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Pediatric Tourette syndrome: insights from recent neuroimaging studies

Jessica A. Church¹ and Bradley L. Schlaggar^{2,3,4,5}

¹Department of Psychology, University of Texas at Austin, Austin, TX 78712

²Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110

³Department of Radiology, Washington University School of Medicine, St. Louis, MO 63110

⁴Department of Anatomy&Neurobiology, Washington University School of Medicine, St. Louis, MO 63110

⁵Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110

Abstract

Tourette syndrome has been examined using many different neuroimaging techniques. There has been a recent surge of neuroimaging research papers related to Tourette syndrome that are exploring many different aspects of the disorder and its comorbidities. This brief review focuses on recent MRI-based imaging studies of pediatric Tourette syndrome, including anatomical, functional, resting state, and diffusion tensor MRI techniques. Consistencies across studies are explored, and particularly important issues involved in acquiring data from this special population are discussed.

Keywords

Tourette; Development; fMRI; DTI; MRI; Anatomy; VBM

Introduction

Tourette syndrome is a common genetic neuropsychiatric disease with pediatric onset, affecting approximately 1% of children and adolescents [1-3]. Tourette syndrome (TS) affects males more than females, and manifests as the inability to keep from making repetitive, stereotyped sounds and movements (vocal and motor tics, respectively) over long periods of time. A diagnosis of TS requires the presence of both motor and vocal tics, not due to some other condition, for over a year with onset prior to the age of 18 years [4].

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Address correspondence to: Jessica A Church PhD, 108 E. Dean Keeton, Stop A8000, Austin, TX 78712, church@austin.utexas.edu, 512-75-7009.

Author Roles: For this review article, both authors conceived, organized, and wrote the article

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While TS is defined by the presence of tics, it is not exclusively a movement disorder. TS has a clinically significant cognitive component as well. Several studies have found that patients with TS have at least subtly impaired executive function, or cognitive control, defined as the set of brain processes that select and modulate downstream moment-to-moment processing relevant to the task at hand [5-7]. However, these findings are controversial because of the potential contribution of co-morbid ADHD present in a substantial portion of patients with TS (e.g. [8, 9]). Even when patients with TS perform similarly to unaffected individuals on tasks that require cognitive control, event-related brain potential measures indicate that they engage greater task monitoring processes via enhanced response to errors [10]. However, one group has found increased cognitive control abilities in pediatric patients with TS during an oculomotor switching task [11]. It could be possible that patients with TS have above average control due to chronic practice resisting unwanted tics. This debate about the impact of TS on cognitive functioning demonstrates one of the substantial difficulties in studying TS; namely, understanding TS requires capturing the mix of comorbidities and the changing profile of TS symptoms, particularly during its period of primary impact (i.e. development) when numerous other cognitive changes occur. This review will focus on the neuroimaging studies that have taken on the challenge of studying TS during development. Along the way, issues important to developmental imaging in general, and TS developmental imaging in particular, will be highlighted.

Goals of this review

This review of the neuroimaging of TS will not seek to be exhaustive, but rather to highlight some of the results that have emerged from the growing number of MRI-based studies in the last decade, and to describe gaps in knowledge that would be prime targets for future investigation. There have been other, excellent reviews on different aspects of TS research published in the last few years that the reader is also encouraged to examine for a more comprehensive perspective on TS [12-18].

We will begin by describing some of the challenges and benefits of studying pediatric TS, and the importance of addressing the challenges to maximize the benefit of results in a developmental population. Then we will review adult and developmental anatomical neuroimaging studies, looking for consistencies in brain regions that appear to be altered in patients with TS. The papers described in this section will include volumetric and/or diffusion tensor neuroimaging (DTI) techniques. Next, the focus will shift to task-based functional neuroimaging studies using functional MRI (fMRI), particularly those studies that have begun examining children with TS. Subsequently, the review will conduct a brief examination of resting-state functional connectivity studies, and their possible advantages in examination of a patient population. Finally, a few “next steps” will be put forward as ways to continue to advance our understanding of TS.

