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Neuroimaging in Tourette Syndrome: Research Highlights from 2014 to 2015

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Abstract Tourette syndrome (TS) is a developmental neuropsychiatric disorder of the central nervous system defined by the presence of chronic tics. While investigations of the underlying brain mechanisms have provided valuable information, a complete understanding of the pathophysiology of TS remains elusive. Neuroimaging methods provide remarkable tools for examining the human brain and have been used to study brain structure and function in TS. In this article, we review TS neuroimaging studies published in 2014–2015. We highlight a number of noteworthy studies due to their innovative methods and interesting findings. Yet, we note that many of the recent studies share common concerns, specifically susceptibility to motion artifacts and modest sample sizes. Thus, we encourage future work to carefully address potential methodological confounds and to study larger samples to increase the potential for replicable results.

Keywords Tourette syndrome · Tic disorders · Neuroimaging · MRI · fMRI · Diffusion · Tractography · Functional connectivity · Spectroscopy

This article is part of the Topical Collection on *Tourette's Syndrome*

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Introduction

Tourette's Disorder and Persistent Tic Disorder, collectively referred to here as Tourette syndrome (TS), are complex developmental neuropsychiatric disorders defined by the presence of chronic motor and/or vocal tics. Understanding the neurobiological basis of TS would help the advancement of improved treatment and clinical care for the 1–6 % of the population who experience chronic tics. Neuroimaging methods, including functional and structural MRI, positron emission tomography (PET), diffusion tensor imaging, and spectroscopy, have been used to study the brain in vivo in TS. In conjunction with post mortem studies and animal models, neuroimaging findings broadly support a hypothesis of dysfunction in cortico-striato-thalamo-cortical networks in TS [1]. However, there are still many inconsistencies across studies [2], and a comprehensive understanding of the specific mechanisms underlying TS remains incomplete. Neuroimaging methods also continue to develop and mature. Thus, neuroimaging research on TS is an active field, and by applying recent advances in neuroimaging methods, we can better interrogate the living TS brain.

Neuroimaging studies published during approximately the past year (2014–2015) reflect the state of the neuroimaging field in TS. Several new methodological approaches have

been applied to groups of patients with TS in addition to more conventional neuroimaging methods. Yet, finding convergence among studies that pushes our knowledge forward remains a challenge. In part, the discordance reflects limited sample size and other methodological concerns that are common with newly developing methods. Here, we highlight several papers from 2014 to 2015 that are particularly noteworthy. For a comprehensive summary of the recent neuroimaging papers in TS, see Table 1. A more general review of neuroimaging in TS can be found in Greene et al. [2].

A Focus on Anatomy

Some of the first neuroimaging papers on TS examined anatomical measures, primarily focusing on subcortical and cortical regional volumes [3–5]. Since then, a number of studies have investigated anatomical structure in TS, implementing structural brain measures such as volumetry, cortical thickness, and diffusion (fractional anisotropy, mean diffusivity, etc.). This line of research has continued in the past year, finding differences between TS and control groups in cortical gray matter volume [6], subcortical gray matter volume [7], and diffusivity of cortical and subcortical regions [7, 8].

We highlight one study that investigated anatomy in TS using novel structural methods that have not been applied to TS before. Muellner et al. [9•] applied advanced techniques to cortical sulci, providing measures of cortical thickness within a sulcus, mean sulcal depth, sulcal length, and cortical fold opening. They studied a commendably large sample of 52 adults with TS and 52 age-, education-, and sex-matched controls. Results demonstrated diminished sulcal depth and reduced sulcal cortical thickness in TS in pre- and post-central sulci and superior, inferior, and internal frontal sulci. These findings are consistent with previous reports of cortical thinning in frontal and sensorimotor cortical regions [10, 11], yet extend the results to more specific measures of cortical morphology. The authors also separately tested those TS patients with comorbid obsessive-compulsive symptoms, finding diminished cortical thickness and larger sulcal openings in the superior temporal and insular sulci. Furthermore, cortical sulci measures correlated with tic severity as well as with obsessive-compulsive symptom severity. Thus, these results provide additional support for structural abnormalities in prefrontal, premotor, and motor cortical regions, and the authors discuss the potential involvement of atypical cortical development mechanisms in TS. This study is highlighted here due to several laudable methodological choices: (1) the large sample size, (2) the novel sulcal morphological measures examined, and (3) the inclusion and subsequent study of symptoms other than tics. It is important to note that there is recent evidence that small movements during MRI data acquisition can affect structural measures, including cortical thickness [12]. Thus, it is possible that motion artifact could bias the sulcal measurements used by Muellner et al. In fact, subject motion in the scanner can cause artifactual results for several neuroimaging techniques, and we discuss this problem and potential solutions below in the "Conclusion."

