SUPPLEMENTARY MATERIAL

Table. *Neuroimaging studies on the premonitory urge and sensory function in patients with Tourette syndrome.*

Authors	Year	Patients	Male gender (%)	Mean age (range)	Adults/ Children	Diagnosis	Mean YGTSS (/50)	Mean PUTS (/36)	Co-morbid disorders	Functional/ structural neuroimaging	Imaging technique	Findings	Limitations
Stern E et al.	2000	6	6 (100%)	37 (25-47)	Adults	TS (DSM-IV)	NA[1]	NA	NA	Functional	PET	Tic occurrence correlated with activity in the medial and lateral premotor cortices, anterior cingulate cortex, dorsolateral-rostral prefrontal cortex, inferior parietal cortex, putamen, and caudate, as well as primary motor cortex, Broca's area, superior temporal gyrus, insula, and claustrum. Aberrant activity in the interrelated sensorimotor, language, executive, and paralimbic circuits could account for the initiation and execution of diverse motor and vocal behaviors that characterize tics in TS, as well as for the urges that accompany them.	Small sample size. Possible medication effect. More subtle tics could have been missed, despite the use of two videotapes and throat microphone. The temporal discrimination achieved with this imaging technique was not due to direct temporal resolution, the timing measures were to the nearest second, possible subcomponents of tics could not be resolved, and it was not possible to establish where the activation in the identified systems began, or whether it occurred in parallel.
Bohlhalter S et al.	2006	10	4 (40%)	31 (17-49)	Adults	TS (DSM-IV-TR)	NA[1]	NA[2]	4 OCD, 2 ADHD	Functional	Event-related MRI	A brain network of paralimbic areas such as anterior cingulate and insular cortex, supplementary motor area and parietal operculum predominantly activated on event-related fMRI before tic onset.	The heterogeneity of recorded tics could have been a confounding factor. Possible contamination by tic suppression
Lerner A et al.	2007	9	7 (78%)	NA (22-44)	Adults	TS (DSM-IV)	NA	NA	7 OCD, 5 ADHD	Functional	PET	Robust activation of cerebellum, insula, thalamus, and putamen during tic release. Abnormal activity in paralimbic areas, in particular insula and anterior cingulate, could generate the discomfort of the premonitory urge	For technical reasons, stage 2 sleep rather than rest was used as a baseline to which the tic state was compared. Motor execution of tics could have contributed to the cerebellar activity

Hampson M et al.	2009	16	13 (81%)	30 (18-56)	Adults	13 TS, 3 CTD	NA	NA	2 OCD, 2 ADHD	Functional	MRI	The supplementary motor area showed a significantly broader profile of cross-correlation to motor cortex during tics than during intentional movements, highlighting the importance of the supplementary motor area in tic generation	Intensity of premonitory urges, severity of illness, and duration of illness were not characterized, therefore the relationship between supplementary motor area activity patterns and these variables could not be investigated
Draganski B et al.	2010	40	30 (75%)	32 (18-56)	Adults	TS (DSM-IV-TR)	29	22	14 OCD, 19 ADHD	Structural	VBM and cortical thickness MRI	The intensity of premonitory urges for tics (assessed by PUTS scores) showed significant positive correlation with grey matter volume and cortical thickness in the left somatosensory cortex and the prefrontal cortex	Referral bias. Lack of screening for some co-morbid psychiatric disorders, such as personality disorders
Wang Z et al.	2011	13	8 (%)	34 (NA)	Adults	TS	24	NA	6 OCD, 1 ADHD	Functional	MRI	Patients with TS showed stronger activity within during spontaneous tics than during voluntary tics in somatosensory and posterior parietal cortices, putamen, and amygdala/hippocampus complex, suggesting that activity in these regions may represent features of the premonitory urges that generate spontaneous tic behaviors.	Small sample size, inclusion of medicated patients and co-morbid disorders, and absence of adults with remitted symptoms. Lack of stringent control for the strength, duration, or pacing of tics across conditions or groups
Biermann-Ruben K et al.	2012	12	10 (83%)	12 (22-54)	Adults	TS (DSM-IV-TR)	21	NA	0 OCD, 0 ADHD	Functional	MEG	Movement-evoked field amplitudes in the self paced movement task were negatively correlated with severity and frequency of tics, suggesting that changes in sensory feedback loops during voluntary movements might also have an impact on tic control and that the sensory system and somatosensory-motor interaction are relevant to tic pathophysiology	Highly selected study sample, not representative of the complexity and variability of TS presentations, where co-morbidities are present in the vast majority of patients
Neuner I et al.	2014	10	7 (70%)	32 (19-56)	Adults	TS (DSM-IV)	22	NA	3 OCD, 0 ADHD	Functional	MRI	Within a single free-ticcing fMRI session, supplementary motor area, ventral primary motor cortex, primary sensorimotor	Low temporal resolution of fMRI-based approach. The use of a MR-compatible camera

