed with the clinical severity scale and FWE corrected ($p < 0.05$) for multiple comparisons.

4.3 RESULTS

4.3.1 Participants

TSpure, TS+OCD, OCD, and Ctrls did not statistically differ in terms of age (H (3) = 2.1, p= 0.54). On the contrary, sex distribution was uneven between TSpure patients and Ctrls ($\chi 2$ [1, N = 28] = 14.1, p <0.001), TS+OCD and Ctrls ($\chi 2$ [1, N = 26] = 5.5, p = 0.02) and TS pure and OCD ($\chi 2$ [1, N = 27] = 3.9, p = 0.05). The Mann Whitney U test revealed comparable YGTSS between TSpure and TS+OCD patients (U = 108.5, p = 0.88). Similarly, the CYBOCS were also comparable between OCD and TS+OCD patients (U = 65, p = 0.53). Demographics and clinical scores of the 4 cohorts are reported in **Table 1**.

Table 1: Demographic variables and clinical characteristics:

Variables	TSpure (n = 16)	TS+OCD (n = 14)	OCD (n = 11)	Ctrls (n = 12)	TS pure vs Ctrls	TSpure vs OCD	TS+OCD vs Ctrls	TS+OCD vs OCD	TSpure vs TS+OCD	OCD vs Ctrls
*Age (years)	9.7 ± 2.1	10.2 ± 2.1	10.7 ±2.5	10 ±1.2	p = 0.26	p = 0.25	p= 0.49	p =0.61	p =0.44	p =0.57
**Male /Female	15/1	10/4	7/4	3/9	p < **0.001**	**p= 0.05**	**p= 0.02**	p= 0.68	p= 0.10	p= 0.06
***YGTSS score (0-50)	17.5 ±6.7	18.1 ±10.8	0.72 ± 1.6	-	-	p **<0.001**	-	p**< 0.001**	p = 0.85	-
***CYBOCS score (0-40)	0.25 ±0.7	16.4 ± 6.1	19.4 ± 7.5	-	-	p **<0 .001**	-	p = 0.53	p **< 0.001**	-

Data are expressed as mean (*M*) ± standard deviation (*SD*), YGTSS: Yale Global Tic Severity Scale, CYBOCS: Children's Yale-Brown Obsessive-Compulsive Scale, OCD: Obsessive Compulsive Disorder

TSpure: Tourette syndrome without Obsessive Compulsive Disorder symptoms.

TS+OCD: Tourette syndrome with Obsessive Compulsive Disorder symptoms.

Ctrls: Controls (age-matched).

*Age difference were assessed between groups via Kruskal Wallis and post-hoc Mann Whitney U test.

* * Gender differences were assessed via chi square ($\chi 2$) test.

*** Mann Whitney (*U*) test between the clinical scores of TSpure, TS+OCD and OCD.

Tic severity was evaluated by summing the motor and phonetic tics (without impairment scores) as per the YGTSS guidelines. Significant *p* values are highlighted in bold font ($p<0.05$)

4.3.2 Patients vs Controls

Cerebellar lobular analysis

The average global cerebellar GM volume after normalization to total intracranial volume was (355.4 ± 11.3 mL) for TS pure, (354.7 ± 11.3 mL) for TS+OCD, (341.8 ± 21.2 mL) for OCD patients, and (345.7 ± 19.4 mL) for Ctrls. No significant differences in either global or lobular cerebellar volumes were discerned between patients and controls **(Fig1).**

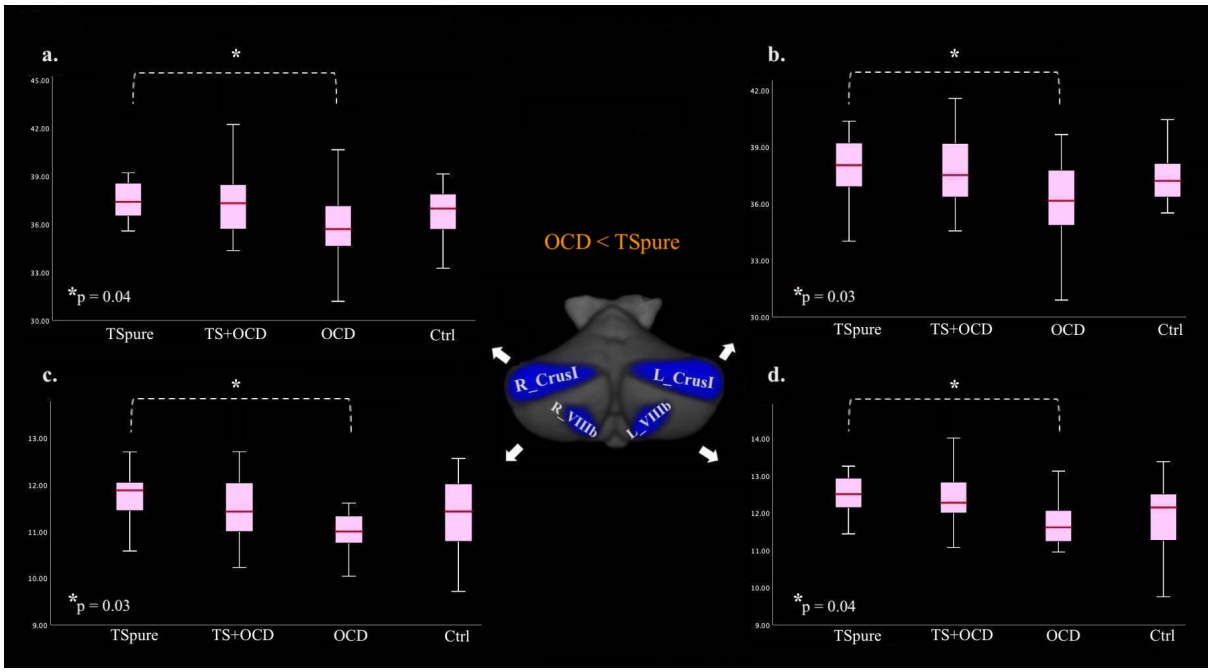


Fig 1. Cerebellar lobular analysis: The figure illustrates volumetric differences of cerebellar lobules between TSpure, TS+OCD, OCD and Ctrls. Grey matter values of each cerebellar lobules were extracted via SUIT cerebellar atlas and assessed for inter-group differences. OCD patients had decreased cerebellar grey matter volume than TSpure in: **a)** Right Crus I, **b)** Left Crus I, **c)** Right VIII b, and **d)** Left VIII b. Blue color indicates decreased lobular volume. Significance was set at ($p < 0.05$, Family wise error (FWE) correction).