Structural Connectivity

While structural neuroimaging methods have typically focused on regional measures, there has been a recent shift to methods that study the connectivity *between* regions. As brain regions are not isolated structures and the connectivity between regions is crucial for normal brain function, investigations of connectivity are of great interest. White matter fiber tracts can be interrogated using diffusion tensor imaging (DTI) analyzed in terms of diffusivity (e.g., fractional anisotropy and mean diffusivity) and probabilistic tractography. Several recent studies in TS have examined diffusivity measures to investigate microstructural alterations in white matter [8, 13•, 14] and probabilistic tractography to study the integrity of connections between regions [13•, 15].

Here, we highlight a study that examined both probabilistic tractography and diffusivity measures in cortico-striato-pallido-thalamic tracts. Worbe et al. [13•] collected diffusion-weighted imaging data from 49 adults with TS and 28 controls and specifically investigated direct connections between the striatum, thalamus, and cortex. Results demonstrated enhanced structural connectivity with the striatum and thalamus in motor (primary motor cortex and supplementary motor area), frontal (inferior frontal cortex, orbitofrontal cortex), parietal (inferior parietal lobule), and temporal (medial temporal cortex, temporo-parietal junction) cortical regions. Furthermore, several of these tracts also demonstrated elevated fractional anisotropy and reduced radial diffusivity in the TS group. Interestingly, enhanced connectivity within motor pathways positively correlated with tic severity, while enhanced connectivity with orbitofrontal pathways positively correlated with obsessive-compulsive symptom severity. The authors further examined the influence of age, sex, and medication status, finding more pronounced effects within cortico-striatal and thalamo-cortical pathways in females compared to males. Thus, this study included complementary analytic techniques (probabilistic tractography and diffusivity measures) in a large sample and examined relationships with symptoms (tics and obsessive-compulsive symptoms), age, sex, and medication use. By implementing an inclusive approach (i.e., including subjects with and without comorbid symptoms, and those on and off medications), this study was able to interrogate the imaging results that relate to particular symptoms. The correlations with different symptoms (tics vs obsessions and compulsions) provide clues as to how symptoms manifest differently across patients. Furthermore, by not