The Benefits and Challenges of Developmental Studies of TS

The pediatric nature of TS is the best reason to focus on pediatric patients and to contextualize results through a thorough investigation of an unaffected, typically developing population. Adults with clinically burdensome tics represent not only a subset of TS patients, as the majority of adults with TS experience at least some relief of symptoms [19],

but they also have had years, perhaps decades, to develop compensatory brain mechanisms or processing strategies to circumvent TS difficulties. Thus, when one images adults with TS, it is unclear if any brain or activity differences found are primary to TS or secondary, reflecting compensation. The long-term effects of TS on the brain may be strikingly dissimilar from its impact during the ages of diagnosis, initial treatment, or worst-ever symptoms. Patients with TS often experience a peak in symptom severity pre-puberty, followed by some relief of symptom burden post-puberty [19, 20]. Many fascinating questions relevant to TS are best asked and addressed at those ages themselves (e.g. who will experience a relief of symptoms and who will not?).

Notwithstanding the appropriateness of their developmental stage for addressing TS issues, pediatric populations bring with them a whole set of concerns related to neuroimaging [21, 22]. In brief, increased movement in pediatric subjects, especially those from patient populations, increased stress in children during the scanning process [23], and overall reduced compliance of children during the experiment are of significant concern when scanning pediatric populations, whether patient or unaffected. When child data are compared to adult data, performance differences need to be accounted for so that brain differences as a result of lower task performance in one group are not confounded with differences due to age [21]. Adult and child data need to be compared in equivalent brain space, so that differences in reference atlas are not driving activity differences, and so that direct statistical comparison can be performed. Side by side comparisons of thresholded images is not a reasonable substitute for direct comparison. Fortunately, many methodological concerns such as these (e.g. the use of a common atlas to compare child and adult groups) have been addressed in the literature [21, 22, 24, 25].

Another challenge that must be considered when studying a pediatric disorder is the separation of typical developmental change, per se, from that of changes related to the disorder. Despite the same 3-year age gap, a 12 year-old patient with TS may be more different from a 9 year-old with TS than is a 21 year-old patient from a 24 year-old patient, because of the substantial developmental transitions throughout childhood and adolescence. Developmental trajectory of brain activity is important to assess in and of itself. Chronological age, of course, is a constantly changing variable and is not necessarily an ideal surrogate for brain maturity. Similarly, a combination of reproductive, stress, and growth hormone levels, and their potential impacts on the brain, all are in flux in the precise age range of highest interest in TS (9-15 years) [26]. While there are no specific methods for disentangling these issues, groups have made attempts to at least quantify hormone levels or pubertal stages using rating scales and/or salivary or blood samples [e.g. 23].

Issues with neuroimaging of TS in general

TS symptoms wax and wane over time. The variable time course of the disorder can complicate simple assessment of an individual's tic profile, and has typically been measured in reference to either worst ever tic burden or current tic burden. The variable impact of common comorbid conditions (e.g. ADHD, OCD, Generalized Anxiety, Affective Disorder) create additional complexities [27]. One approach to addressing these differences between patients is to gather a large number of subjects to enable subgroup comparisons of patients

with different comorbid diagnoses. Another approach is to try to limit the study to a clean TS sample of patients without any comorbidities. However, studies that attempt to scan only “pure” TS (no co-morbid conditions) are limiting their results to approximately 10% of the TS population [28]. The patients most often seeking medical care are those who may benefit the most from any research; they are more often complicated cases, having comorbid conditions and receiving pharmaco- and/or behavioral therapy. Hence, while such pure populations may seem ideal from an experimental design standpoint, it is critical that studies also shed light on the most clinically compelling patients.