Cerebellar peduncles white matter analysis

When compared to Ctrls, both TSpure and TS+OCD patients showed significantly higher FA (**Fig.2 a, b),** whereas OCD patients exhibited lower FA in all three cerebellar peduncles **(Fig.2 c).** MD analysis showed consistent findings, i.e., lower values in both TSpure and TS+OCD and higher in OCD compared to Ctrls within the same areas (results not shown). Thus, further

analysis, was restricted to FA changes. For each peduncle, mean FA values were calculated in those areas of increased or decreased FA in respect to Ctrls, in Tspure, TS+OCD and OCD patients.

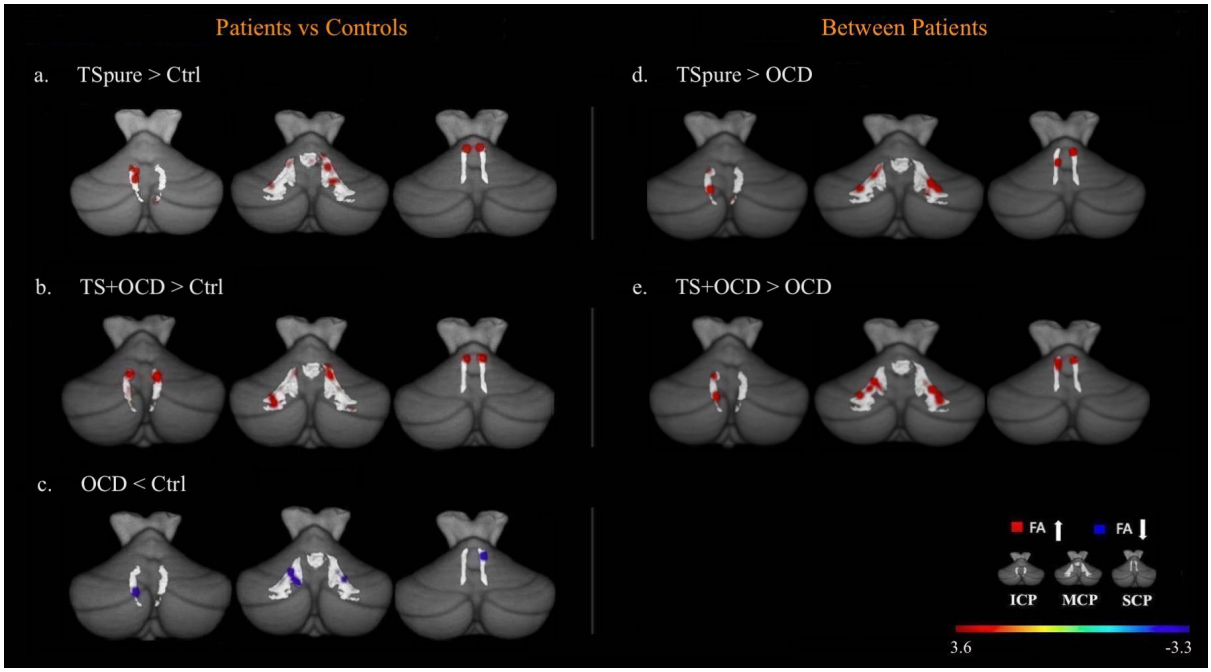


Fig.2 Cerebellar peduncles white matter analysis:

(Patients vs Controls): Fractional anisotropy (FA) alterations between patients and controls within three cerebellar tracts: Inferior cerebellar peduncle (ICP), Middle cerebellar peduncle (MCP) and Superior cerebellar peduncle (SCP). **Fig.2: a** and **b)** illustrates higher FA in TSpure and TS+OCD patients than Ctrls. **c)** represents lower FA in OCD patients compared to controls. **(Between Patients):** FA alterations between patient cohorts within the three cerebellar peduncles (ICP, MCP and SCP). **Fig.2: d** and **e)** illustrate higher FA in TSpure and TS+OCD than OCD patients. The cerebellar peduncles are represented by light-grey color overlayed on a 3-dimensional suit template post tbss_fill for better illustration. Red color represents significant voxels with higher FA while blue represents lower ($p < 0.05$, false discovery rate (FDR) corrected). The color-bar shows t values.

Dentate nucleus functional connectivity

Both TSpure and TS+OCD patients, in comparison to Ctrls, exhibited decreased DNFC with right precentral gyrus, right prefrontal cortex, left postcentral gyrus, bilateral thalamus, left inferior temporal gyrus, left cerebellar IX lobule, and left crus II. They also showed increased DNFC with bilateral lobule VI and right crus I **(Fig.3 a, b).** OCD patients, in comparison to Ctrls, exhibited decreased DN-FC with right precentral gyrus, left postcentral gyrus, bilateral thalamus, left inferior temporal gyrus, and left crus II, and increased DNFC with and left crus

I. Differently from TS subgroups, OCD patients showed increased DNFC with the prefrontal cortices bilaterally, and left orbitofrontal cortex (**Fig.3 c).**

