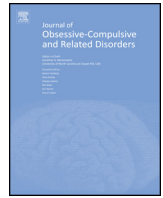




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Pediatric Tourette syndrome: Insights from recent neuroimaging studies



Jessica A. Church^{a,*}, Bradley L. Schlaggar^{b,c,d,e,1}

^a Department of Psychology, University of Texas at Austin, 108 E. Dean Keeton, Stop A8000, Austin, TX 78712, United States

^b Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110, United States

^c Department of Radiology, Washington University School of Medicine, St. Louis, MO 63110, United States

^d Department of Anatomy & Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, United States

^e Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110, United States

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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.

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1. Introduction

Tourette syndrome is a common genetic neuropsychiatric disease with pediatric onset, affecting approximately 1% of children and adolescents (Albert, Robertson, & Miall, 2009; Freeman et al., 2000; Walkup et al., 1996). 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 (Gilbert, 2006).

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 (Eddy, Rizzo, & Cavanna, 2009; Harris et al., 1995; Schuerholz et al., 1996). 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., Mahone et al., 2002; Sukhodolsky et al., 2010). 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 (Johannes et al., 2002). However, one group has found increased cognitive control abilities in pediatric patients with TS during an oculomotor switching task (Mueller et al., 2006). 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.

1.1. 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

* Corresponding author. Tel.: +1 512 475 7009.

E-mail address: church@austin.utexas.edu (J.A. Church).

¹ For this review article, both authors conceived, organized, and wrote the article.

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 (Frey & Albin, 2006; Greene & Schlaggar, 2012; Marsh, Maia, & Peterson, 2009; Plessen, Bansal, & Peterson, 2009; Rickards, 2009; Stern, Blair, & Peterson, 2008; Zinner & Coffey, 2009).

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.

1.2. *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 (Leckman et al., 1998), 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 (Leckman et al., 1998; Robertson, Eapen, & Cavanna, 2009). 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 (Church, Petersen, & Schlaggar, 2010; Palmer et al., 2004). In brief, increased movement in pediatric subjects, especially those from patient populations, increased stress in children during the scanning process (Corbett et al., 2008), 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 (Palmer et al., 2004). 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 (Burgund et al., 2002; Church et al., 2010; Ghosh et al., 2010; Palmer et al., 2004).

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) (Blakemore, Burnett, & Dahl, 2010). 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., Corbett et al., 2008).

1.3. *Issues related to 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 (Gaze, Kepley, & Walkup, 2006). 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 (Robertson, 2000). 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 (Kamrilloff-Smith, 2010; Thomas et al., 2009). 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 comorbidity 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

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