Also, while a number of studies have either excluded medicated subjects or done small subgroup analyses of medicated groups, much remains to be done to explore the effects of medication on TS, and how brain differences related to TS interact with medication use. TS patients are prescribed medications from a variety of drug classes, and medicated patients often have the most severe symptoms. This particular confound can magnify the difficulty of obtaining large datasets with which to elucidate the brain impact of different medications due to loss of data from excessive movement or poor compliance, as well as a possible symptom severity confound between different subgroups of the successfully acquired data points.

Longitudinal research of individuals with TS over time may be a key approach to understanding TS, as it is for understanding typical development and other developmental disorders [29, 30]. These analyses may provide clearer results than traditional cross-sectional studies with respect to tracking the time course of TS symptoms over age. However, these issues become even more problematic when considering longitudinal analysis because of the dynamic nature of the comorbidities and their clinical burden. Medications, symptom severity, and co-morbidity burden can, and are indeed expected to change within an individual, making the effective study of an individual over time a complex and moving target. The goal of obtaining a pure and unmedicated TS sample longitudinally is highly selective and is likely to be a quixotic endeavor, as a vast number of patients will have changing comorbid profiles and/or medication additions over the time course of the disorder. A 7-year-old boy with pure TS may additionally develop OCD and start taking clonidine and sertraline by age 10. Do we still consider him to have been “pure TS” at the initial assessment, or is he TS with latent OCD? From a biological plausibility standpoint, the latter is far more likely to be accurate.

Thus, the true nature of TS as a disorder is rarely clean and isolable from additional factors, and efforts to manipulate or quantify these different factors (e.g. dimensional severity of ADHD, anxiety, or depression burden, in addition to medication history, parental stress, etc.) may be more successful than looking for narrow segments of the population. Gathering large, well-characterized samples and placing the burden of diverse symptomatology on sophisticated statistical analysis may be the most effective approach to dealing with these complex issues.

Finally, in addition to the complexities of TS symptom measurements and TS group definitions, an important issue in TS neuroimaging research is the choice of whole-brain versus region-specific analysis of neuroimaging data. One explanation for the diverse and

often inconsistent neuroimaging findings, summarized briefly below, is that investigators may be suffering from the phenomenon of finding results only where we look. As each study may define and examine only a small set of a priori regions of interest (ROI) instead of examining the whole brain, we could all be capturing different pieces of the ground truth. Thus, we have made note of cases where whole brain analyses were employed with appropriate multiple comparison corrections.

Anatomical studies: Subcortical

Studies of anatomy in TS have typically focused on subcortical structures, such as the basal ganglia, due to their recognized involvement in movement disorders. However, these studies have had mixed results, possibly due to different measurement techniques and a variety of sample sizes. Wang and colleagues [31] found no significant basal ganglia or thalamic structural differences in a group of adults with TS and adult controls using large-deformation high dimensional brain mapping. Similarly, Zimmerman and colleagues [32] compared 7-15 year-old girls with TS to unaffected girls and found no subcortical structural differences.

Within individual basal ganglia nuclei, a growing number of studies have found smaller caudate volumes in children with TS [33-36]. In a remarkable prospective longitudinal study, caudate volumes of children with TS inversely correlated with their individual TS and OCD symptom burden an average of 7.5 years later, in early adulthood, but not at the time of the child scan [36].

The other basal ganglia findings have not been as consistent. Smaller left lenticular volumes were found in adults with TS [35, 37]. But other groups have found enlargement of structures such as the thalamus [38], amygdala and hippocampus [39], and putamen [40]. Alternatively, some studies have found different asymmetries (a difference between left-hemisphere and right-hemisphere volumes) in basal ganglia structures compared to unaffected participants, in the globus pallidus [41], putamen [42], or thalamus [40].

In the corpus callosum, two adult studies have found decreased corpus callosum volumes [43, 44]. However, one study has found larger volumes in adults with TS, and smaller volumes in children with TS [45]. Yet another pediatric study has found increased volumes in children with TS [46]. These contrasting findings are somewhat inconsistent with the more replicated findings across studies using diffusion tensor imaging (see DTI section below).