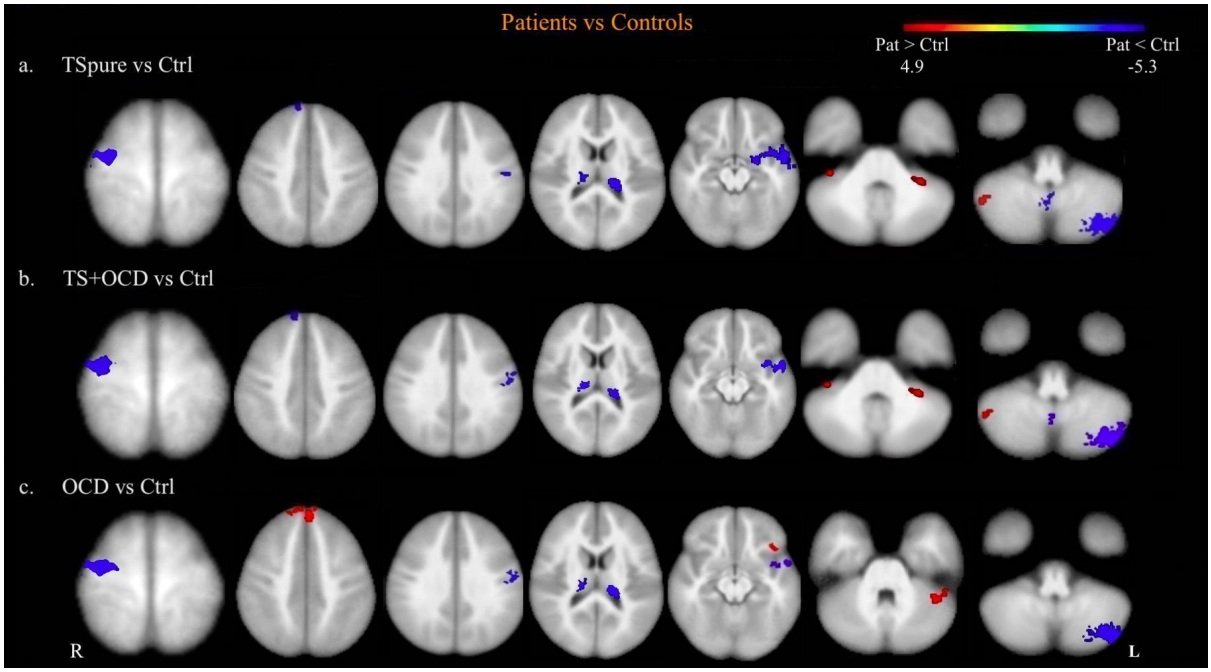


Fig.3 Cerebellar functional connectivity (Patients vs Controls): Group differences in dentate nucleus functional connectivity (DN-FC) between patients and controls. **Fig.3: a** and **b)** represents decreased DN-FC in TSpure and TS+OCD patients with the right precentral gyrus, right prefrontal, left postcentral gyrus, bilateral thalamus, left inferior temporal gyrus, left lobule IX and left crus II, and an increased DN-FC with the bilateral lobule VI and right crus I compared to Ctrls. **c)** represents decreased DN-FC in OCD patients with right pre and left postcentral gyrus, bilateral thalamus, left inferior temporal gyrus and left crus II and increased DN-FC with bilateral prefrontal, left fronto-orbital cortex, and left crus I compared to Ctrls. Light blue color indicates reduced DN-FC while red indicates increased DN-FC. Significant clusters ($p < 0.05$, FDR corrected) are superimposed on a customized T1 template. The color-bar represents t values.

4.3.3 Between Patients

Cerebellar lobular analysis

Compared to TSpure patients, OCD patients had significant lower GM volume in bilateral Crus I **(Fig.1 a, b)** and bilateral VIII b **(Fig.1 c, d), (Table2).** No significant difference was found in the global cerebellar volume between patient cohorts.

Table 2: Cerebellar grey matter changes between OCD and TS pure patients:

Cerebellar lobules	Cerebellar Grey matter volume (mL)				F/p value
	TS pure*	TS+OCD	OCD*	Ctrls	OCD < TS pure*
Right Crus I	37.51 ± 1.2	37.5 ± 1.8.	35.9 ± 2.5	36.9 ± 2.1	2.9 / 0.04
Left Crus I	37.9 ± 1.6	37.7 ± 2.1	36.1 ± 2.5	37.2 ± 1.6	3.1/0.03
Right lobule VIIIb	12.0 ± 0.6	11.5 ± 0.7	11.1 ± 0.7	11.4 ± 0.8	3.3/ 0.04
Left lobule VIIIb	12.5 ± 0.5	12.4 ± 0.9	11.7 ± 0.6	12.0 ± 0.9	2.7/ 0.02

Table 2: depicts significant cerebellar grey matter (GM) differences in bilateral crus I and bilateral VIIIb between Obsessive compulsive disorder (OCD) and TS patients without comorbidity (TSpure).
* denotes significant group differences obtained via MANCOVA followed by posthoc two-sample ttest. Results are FWE corrected ($p < 0.05$) for multiple comparisons.

Cerebellar peduncles white matter analysis

No significant difference was found in FA between TSpure and TS+OCD patients in any of the cerebellar peduncles. On the contrary, both TSpure and TS+OCD patients exhibited higher FA in all three cerebellar peduncles in comparison to OCD patients **(Fig.2 d, e)**. Similarly, no difference in MD was found between TSpure and TS+OCD patients, while both TSpure and TS+OCD patients exhibited lower MD in comparison to OCD patients.