Table 1 Published TS neuroimaging studies in 2014–2015

	Subjects	Method	Findings
Muellner et al. [9•]	52 adults with TS 52 adult controls	T1-weighted MRI Measures: sulcal cortical thickness, mean depth, length, cortical fold opening	Diminished sulcal depth and sulcal cortical thickness in frontal and pre- and post-central sulci in TS
Ganos et al. [6]	14 adults with TS 15 adults controls	T1-weighted MRI Measures: VBM gray matter and white matter volume	Reduced gray matter volume in prefrontal regions in TS. No differences in white matter volume and no significant correlations with clinical scores.
Debes et al. [7]	22 adolescents and young adults with TS 21 adolescent and young adult controls	T1-weighted MRI and Diffusion-weighted imaging Measures: VBM gray matter density, FA, mean diffusivity, parallel and perpendicular diffusivity Longitudinal study	Decreased gray matter volume in putamen over time in controls, but no such change in TS. Parallel and perpendicular diffusivity increased over time in controls, but decreased over time in TS. Decrease in mean diffusivity in right striatum, right thalamus, and right frontal lobe more pronounced in TS.
Jeppesen et al. [8]	24 children with TS 18 child controls	T1-weighted MRI and Diffusion-weighted imaging Measures: VBM gray matter density, FA, ADC, parallel and perpendicular diffusivity	No differences found in the seven regions of interest: cingulate, corpus callosum, optic radiation, forcep minor, thalamus, striatum, middle cerebral peduncle
Muller-Vahl et al. [14]	19 adults with TS 20 adult controls	Diffusion-weighted imaging Measures: FA, ADC	Microstructural alterations in white matter in frontal regions, corpus callosum, cingulate, thalamus, and putamen in TS
Cheng et al. [15]	15 adults with TS 15 adult controls	Diffusion-weighted imaging Measures: probabilistic tractography	Reduced connectivity between cortical and subcortical motor control regions in TS
Worbe et al. [13•]	49 adults with TS 28 adult controls	Diffusion-weighted imaging Measures: probabilistic tractography	Atypical connectivity between striatum/thalamus and cortical regions in TS, primarily enhanced connectivity.
Ganos et al. [19]	14 adults with TS 15 adult controls	fMRI during a stop signal task Measures: task performance, fMRI activity during task conditions	Behavioral performance did not differ between TS and controls, but activity in dorsal premotor cortex differed; stronger activity for successful stop than successful go trials in controls, while stronger activity for successful go than successful stop trials in TS.
Thomalla et al. [20]	15 adults with TS 15 adult controls	fMRI during a Go/NoGo task Measures: task performance, fMRI activity during task conditions	Slower RT on Go trials accompanied by reduced activity in motor regions (M1, SMA, dorsal premotor cortex) in TS
Ganos et al. [24]	14 adults with TS	fMRI during tic inhibition and free ticcing Measures: resting state fMRI regional homogeneity	Increased regional homogeneity in left inferior frontal gyrus during tic inhibition vs. free ticcing
Cui et al. [23]	17 children with TS 15 child controls	Resting state fMRI Measures: amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF)	Decreased ALFF and fALFF in frontal and parietal regions; increased fALFF in subcortical regions (correlated with tic severity in thalamus)
Neuner et al. [25]	16 adults with TS (subset of 10 used for tic-related fMRI analysis)	fMRI Measures: tic-related fMRI activity 2 s before a tic, 1 s before a tic, and at tic onset, resting state networks (RSN) analysis	Cortical regions were active before subcortical regions during tics. Tic severity correlated with RSN network integrity in SMA regions
Shprecher et al. [26]	9 adults with TS 10 adult controls	Resting state fMRI Measures: functional connectivity in 116 regions from the AAL atlas	Increased short distance connectivity and decreased long distance connectivity in TS (note that this result is consistent with motion artifacts)
Tinaz et al. [27]	13 adults with TS	Resting state fMRI	

Table 1 (continued)

	Subjects	Method	Findings
	13 adult controls	Measures: functional connectivity in 35 nodes constituting a "urge-tic network", graph theory metrics	Functional connectivity reduced in dorsomedial frontal regions, but increased in thalamus, putamen, insula and between dorsomedial frontal regions and dorsal anterior insula
Deckersbach et al. [43•]	8 adults with TS 8 adult controls	fMRI during a visuospatial priming task Measures: task activity pre and post CBIT	Greater activity in putamen in TS pre CBIT. Reduced activity in putamen in TS post CBIT.
Wu et al. [36]	12 children to young adults (10–22 years); half in active group, half in sham control group	fMRI during finger tapping task Measures: task activity pre and post TMS over the SMA, tic severity pre and post TMS	Improvement in tic severity in both active and sham groups. Reduced fMRI activity in motor regions in active group vs. sham group
Abi-Jaoude et al. [57]	11 adults with TS 11 adult controls	[^{11}C]raclopride PET and [^{11}C]-(+)-PHNO PET Measures: striatal binding potential	No group differences in striatal binding potential, and no significant correlations with symptom severity.
Kumar et al. [58]	12 children with TS 17 children with PANDAS 15 adult controls	^{11}C-[R]-PK11195 PET Measures: ligand TSPO receptor binding in basal ganglia and thalamus	Increased binding potential in the caudate in TS, and increased binding potential in the caudate and lentiform in PANDAS, compared to controls.
Black et al. [59]	5 adults with TS 5 adult controls (pilot study)	[^{11}C]raclopride PET Measures: synaptic dopamine release before and during levodopa or placebo infusion, [^{11}C]raclopride (RAC*) binding potential	In the midbrain, levodopa displaced RAC* by 59 % in controls, but increased RAC* binding potential by 74 % in TS. No differences in the striatum.
Draper et al. [45•]	15 adolescents with TS 15 adolescent controls	Multimodal: GABA MRS, T1-weighted MRI, fMRI during finger tapping, TMS, diffusion-weighted imaging Measures: GABA concentration, CSF, gray matter, and white matter volume, finger tapping activity, cortical-spinal excitability, FA Focus on M1, SMA, primary visual cortex	Elevated GABA in SMA, but not in M1 or visual cortex, in TS. Increased GABA in SMA related to decreased fMRI activity in SMA and cortical excitability. Increased GABA in SMA related to increased motor tic severity and FA within a region of the corpus callosum that projects to the SMA.
Tinaz et al. [44•]	15 adults with TS 15 adult controls	Multimodal: T1-weighted MRI, resting state fMRI, GABA MRS, MEG Measures: cortical volume and thickness, seed-based functional connectivity, GABA concentration(?), beta band power Focus on sensorimotor cortex	In the sensorimotor cortex, no significant group differences in GABA or beta band power, but the relationship between was opposite in TS. Trend for increase functional connectivity between the insula and sensorimotor cortex in TS.