Overall, from this variety of different subcortical anatomical studies, the most replicable finding appears to be decreased volume of the caudate nucleus, perhaps indicative of dysfunction there. However, the lack of consistency of findings within other subcortical regions is potentially suggestive of a communication problem between multiple nuclei within a circuit as opposed to an issue at the level of one particular nucleus in TS. Subtle size or functional differences at any of multiple points in a circuit could result in decreased functioning, perhaps leading to TS symptoms. Most of the studies summarized here have included children, in some cases exclusively, and are thus more likely to be describing primary disorder effects. However, despite these efforts, the lack of consistency beyond the

caudate results leaves open many questions. New efforts with higher resolution (7T) imaging may hold promise for a finer grain analysis in the future [47].

Anatomical studies: Cerebellum

Few recent studies have examined the cerebellum for anatomical differences in TS using MRI techniques [48, 49]. Volume analysis in both of these studies found no differences in the TS group, either in children [48] or a wide age range including both children and adults [49]. However, when Tobe and colleagues [49] used surface morphology and volume preserved warping (VPW) techniques, they found significant differences in the TS group. Specifically, the TS group across age showed gray matter reductions in the lateral cerebellar hemispheres that appeared to correlate with tic severity. Thus, while long not a location of focus in TS research, the cerebellum may well be playing a significant role in TS; a consideration that warrants further investigation [49].

Anatomical studies: Cortical

There seems to be more consistency in studies of TS that investigate cortical structure. Whether this consistency is due to a greater number of tools available to study cortical surfaces, greater use of a whole brain approach, actually more consistent underlying data, or larger structure definition allowing for less anatomical precision in results is unclear. A few studies have reported overall brain volume decreases in pediatric TS subjects [38, 48], while most have found thinner cortex or decreased volume in several different cortical areas in adults or children with TS (but see [56] below). For example, in 3 studies of adults, cortical thinning or a decrease in gray matter volume was observed in sensorimotor and premotor cortex, and cortical thinning or a decrease in white matter volume in inferior frontal gyrus (IFG) compared to matched controls [50-52].

In children, Sowell and colleagues [53] found thinner cortex in pediatric TS participants in sensory and motor areas, as well as parts of frontal, parietal, and occipital cortex. Fahim and colleagues [54] also reported thinner cortex in pediatric TS in pre- and post-central gyrus, though with visually different centers of intensity in those areas than Sowell et al. [53]. Fahim and colleagues found even thinner cortex in TS boys compared to girls, and an increasing thinning with age across TS participants.

Using a different type of analysis, Peterson and colleagues [55] found larger volumes in dorsal prefrontal and parieto-occipital cortex in young children with TS, while the prefrontal difference decreased in older children and in fact showed the opposite pattern in TS adults. The authors suggest that this changing prefrontal measure could reflect incorporation of compensatory mechanisms in frontal cortex to regulate or suppress tics.

Perhaps similar to the older children in the Peterson et al. study, but not limited to the prefrontal cortex, Roessner et al. [56] found no brain volume differences in their TS group of children ages 10-15 years compared to a control group of unaffected 10-15 year-olds using voxel-based morphometry.

Thus, there seems to be growing evidence of cortical thinning or volume changes in at least motor and frontal and parietal cortex in childhood, and these structural differences may

persist into adulthood [57]. There is clearly the need for further study using a variety of structural imaging techniques.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) can measure the movement of water molecules throughout the brain. When water molecules diffuse primarily in a single direction within a voxel (3D pixel used in imaging) as might be expected in insulated axons, this creates a fractional anisotropy (FA) index that can allow quantification of white matter tract organization and tracing of white matter tracts. Like anatomical studies, DTI findings can be limited by the ROIs applied, and only very recent studies are taking a more whole brain approach.