Dentate nucleus functional connectivity

When comparing DNFC between patients, TSpure in comparison to TS+OCD patients demonstrated lower DNFC with the bilateral precentral gyrus, left crus II and higher DNFC with the bilateral prefrontal cortex (**Fig.4 a).** With respect to OCD, both TSpure and TS+OCD patients exhibited higher DNFC with right pre and left postcentral gyrus, right crus I and left lobule VI. They also showed lower DNFC with the bilateral prefrontal cortex, left crus I and crus II (**Fig.4 b, c).**

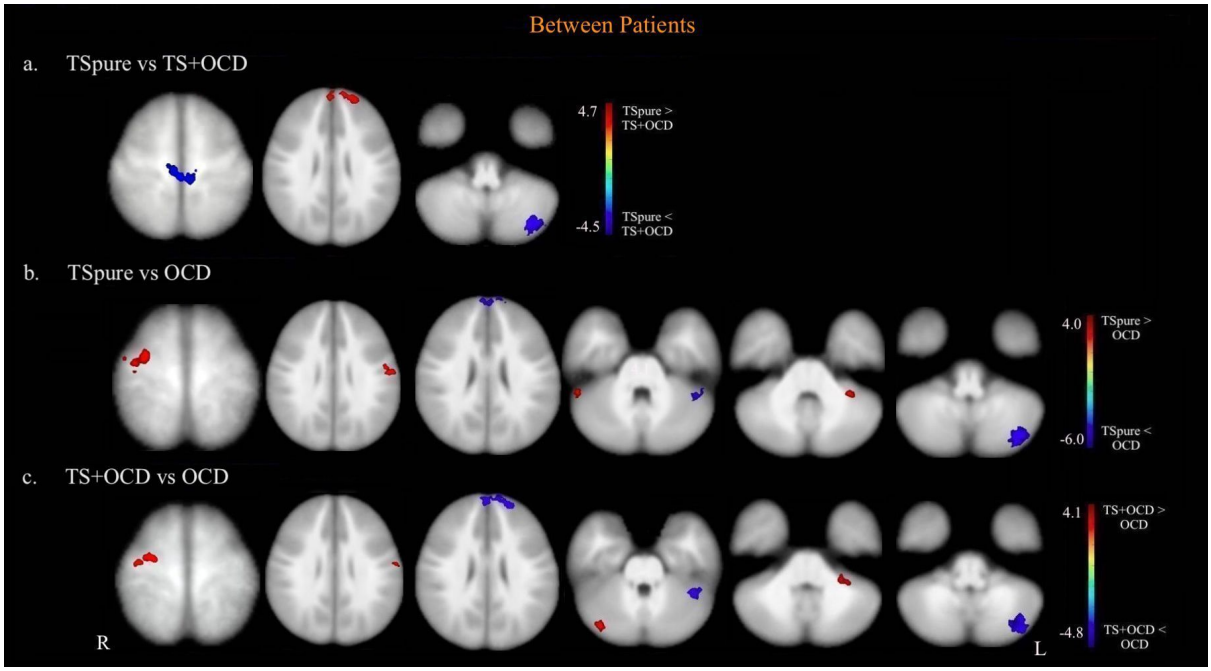


Fig 4. Cerebellar functional connectivity (Between Patients): Group differences in seed-based dentate nucleus functional connectivity (DN-FC) between patients. **Fig.4: a)** represents decreased DNFC in TSpure patients with bilateral pre-central gyrus and left crus II and an increased DNFC with bilateral prefrontal cortex compared to TS+OCD patients. **b** and **c)** depict increased DNFC in TS pure and TS+OCD with right pre and left postcentral gyrus, left lobule VI and right crus I and decreased DNFC with bilateral prefrontal cortex, left crus I and left crus II in comparison to OCD patients. Significant clusters ($p < 0.05$, FDR corrected) are superimposed on the customized T1 template. The color-bar represents t values.

4.3.4 Correlations

Cerebellar lobules with clinical severity

No significant correlations were found between altered cerebellar grey matter lobules and clinical severity scores in any patient cohort.

Altered FA with clinical severity

No significant correlation was found between altered FA and clinical severity in any of the patient cohorts.

Altered DNFC with clinical severity

In TSpure patients, the DNFC with the right prefrontal cortex negatively correlated with the YGTSS while the DNFC with the left lobule VI positively correlated with the YGTSS **(Fig.5 a, b).** No significant correlation was found between altered DNFC in TS+OCD patients with

any of the severity scores. In OCD patients, the DNFC with the bilateral prefrontal and left orbitofrontal cortices positively correlated with the CYBOCS **(Fig.5 c, d).**