Subject numbers refer to those subjects included in final analyses

ADC apparent diffusion coefficient, *CBIT* comprehensive behavioral intervention for tics, *FA* fractional anisotropy, *M1* primary motor cortex, *MEG* magnetoencephalography, *MRS* magnetic resonance spectroscopy, *PET* positron emission tomorgraphy, *SMA* supplementary motor cortex, *TMS* transcranial magnetic stimulation, *VBM* voxel-based morphometry

excluding those patients who are most typical of TS (as only ~10 % of TS patients have no comorbid conditions [16]), the results are more generalizable to real-world patients [17]. We favor such an inclusive approach for neuroimaging studies in TS and developmental neuropsychiatric disorders in general [18].

Functional Activity and Connectivity

Functional neuroimaging has seen a similar shift in focus from independently activated brain regions to functional connectivity. Conventional fMRI studies examine task activation, that is, changes in brain activity while subjects perform cognitive or motor tasks (or change state, e.g., sleep, or are given a drug). This method identifies brain regions that show modulated activity in response to certain cognitive demands or states. Task fMRI continues to provide insight into cognitive processes in TS, and recent studies have shown atypical activation in motor and premotor regions in TS during tasks of inhibitory control [19, 20].

In contrast to task fMRI, functional connectivity MRI examines the temporal correlation between different brain regions' activity. To study functional connectivity, many investigators use resting state fMRI. Resting state fMRI measures spontaneous, low-frequency brain activity in the absence of a task (i.e., subjects "rest" while awake in the scanner). The use of this technique has increased exponentially in recent years [21] and has demonstrated that fMRI activity is highly correlated between functionally related brain regions, allowing for the study of functional brain networks [22]. A number of neuroimaging papers in TS during 2014–2015 used resting state fMRI. Some found differences between TS and controls using regional measures derived from resting state fMRI, including amplitude of low-frequency fluctuations [23] and regional homogeneity [24]. However, these measures do not directly measure functional connectivity between brain regions, and biological interpretation of these particular measures is obscure. Other recent studies have implemented a network science approach, directly examining functional connectivity (i.e., correlations) between brain regions in order to interrogate functional brain networks in TS [25–27]. Unfortunately, the sample sizes in these reports were relatively small, and in-scanner movement confounds were not adequately addressed (as discussed in the "Conclusion," below). In addition, while we commend the application of network science to study functional connectivity in TS, researchers must keep in mind the inherent problems with applying certain analytic tools to the correlation networks used in functional connectivity studies. In particular, graph theory is often used to interrogate networks; a network is composed of nodes (here, brain regions) and edges (the correlations between brain regions), allowing information about the network to be measured, including node degree (number of connections) and path length (number of edges between two given nodes). Unfortunately, graph theory metrics based on node degree or path length, such as global efficiency (a measure of functional integration) and betweenness centrality (a measure of a node's centrality within a network), must be viewed with caution, as such metrics are much less interpretable for a correlation-based network than for traditional networks such as social or airport networks [28, 29].