Several studies of children and/or adults with TS have found decreased FA in the corpus callosum, the major site of axons crossing between hemispheres [57-63] (but, see [64, 65]). This finding of decreased FA in the corpus callosum has been argued by some to be a compensatory dampening of communication between hemispheres to reduce unwanted behaviors, but by others as a primary effect of the syndrome, perhaps resulting in a decrease of appropriate inhibition from contralateral brain regions. A study of DTI of the corpus callosum combined with transcranial magnetic stimulation (TMS) provides some evidence for altered structural-functional relationships in the corpus callosum, in the absence of size or FA differences between groups of adults with and without TS [65].

Beyond the corpus callosum, some studies have also found increased FA in pre- and post-central gyrus in adults with TS, perhaps as a result of tic-related overactivity [57, 66]. It is unclear whether this increased FA is related to the gray matter thinning observed in these cortical areas (see cortical section above). In contrast to increased FA in motor areas, a recent study of adults with TS has found decreased connectivity between ROIs in supplemental motor areas or motor cortex and other cortical and subcortical ROIs [67]. Similarly, a whole-brain study of adults with TS found decreased FA in frontal, parietal, occipital and cingulate regions [63].

Makki and colleagues found differences in probability of connectivity between a seed in the caudate and anterior dorsolateral frontal cortex using DTI data in a pediatric sample, as well as increased mean diffusivity in bilateral putamen in a separate study [68; 34]. Another study has found increased serotonin binding and lower FA in the caudate in a combined PET and DTI study in children [69].

In the small but growing DTI literature, results appear to be aggregating around the corpus callosum, somatosensory and motor cortex, and caudate. There is growing interest in relating DTI findings to structural and functional results.

Functional Imaging Studies: Tic-related studies

Functional magnetic resonance imaging (fMRI) is an imaging technique that indirectly tracks neural activity via a blood oxygenation level dependent (BOLD) contrast signal during different tasks. A subset of studies using fMRI has examined the process of movement itself in TS, primarily in adults [70-73], but also in children [74]. During tic suppression in adults, there was decreased putamen and cortical activity, and an increase in

right caudate activity [70], while during tic production in adults there was greater motor activity in supplementary motor and primary motor cortex at tic onset [71, 72], and greater activity in brain regions implicated in cognitive control immediately prior to tic onset [71]. When spontaneous tics were compared with simulated tics in adults with TS, Wang and colleagues observed excessive motor activity and decreased task control-related activity in the spontaneous tics [73]. When TS participants (both children and adults) were asked to refrain from making eye blinks, many regions implicated in task control, including frontal cortex and striatum, were more activated in the TS group compared to the unaffected controls [74]. The interpretation by the authors was that activation of these control systems may help to maintain control over tics as well as eye blinks, and thus these systems are more constantly active in patients with TS, resulting in greater activity when there is additional demand, such as from a directed task. In addition, Serrien et al. have found that secondary motor areas are already active at baseline in adult TS patients and thus are not able to be recruited additionally during a motor task, suggesting that movement organization in TS is modulated to either compensate for, or as a result of, tic-related movements [75].

Functional Imaging studies: Cognitive studies

Other fMRI studies, particularly those studying children, have attempted to learn more about TS by studying cognitive tasks, with the hypothesis that the TS group will have aberrant task control in a manner analogous to their lack of control over unwanted movements. The idea of aberrant task control is an appealing, if somewhat controversial, motivation, as some investigators argue that highly co-morbid conditions carry the executive control difficulties more than TS (as discussed above, e.g. [9]). However, there have been some intriguing results indicating that cognitive control systems are implicated in TS, per se. In a behavioral and fMRI study, Bunge and colleagues [76] found that tic severity in unmedicated children with TS was positively correlated with two aspects of cognitive control: difficulty switching between task rules, and difficulty selecting between competing responses. Importantly, these cognitive deficits could not be attributed to co-morbid Attention Deficit Hyperactivity (ADHD), Obsessive-Compulsive Disorder (OCD), anxiety, or overall IQ levels in the children. The authors found a region in left frontal cortex that was more active in the TS group for the most difficult trial type of a rule-switching task, indicative of greater recruitment of control-related regions to achieve successful performance.