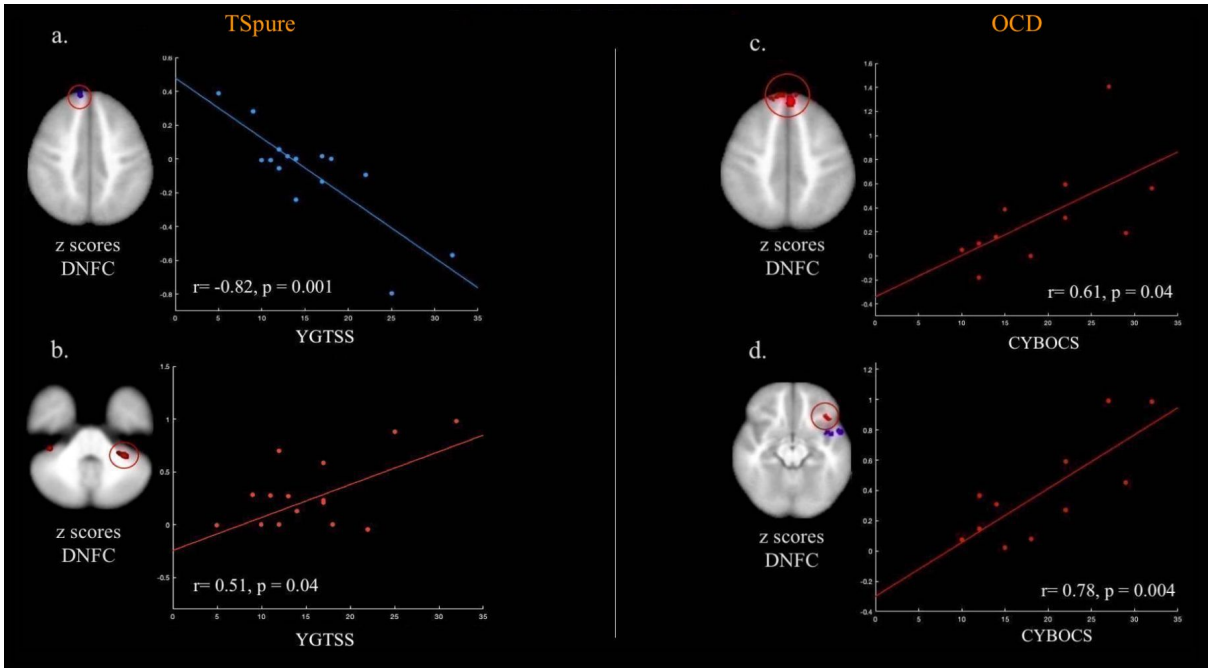


Fig 5. (Correlation of altered DNFC with clinical measures): Correlation of altered DNFC (z scores) with clinical severity scale (Yale global tic severity scale-YGTSS and children's yale brown obsessive-compulsive scale-CYBOCS) in TSpure and OCD patients respectively.

Fig 5. a) DNFC with the right prefrontal cortex negatively correlated with YGTSS. **b)** DNFC with the left lobule VI positively correlated with the YGTSS. **c)** DNFC with the bilateral prefrontal cortex positively correlated with the CYBOCS. **d)** DNFC with the left orbitofrontal cortex positively correlated with the CYBOCS. Statistical significance was set at $p < 0.05$, FWE corrected for multiple comparisons.

4.4 DISCUSSION

To our knowledge, this is the first comprehensive study that provides evidence of early-stage alterations in structural and functional connectivity (FC) of the cerebellum in medication-naive children with TSpure, TS+OCD, and OCD. In particular, we found alterations in cerebellar white matter connections, and cerebellar FC in all patient cohorts relative with Ctrls. Our findings highlight the potential role of cerebellum in the pathophysiology of TS and OCD.

Cerebellar lobular analysis

In agreement with a prior study (Hong et al., 2002), cerebellar lobular analysis revealed no significant differences in grey matter volume in TSpure as well as in TS+OCD patients compared to Ctrls. TSpure and TS+OCD patients also had comparable changes in cerebellar grey matter volumes. Our findings apparently disagree with two prior studies reporting reduced cerebellar volume in crus I and VIII b lobule in TS patients (Sigurdsson et al., 2020; Tobe et al., 2010) . Such inconsistency might be attributed to methodological differences (voxel-based morphometry vs lobular measurements) or to the possible confounding effect of heterogeneous clinical features including chronic drug treatment.

When comparing OCD with Ctrls, we found no significant differences in cerebellar lobules, in agreement with the majority of the previous whole brain volumetric studies in OCD patients (Bochao Cheng et al., 2016; Christian et al., 2008; Gonçalves et al., 2017; Peng et al., 2012). However, a few previous studies reported decreased (Kim et al., 2001; Koprivová et al., 2009) or increased (Pujol et al., 2004) cerebellar grey matter volume in OCD. Again, we suggest that such inconsistencies would reflect the heterogeneous clinical features of the OCD cohorts previously examined.

Lastly, our between-patients' analysis revealed lower grey matter in bilateral crus I and bilateral lobule VIIIb in OCD than in TSpure. All in all, our findings indicate focal and symmetrical differences in cerebellar lobular structures only between TS and OCD.

Cerebellar peduncle analysis

When compared to Ctrls, patients with TSpure and TS+OCD were both characterized by higher FA in all three cerebellar peduncles in line with a previous observation (Thomalla et al., 2009). Furthermore, we found no microstructural alterations when comparing TSpure and TS+OCD patients. Conversely, OCD patients had lower FA than Ctrls in the three cerebellar peduncles, a finding again in keeping with a prior study (Zhong et al., 2019).

Lastly, when comparing TSpure and TS+OCD with OCD patients, our analysis demonstrated higher FA in TSpure and TS+OCD than in OCD. Considering FA as a measure of axonal package density and overall white matter integrity (Beaulieu, 2002; Winston, 2012), our data suggest that axonal density in the three cerebellar peduncles is increased in both the sub-cohorts of TS while it is decreased in OCD patients. Overall, our findings indicate an adaptive reorganization of white matter integrity in TS children aiding them to gain control over their tics following subsequent regression into adulthood (Thomalla et al 2009, Jackson

et al 2011, Bloch et al 2006). Conversely, lower FA values found in OCD children indicates an augmentation in severity of compulsions at later age (Bloch et al 2006).

Cerebellar functional connectivity

When compared to Ctrls, TSpure patients had decreased DNFC with the pre- and postcentral gyrus, bilateral thalamus, and inferior temporal gyrus, a finding coherent with prior research (Ji et al., 2016; Liao et al., 2017; Thomalla et al., 2014). The activation of the sensorimotor cortex and thalamus are known to be involved in tic generation as well as in the urge-tic network (Draper et al., 2016; Neuner et al., 2014; Tinaz et al., 2014). Similarly, the temporal gyrus is implicated in directing control of urge-inhibition in TS (Berman et al., 2012; Mazzone et al., 2010). Accordingly, our observations would reflect the inability to control premonitory urges in TS (Andrea E. Cavanna et al., 2017).

Our seed-based FC analysis also revealed decreased DNFC with the right prefrontal cortex in TSpure, a finding again coherent with prior reports in children (Y. Cui et al., 2014a) and adults with TS (Ramkiran et al., 2019). Prefrontal cortex is thought to be involved in maintaining adaptive control and regulating attention processing in TS patients (Dosenbach et al., 2008; S. Fan, van den Heuvel, et al., 2018). Additionally, the DNFC with the prefrontal cortex anticorrelated with the YGTSS, indicating that lower FC is associated with higher tic severity. The decreased FC in the prefrontal cortex points to an impairment in cognitive control and executive function in TS (Andrea E. Cavanna & Nani, 2013b).