A common approach used in functional connectivity studies is to narrow the search space, focusing on a subset of a priori brain regions or selecting particular networks to include in analyses. Several TS studies of functional connectivity have taken this approach [26, 27, 30, 31]. However, investigating many brain regions or networks at the same time may provide a more comprehensive understanding of how the brain functions in any particular neuropsychiatric disorder. Our laboratory recently used such an approach to study functional connectivity in 42 children with TS and 42 controls [32], while applying the strictest methods in the field to minimize potential motion artifacts [33]. We investigated all ~34,000 pairwise correlations among 264 functionally defined regions that constitute many well-described functional networks [34]. Traditional univariate methods—namely independent sample *t* tests for each correlation pair, with proper multiple comparisons correction—did not detect significant differences between children with and without TS, whereas a multivariate approach—namely, support vector machine classification—was able to significantly discriminate the groups based on whole-brain functional connectivity patterns. Functional connections within and between motor networks and executive control networks were able to account for most of the discriminability between groups. Thus, taking a multi-network approach is useful, but can suffer from problems of multiple comparisons when using traditional univariate analyses. Fortunately, with continuing advances in multivariate methods, researchers will be able to study whole-brain connectivity more readily in TS, and continued application of these methods will lead to a more comprehensive understanding of the underlying mechanisms.

Treatment Effects

Understanding the mechanisms of treatments is a fruitful avenue of study and can lead to treatment advances and a better understanding of the underlying disorder. TS is most commonly treated with psychoactive medications, including antipsychotics and centrally acting adrenergic agents. However, medications are not effective for all patients and have the potential for adverse effects [35]. Therefore, nonpharmacological therapies are desirable. This year, two studies used neuroimaging to investigate the brain mechanisms underlying some of these treatments.

One small study in 10–22 year olds with TS investigated fMRI activity during a motor task before and after transcranial magnetic stimulation (TMS) over the supplementary motor area (SMA) [36]. While previous studies have suggested that TMS over the SMA may be an effective treatment for TS [37, 38], Wu et al. did not find differences in tic severity improvement between the active TMS group and a sham control group, as half of the subjects in both groups improved. Thus, although they found reduced fMRI activity in motor regions in the active TMS group compared to the sham control group, it is difficult to attribute these changes to the treatment.

Another recent study that examined brain activity before and after treatment investigated comprehensive behavioral intervention for tics (CBIT). CBIT is an extension of habit reversal therapy and involves training in tic urge awareness, executing competing responses, relaxation, identification of tic-inducing situations and settings, and tic disorder knowledge [39]. The evidence for CBIT's efficacy in treating tics is stronger than for any class of medications other than dopamine antagonists [40], and its effect size is similar to that of risperidone [41, 42]. Given its efficacy and its demonstrated absence of side effects, CBIT has become a promising alternative to medications. The same group that conducted the randomized trials recently investigated the brain mechanisms underlying CBIT, publishing the first study to examine functional activity in the brain before and after CBIT [43•]. In a small group of adults with and without TS, they demonstrated group differences in putamen fMRI activity during a visuospatial priming task both before and after the TS group underwent CBIT. Specifically, at baseline (before CBIT), the TS group demonstrated greater putamen activation during this response inhibition task compared to controls, but reduced putamen activation compared to controls after CBIT. The authors suggest that CBIT may normalize aberrant putamen activity in patients with TS, providing a clue into the mechanisms underlying this treatment. While the sample size was small, the results hold promise for future larger studies and represent a significant step in understanding the effects of behavioral treatment of tics.

Converging Imaging Methods

Applying multiple neuroimaging methods to the same subjects can identify converging findings and can help construct a multi-level understanding of the research question under study. Two studies from 2014 to 2015 investigated GABA concentration using magnetic resonance spectroscopy (MRS) in addition to several other structural and functional MRI measures, targeting specific regions of interest [44•, 45•]. Tinaz et al. [44•] measured GABA, cortical volume and thickness, seed-based resting state functional connectivity MRI, and beta band power (using magnetoencephalography (MEG)). Focusing on sensorimotor regions, they found no group differences in volume, thickness, GABA, or beta band power; yet, the relationship between GABA and beta band power differed between groups. Thus, studies using single methods would find no difference between groups; yet, by using multiple methods, the authors were able to identify group differences in the relationship between measures. Draper et al. [45•] investigated GABA, regional volume, fMRI activity during finger tapping, cortical-spinal excitability (using TMS), and fractional anisotropy, targeting left primary motor cortex (M1), SMA, and primary visual cortex (V1; as a control region). Results demonstrated elevated GABA concentration in the SMA, but not in M1 or V1, in TS. Further, increased GABA in the SMA was associated with decreased fMRI activity and cortical excitability in the same regions. By contrast, increased GABA in the SMA was associated with increased motor tic severity and FA within a region of the corpus callosum that projects to the SMA. The authors discuss their findings in the context of tonic inhibition in TS (related to enhanced control), positing that increased extracellular GABA in the SMA leads to tonic inhibition. These findings underscore that the complex pathobiology of TS may best be identified through a methodology that embraces such complexity.