In another study of development, our group demonstrated that sustained and start-cue-related activity (signals thought to be important in task control) during a semantic judgment task were different in a group of older children and adolescents with TS [77]. The brain regions particularly affected in the start-cue analysis were bilateral, and involved frontal, motor, temporo-parietal, precuneus, and thalamic brain regions. The sustained signal differences in the TS children were limited to bilateral frontal and motor cortex. We were able to get interpretive leverage on the differences in the TS group by comparing them not just to age-matched unaffected children, but also to groups of unaffected adults and younger children. Using this approach we found that the sustained signal differences in the TS group appeared functionally immature (more similar to the younger control children), while the start-cue activity appeared atypical (not similar to any of the 3 age groups). These interpretative differences would not have been possible without a firm understanding of the

typical developmental trajectories of brain regions and activity for a given task. In addition, while performance was matched between the TS and unaffected adolescents, the TS group brain activity differences support the idea of different brain organization in patients with TS to arrive at the same behavioral endpoint.

When group brain differences are observed despite a lack of behavioral difference, we consider the existence of a “behavioral phenocopy” [78], the concept that apparently identical overt performance can be supported by non-identical functional neuroanatomy. The findings of a behavioral phenocopy in this situation suggests that patients with TS may have recruited different brain regions or engaged similar regions to a different extent in order to achieve the same level of overt performance as their peers [22, 77, 79].

Roessner and colleagues similarly found that children with TS had to recruit additional motor and task control-related regions of the brain to achieve the same performance level as their peers during a finger-tapping task [80, 81]. In a study of the Simon task (in this case reporting the direction of arrows that are either congruent or incongruent with the side of the visual field in which they are presented) across child and adult groups, Raz and colleagues found greater fronto-striatal activity in adults overall, and in adults with TS in particular, suggestive that adults with persistent TS have adapted to either chronic greater control demands, or inefficient use of fronto-striatal control mechanisms [82]. Relatedly, in a study of the Stroop interference task, Marsh and colleagues found that children and adults with TS co-opt control-related regions, including fronto-striatal regions, to maintain successful task performance, resulting in greater activity in those regions in the TS groups during the task [83].

Recently, however, Debes and colleagues failed to find any cortical differences specific to TS in children when controlling for age, sex, and IQ, and directly testing executive function tasks (e.g. Stroop, Go/No-go) [84].

In summary, functional MRI studies of controlled motor or cognitive tasks largely demonstrate some differences in both cortical and subcortical regions between unaffected participants and those with TS, perhaps revealing ways in which the brain is affected by, or compensating for, TS. However, results from these studies do not support the sort of task-general motor/premotor differences across a variety of tasks that one might predict based on the studies demonstrating general motor and premotor cortical thinning [53] and the functional neuroanatomy of tic suppression [70]. Rather, results indicate that TS patients may be utilizing task control-related regions of the brain at a higher level in order to achieve successful task performance. This conclusion has been forwarded by a majority of studies, but it is worth noting an interesting opposing argument that has been made by a few groups. Some evidence has been found for superior controlled processing in TS, potentially as a result of engaging control-related regions to suppress tics on a regular basis [11, 64]. We think this reconceptualization is quite intriguing, potentially of great clinical and heuristic value, and deserving of additional investigation.