We identified lower DNFC with the left lobule IX and crus II and higher DNFC with the right crus I and bilateral lobule VI in TSpure patients, in line with prior studies (Liu et al., 2017a; Ramkiran et al., 2019; Tikoo, Cardona, et al., 2020). The Crus I and lobule VI are involved in language processing while lobule IX and crus II are typically engaged during visuospatial tasks (Glickstein et al., 1994; Stoodley, 2012). Also, the increased FC of lobule VI positively correlated with YGTSS possibly reflecting speech and language disorders in TS (Burd, 2014). Lastly, the decreased DNFC with the lobule IX and crus II might point to visuo-spatial deficits in TS (Bloch et al., 2006; Khalifa & Eklund, 2017).

When comparing TS+OCD patients with Ctrls, we observed similar pattern of DNFC as of TSpure patients. Additionally, in comparison to TS+OCD patients, TSpure patients were characterized by decreased DNFC with the bilateral precentral gyrus and left crus II and by increased DNFC with the bilateral prefrontal cortex. Altogether, our findings indicate FC changes in the cerebello-thalamo-cortical (CTC) network in both TSpure and TS+OCD thus

asserting on a new pathophysiological model implying the impairment of the CTC circuit in TS (Caligiore et al., 2017a; Ramkiran et al., 2019). We speculate that DNFC differences between TSpure and TS+OCD would reflect a different burden of the disease when associated with psychiatric comorbidity.

In OCD patients, we discovered decreased DNFC with right pre and left postcentral gyrus and increased DNFC with bilateral prefrontal cortex which is in line with prior evidence (Apergis-Schoute et al., 2018; Y. Chen et al., 2016; G. Cui et al., 2020; P. S. Moreira et al., 2017; Pedro Silva Moreira et al., 2019; Xing et al., 2020). A decreased FC in the pre- and postcentral gyrus may explain the inability of OCD patients to suppress internally repetitive and intrusive thoughts and behavior (Ahmari et al., 2012; G. Cui et al., 2020; Russo et al., 2014). Altered prefrontal cortex activity is likely linked to abnormal performance monitoring in OCD patients(Fitzgerald et al., 2010; van Noordt & Segalowitz, 2012). Moreover, we also found a positive correlation between increased DNFC with prefrontal cortex and CYBOCS which likely explains an excessive concern for correct task performance in OCD patients (Fitzgerald et al., 2010).

We also found decreased DNFC with the bilateral thalamus and increased DNFC with orbitofrontal cortex which is again consistent with prior works (Beucke et al., 2013; Y. Chen et al., 2016; J.-M. Hou et al., 2014; Niu et al., 2017; Qiu et al., 2017; Xing et al., 2020). Disruption of the fronto-striato-thalamic circuit routing through the orbitofrontal cortex is thought to play the main role in the pathophysiology of OCD where any inhibition at the level of thalamus will hyperactivate the orbitofrontal cortex (Menzies et al., 2008). Prior studies have reported the involvement of orbitofrontal cortex in in emotion regulation (Ochsner et al., 2002; Ochsner & Gross, 2005). Additionally, we also found a positive correlation between higher DNFC with the orbitofrontal cortex and CYBOCS. Taken together, our findings demonstrate an impairment in the regulation of anxiety following recurrent intrusive thoughts (Paul et al., 2016; Yap et al., 2018).

We also detected a decreased DNFC with the left inferior temporal gyrus which is in accordance with prior research (J.-M. Hou et al., 2014; T. Yang et al., 2010; X. Yang et al., 2019; T. Zhang et al., 2011). In OCD patients the temporal cortex has been associated with maintaining the 'level of insight' defined as the ability to recognize the excessiveness of one's own obsessive-compulsive symptoms (de Avila et al., 2019). Our results of decreased DNFC with the temporal areas reflects 'poor insight level' or lack of self-awareness in OCD patients (J. Fan, Zhong, Zhu, et al., 2017).

Lastly, we detected an increased DNFC with the left crus I and decreased DNFC with the left crus II regions in OCD patients compared to Ctrls, which is in accordance with prior studies (Anticevic et al., 2014b; J. Hou et al., 2012; J.-M. Hou et al., 2014; Nabeyama et al., 2008; Ping et al., 2013; Tian et al., 2016; Xing et al., 2020; H. Zhang et al., 2019) . As discussed before, cerebellum plays an integral role in cognitive functioning where Crus I involvement is in language processing and crus II is engaged during visuospatial tasks (Stoodley, 2012). A higher FC in the left crus I and lower FC in the left crus II may explain the wide-ranging cognitive deficits observed in OCD patients (Jansen et al., 2020; Kamaradova et al., 2016; Shin et al., 2014).

When comparing TSpure/TS+OCD and OCD we observed a higher DNFC in the pre-postcentral gyrus, and lower DNFC in the prefrontal cortex relative to OCD patients. Moreover, both the TS sub-cohorts had higher DNFC with the right crus I and left lobule VI and lower DNFC with the left crus I and crus II in comparison with OCD patients. Hence, our findings reveal hyperconnectivity in the sensorimotor areas and hypoconnectivity in the prefrontal cortex in both TSpure and TS+OCD compared to OCD. Lastly, we report an impairment in the cognitive cerebellum in all three patient cohorts. All in all, our findings highlight significant alterations in the CTC circuit in OCD patients (Sha et al., 2020; H. Zhang et al., 2019).