Conclusion and Comments

In this brief review, we discuss and highlight several TS neuroimaging studies published during 2014–2015. For a more complete list of studies, see Table 1. While this recent research has provided some interesting findings, some concerns are common to many of these studies, namely motion confounds and modest sample sizes.

Subject movement in the scanner is a known problem for neuroimaging. Thus, motion correction steps are universal to analyses of structural MRI, fMRI, and diffusion-weighted MRI data. However, during the past several years, neuroimaging researchers have discovered lingering effects of motion, despite such correction, that can induce apparent group differences. In 2012, several groups reported on a motion artifact present in functional connectivity data even after standard motion correction procedures [46–48]. Specifically, small-amplitude (sub-millimeter) head movements induce a distance-dependent artifact, such that functional correlations between nearby brain regions are inflated compared to functional correlations between spatially distant brain regions. At the time, several prominent developmental and aging neuroimaging studies showed that children and older adults had stronger short-distance correlations and weaker long-distance correlations compared to young adults, suggesting increased local connectivity during childhood and during aging [49, 50]. Further, groups studying clinical populations

(including our own) found similar distance-dependent effects when comparing patient and control groups [e.g., 30, 51, 52]. Specific to TS, results were then interpreted as reflecting immature functional connectivity [30, 31]. Unfortunately, children and older adults move more than young adults, and patients often move more than controls. Thus, these findings of local hyperconnectivity and long-distance underconnectivity were likely driven, at least in part, by motion artifacts not accounted for by standard motion correction procedures nor by matching groups on average motion estimates.

Recent and future functional connectivity studies in TS should therefore pay increased attention to motion confounds and should implement processing steps that minimize artifactual results. Results that demonstrate increased local connectivity in subjects with TS, who likely have greater in-scanner motion than controls, should be viewed with caution and should warrant further investigation of the effects of motion (for a review of methods to reduce motion effects, see [53]). In our recent functional connectivity study in children with TS [32], we implemented strict processing methods to minimize motion artifact. Interestingly, we did not find evidence for immature functional connectivity in TS (i.e., machine learning tools predicted chronological age comparably for children with and without TS based on patterns of functional connectivity), suggesting strongly that group differences reflect atypicality, not immaturity. In addition to functional connectivity, recent work has shown that subject movement also can affect measures of structural MRI volume and cortical thickness [12] and diffusion-weighted imaging measures [54, 55]. Further, Yendiki et al. [55] demonstrated that certain white matter tracts are more prone to motion artifacts than others. Thus, the neuroimaging studies discussed in this review should be considered in light of the potential for motion artifacts, and future studies in TS should better address issues of motion.

Another common limitation in many of the recent studies is that they examined modest sample sizes. Low power from small samples is a natural and perhaps even appropriate early step in developing new methods for studying TS. However, this limitation makes it difficult to determine whether a negative finding reflects a true null result or an underpowered study. In addition, small sample sizes are more likely to lead to inconsistent results across studies [56]. Larger samples not only reduce type I and type II error, but also can allow for subgroup analyses and for more reliable examination of relationships between neuroimaging measures and continuous measures of symptoms or behavior. Thus, we encourage future studies to increase sample sizes, as studies with 10–15 subjects per group are likely underpowered.

Overall, the TS neuroimaging studies published in 2014–2015 provide interesting preliminary results. In the future, some of these findings certainly will be replicated and push our knowledge forward, and neuroimaging methods will continue to be developed and applied to the study of TS. We look forward to further novel studies in addition to larger, more definitive studies [57, 58].

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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