Functional studies: Resting-state functional connectivity

Resting-state functional connectivity examines inter-regional correlations of low-frequency (0.01-0.1 Hz) spontaneous fluctuations of the BOLD signal obtained when subjects are lying quietly in the scanner without explicit task instructions (other than to hold still). This resting state signal has been shown to consistently correlate between functionally related regions (e.g. the motor system of the brain) despite the absence of an overt task [e.g. 85]. This analysis approach has proved useful for examining many patient populations for which task burden and scanner requirements (e.g. restricted movement) are prohibitive [86-90]. Our group has found evidence of immature task control networks in children with TS, involving regions throughout the brain, but particularly unusual correlated activity involving regions of the fronto-parietal network, proposed to be important in adaptive task control [86, 91, 92]. It is important to note, however, that recent studies have highlighted the importance of extremely strict control of movement during resting-state acquisition, and the confounding effects of even small movements on resting-state analyses [e.g. 93, 94]. A more recent study has specifically targeted cortical-subcortical networks and found altered network relationships in adults with TS [95]. This resting-state functional connectivity approach has not yet been widely carried into studies of TS, but it may prove illuminating, as it may allow study of participants who are unable to achieve both a certain performance level on tasks at the same time as certain imaging requirements (low movement, compliance, etc.).

Issues for future exploration

As was discussed in the introduction, the roles of medication and comorbid profiles on TS and on the brain remain large open questions for future exploration that are highly relevant to our understanding and treatment of TS. What we have not mentioned as much, but is proving to be decidedly important, is the confounding effect of movement on neuroimaging results [96]. Multiple investigators, including us, have described the corrupting influence of movement, particularly in resting-state data, as described briefly above [93, 94], but also in task fMRI data [96]. This problem is enhanced when studying populations such as children, older adults, and patients, all of whom are known or expected to move more during scans than healthy young adults [22]. Because TS is a movement disorder by definition, all researchers studying TS, whether in children or in adults, must exercise caution and conservatism when interpreting imaging results, and whenever possible, control for or remove the confounding effects of head and body motion, as suggested by [93, 96].

Three other questions that are fascinating relate to the issues of transient tics, the improvement in post-puberty of a number of patients with TS, and the functional neuroanatomical consequences of a very effective form of behavioral therapy for tics called CBIT (comprehensive behavioral intervention for tics), that is based on habit reversal therapy and reward system manipulation.

At least 10-20 fold more children have transient tics at ages 6 or 7 than go on to develop TS or chronic tic disorders. Being able to predict who will continue to have difficulty, and who belongs in the transient tic category would be most helpful to families and clinicians.

Similarly, being able to understand who will experience a relief of tic burden with age, and who will continue to experience lifelong difficulties with TS would be of enormous importance to our understanding of the disorder. Bloch et al. provide one illustration of how a longitudinal study design may go a long way towards understanding and predicting TS burden by tracking how child anatomical measurements correlate to TS symptoms in those same participants in adulthood [36].

CBIT is a clearly effective, but sorely underutilized (due to the dearth of clinicians with the expertise to provide the therapy) intervention for tics [97]. A fascinating and critically important set of questions regarding CBIT includes what changes in the functional architecture of the brain in patients with TS post-treatment? How are CBIT induced changes similar to and/or different from changes that may be seen with successful pharmacotherapy or to what may be seen when tics dissipate in late adolescence? Finally, as with all treatment approaches, since predicting who will and will not benefit from a particular therapy is of keen interest to clinicians and families alike, it will be important to determine whether information present in imaging data can be used to make such predictions on an individual patient basis.

Conclusions

In this brief review of some of the anatomical and functional studies of TS using MRI in the last decade, we have observed a growing number of studies including children and large sample sizes, both of which we think are key to honing in on results that will be meaningful into the future. While there is a general lack of consistency in anatomical and functional studies, some results indicate abnormalities either functionally or structurally in frontal or striatal brain regions. However, a growing number of results point to TS involving more than just fronto-striatal relationships as may have been initially believed. By opening up analyses to the whole brain, we may more quickly produce replicable results. While there is strong reason to believe that cortico-striatal-thalamic-cortical loops are involved in TS, their interplay with the rest of the brain should allow for greater chances of discovery. As neuroimaging techniques such as rs-fcMRI and others become more widespread and accessible, there become even more directions with which to direct research about TS, and there is reason for optimism that neuroimaging will facilitate the treatment and understanding of TS.

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