Pathophysiological role of cerebellum in TS and OCD

A handful of studies have recently begun to indicate the salient role of the cerebellum in the pathogenesis of tics and compulsions (Debes et al., 2017; Hazari et al., 2019; Sigurdsson et al., 2020; Zhong et al., 2019). However, cerebellum is still underrepresented in TS and OCD research, and its involvement has to be characterized in detail. The cerebellum has been increasingly linked to play a crucial role in both motor and higher-level cognitive functions (Castellazzi et al., 2018; Moberget & Ivry, 2019; Rapoport et al., 2000). The cerebellum, especially dentate nucleus anatomically connects to the contralateral thalamus and various cortical and subcortical areas via SCP, subserving both motor and cognitive functions .Hence the involvement of dentate nucleus in the neocerebellar functions is thought to subserve both motor and non-motor (cognitive) functions (Bernard et al., 2014; Tikoo, Pietracupa, et al., 2020).

4.5 LIMITATIONS

When considering our results few limitations should be considered. Firstly, no online tic measurement was collected during rs-fMRI acquisition, thus possibly masking the exact neural framework of TS. Second, there was an uneven gender distribution among our study cohorts that may have influenced the results, although sex was inserted in the analyses as variable of no interest. Third, functional connectivity was performed by placing a spherical seed on the dentate nucleus, without considering the distinction between dorsal and ventral areas since specific investigations of dentate nucleus subareas may be technically challenging. However, this approach has already proven to be a reliable technique in our prior studies (Tikoo, Pietracupa, et al., 2020; Tona et al., 2017).

4.6 CONCLUSIONS

Our findings indicate lower grey matter volume in OCD patients than both Ctrls and TS sub-cohorts. Accordingly, OCD patients had with decreased axonal density of cerebellar WM connections, while TSpure and TS+OCD patients had increased. We again emphasize to have found no changes in structural cerebellar architecture between TSpure and TS+OCD patients. Our cerebellar FC analysis revealed a hypoconnectivity between the cerebellum and prefrontal regions in TSpure and TS+OCD in contrast to the hyperconnectivity found in OCD patients. Based on these observations we concluded that TSpure and TS+OCD patients have an impaired executive functioning which affects their ability to navigate everyday tasks. In contrast OCD patient are characterized by overactive cognitive control leading to an excessive urge to repetitively perform a task. Lastly, we highlighted a disruption in cerebellar FC of language processing and visuospatial areas in TSpure, TS+OCD and OCD patients. Overall, our findings provide novel evidence to expand our understanding of cerebellar involvement in the pathophysiology of TS and OCD.

CHAPTER 5

General discussion and conclusions

To understand the neural underpinnings of two highly comorbid disorders i.e., TS and OCD. Our first study (Chapter 3) focused on investigating resting state – FC patterns in a medication naive independent cohort of TSpure, TS+OCD and OCD along with age-matched controls. To achieve this, we incorporated a data-driven approach i.e., independent component analysis (ICA) to study FC changes in predefined resting state networks (RSNs) of interest. Based on the findings from prior studies (Y. Cui et al., 2014a; J. Fan, Zhong, Gan, et al., 2017; Liu et al., 2017b; Stern et al., 2012; Weber et al., 2014b) we selected seven RSNs namely basal ganglia (BGN), cerebellum (CBN), frontoparietal (FPN), default mode (DMN), orbitofrontal (OBF), salience (SAN) and sensorimotor network (SMN). Out of these seven RSNs we found significant functional connectivity alterations in six RSNs in all patient cohorts. In particular we found that TSpure and TS+OCD patients share similar patterns of increased resting state-FC in BGN, SMN, CBN, DMN followed by decreased resting-state FC in FPN and SAN when compared to controls. Conversely, the OCD patients were characterized by increased resting-state FC in all six RSNs. A between patient comparison revealed no significant differences in resting-state FC patterns between TSpure and TS+OCD patients. Additionally, we also found that OCD patients had higher resting-state FC in FPN and CBN than both the TS sub cohorts. A novel finding of this study was that both TS and OCD patients showed increased FC in the CBN, though FC was significantly higher in OCD than in TS patients. Moreover, this increased cerebellar-FC correlated negatively and positively with tic severity and compulsive scores respectively. These correlations suggested a different functional role of FC changes in the two disorders. Since higher FC in the CBN was associated with lower tic severity in TS, CBN FC may reflect neuroplastic mechanisms likely involved in the modulation of tic expression. On the other hand, the direct association between FC and OCD clinical severity suggests that increased cerebellar FC could represent an abnormal mechanism of neuroplasticity affecting symptoms' severity. Thus, our evidence suggested CBN involvement in the pathophysiology of TS and OCD.

The novel cerebellar findings from our first study (chapter 3) prompted us to characterize in detail the potential involvement of cerebellum in TS and OCD. In order to

achieve this, our second study (chapter 4) focused on investigating structural and functional connectivity of the cerebellum in the same medication naive cohorts of TSpure, TS+OCD and OCD patients along with controls. In particular we explored structural changes in cerebellar grey matter (GM) lobules and white matter (WM) fiber integrity of cerebellar peduncles. We also analyzed functional connectivity of the dentate nucleus with respect to the whole brain (DNFC). Lastly, we investigated the possible association between structural and functional alterations and clinical severity. We hypothesized to have found significant abnormalities in cerebellar grey matter volume and white matter fiber integrity of the cerebellar peduncles. Moreover, we also anticipated to find alterations in cerebello-thalamo-cortical (CTC) network in all three patient cohorts. Lastly, we expected to see possible correlation of altered structural and functional connectivity with clinical severity scores which would aid in elucidating the precise role of cerebellum in modulation of tics and compulsions.

Our structural analysis of cerebellar grey matter volume revealed no significant changes between patients and controls. Although we did reveal lower GM in crus I and lobule VIIIB in OCD patients than TSpure indicating subtle differences in cerebellar GM between these two conditions, symmetrically affecting specific lobules, i.e. Crus I and lobules VIII, which are known to contribute to cognitive and sensorimotor functions, respectively (Stoodley, 2012).

Our WM analysis of cerebellar peduncles revealed higher FA in TSpure/TS+OCD patients followed by lower FA in OCD patients than controls. Consequently, patients of TS sub-cohorts significantly differed in WM microarchitecture of cerebellar connections from OCD. Considering FA as a measure of axonal package density and overall WM integrity (Beaulieu, 2002; Winston, 2012), our findings suggested that axonal density increases in both TS sub-cohorts, whereas it decreases in OCD. In current literature, there is no punctual understanding of correlation between WM changes and symptom expression in both TS and OCD. However, increased FA has been reported in TS in sensorimotor (Thomalla et al., 2009) and prefrontal regions (Jackson et al., 2011) and associated to reduced tic severity and better control of motor behavior thus increased FA in TS patients might indicate adaptive brain reorganization involving cerebellar WM connections likely aiming at the control of tics. Conversely, in OCD children, lower FA values might represent a pathophysiological mechanism, which may be partly reversed by cognitive-behavioral therapy (Zhong et al., 2019). All in all, the pediatric and drug-naive feature of our cohorts enabled us to detect early-

stage WM abnormalities in the cerebellar peduncles of TS and OCD patients and to further vindicate the role of abnormal WM in the pathophysiology of the two disorders.

Our cerebellar FC findings demonstrated alterations of the dentate nucleus with the thalamus, and various regions of the cerebellar hemispheres and cerebral cortex which further points to functional disconnection of the cerebello-thalamo-cortical (CTC) circuit affecting both TS and OCD. In particular, we unveiled that cerebello-prefrontal FC is reduced in TS and increased in OCD, postulating that the cerebellum engages with the PFC in a distinct manner in TS patients than OCD. The contrasting correlation between cerebellar-prefrontal FC and clinical severity (i.e., negative vs positive) found in TS and OCD further supports a different contribution of the disruption of this circuit, mainly involved in executive functions, in the pathophysiology of these two disorders.

Noteworthy, by pointing out differences within cerebellar resting state network (chapter 3) and in cerebellar-prefrontal FC and cerebellar peduncle microarchitecture (chapter 4) between drug-naive pediatric TS and OCD patients, this thesis provides novel insights into the pathophysiological involvement of the cerebellum that characterizes the early phases of these two disorders.

ACRONYMS

TS - Tourette Syndrome

OCD- Obsessive compulsive disorder

TOCD- Tourettic OCD

MRI- Magnetic resonance imaging

DWI- Diffusion-weighted imaging

rs-fMRI-Resting state functional magnetic resonance imaging

VBM- Voxel-based Morphometry

TBSS- Tract-Based Spatial Statistics

ICA- Independent component analysis

SCA- Seed-based correlation analysis

CSTC- cortico-striatal-thalamo-cortical

PUs- Premonitory urges

HRT- Habit reversal therapy

CBIT- comprehensive behavioral intervention

CBT- Cognitive-behavioral treatment

FBI- function-based interventions

RT- Relaxation training

DSM-5- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

SSRIs- Selective serotonin reuptake inhibitors

ERP- exposure and response prevention

RF- radio frequency pulse

FA- Fractional Anisotropy

MD- Mean diffusivity

BOLD- Blood Oxygen Level Dependent

BGN- basal ganglia network

SMN- sensorimotor network

CBN- cerebellum network

FPN- frontoparietal network

DMN- default-mode network

OBFN- orbitofrontal network

SAN- salience network

AROMA- Automatic Removal of Motion Artifacts

FWHM- full width at half maximum

SPSS- Statistical Package for the Social Sciences

GLM- general linear model.

YGTSS- Yale Global Tic Severity Scale

CYBOCS- Children's Yale-Brown Obsessive Compulsive Scale

FSL- FMRIB Software Library

BET- Brain Extraction Toolbox

ANOVA- Analysis of variance

FDR- false discovery rate

FWE- family wise error rate

GM- grey matter

WM- white matter

CSF- cerebrospinal fluid

TIV- Total intercranial volume

RSN- resting state networks

JOURNAL PUBLICATIONS

Tikoo, S, Pietracupa, S., Tommasin, S. et al. Functional disconnection of the dentate nucleus in essential tremor. J Neurol 267, 1358–1367 (2020).

Tikoo S, Cardona F, Tommasin S, Giannì C, Conte G, Upadhyay N, Mirabella G, Suppa A, Pantano P. Resting-state functional connectivity in drug-naive pediatric patients with Tourette syndrome and obsessive-compulsive disorder. J Psychiatr Res. 2020 Oct; 129:129-140.

CONFERENCE PUBLICATIONS

Rajanikant Panda, Rose Dawn Bharath, Shriram Varadharajan, **Sankalp Tikoo**, Sarbesh Tiwari, Surabhi ramawat, Shiva Karthik, Indira Devi Bhagavatula, and Arun Gupta. Why a clinical sign does not always correlate with lesion location? International Society for Magnetic Resonance in Medicine (ISMRM-May 2016), Singapore.

S. Pietracupa, **S. Tikoo**, S. Tommasin, M. Bologna, N. Petsas, K. Bharti, G. Grillea, A. Berardelli, P. Pantano. Dentate nucleus functional connectivity changes and their relationship with motor and non-motor symptoms in patients with essential tremor. Movement disorder conference(MDS) Nice, France, September 22-26 2019.

S. Tikoo, F. Cardona, S. Tommasin, C. Giannì, N. Upadhyay, K. Bharti, G. Conte, G. Mirabella, A. Suppa, P. Pantano.Resting-state Functional Connectivity differences in pediatric patients with Tourette syndrome and obsessive-compulsive disorder. Movement disorder conference(MDS) Nice, France, September 22-26 2019.

M. Mancuso, A. Fabbrini, G.Leodori, **S. Tikoo**, A. Suppa, A. Berardelli. Visual Hallucinations and Dorsal Attention Network in Parkinson's disease and Lewy body dementias: a combined TMS-EEG study.Conference: SINDEM4JUNIOR (January 2020)-8th Winter seminar on Dementia and Neurodegenerative Disorders, Bressanone, Italy

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