												cortex and parietal operculum activated 2 seconds before tic onset; anterior cingulate, putamen, insula, amygdala, cerebellum and the extrastriatal-visual cortex activation 1 second before tic onset; thalamus, central operculum, primary motor and somatosensory cortices activated at tic onset.	system to introduce objectivity in the definition of onset and duration of tics also introduced a potential factor contributing to data loss. By including moderate-to-severely affected TS, the study sample exhibited a high ratio of medicated participants
Tinaz S et al.	2014	15	12 (80%)	31 (18-52)	Adults	TS (DSM-IV)	21	31	10 OCD, 2 ADHD	Structural + functional	MRI + MRS + MEG	Correlation between the baseline beta band power and GABA+/creatine ratio was abnormal and the anterior insula showed increased functional connectivity with the sensorimotor cortex in patients with TS. Altered limbic input to the sensorimotor cortex and abnormal GABA-mediated beta oscillations in the sensorimotor cortex may underpin some of the sensorimotor processing disturbances in TS and contribute to tic generation	Heterogeneity of patient cohort in terms of age and co-morbid disorders. Possibility that creatine is not the most stable reference in TS. Inherent limitations of the GABA ^{1}H MRS technique. No test for lateralization effects associated with tics
Puts NA et al.	2015	23	22 (96%)	11 (8-12)	Children	TS	20	NA	6 OCD, 11 ADHD	Structural	MRI + MRS	Reduced primary sensorimotor cortex GABA concentration in children with TS compared with healthy controls, as well as patterns of impaired performance on tactile detection and adaptation tasks, consistent with altered GABAergic function	MRS of GABA was limited by low signal-to-noise ratio, so that a single measurement of total GABA was acquired from a large region that includes primary motor and sensory cortices. The sensorimotor GABA signal was the sum of motor and somatosensory GABA signals
Tinaz S et al.	2015	13	10 (77%)	NA (18-46)	Adults	TS	22	30	NA	Functional	MRI	The right dorsal anterior insula demonstrated higher resting-state functional connectivity, especially with the frontostriatal nodes of the urge-to-tic network in patients	The possible role of the cerebellum in the urge-tic network was not addressed, as cerebellar coverage was not

												with TS, compared with controls. The functional connectivity between the right dorsal anterior insula and bilateral supplementary motor area also correlated positively with urge severity in patients. The right dorsal anterior insula might be responsible for heightened awareness of bodily sensations generating premonitory urges in TS	obtained for every subject during scanning. The standard instruction to avoid head motion as much as possible could have made the patients more self aware of their urges, and more prone to actively suppress their tics
Draper A et al.	2016	29	26 (90%)	14 (8-21)	Children and young adults	TS	23	17	6 OCD, 1 ADHD	Structural	MRI	Premonitory urges were inversely associated with grey matter thickness measurements within the insula and sensorimotor cortex. Grey matter thickness was significantly reduced in sensorimotor cortex, insula, and anterior cingulate cortex in patients with TS relative to controls	Participants were required to remain still while being scanned and tic suppression could have resulted in substantial additional self-monitoring in patients with TS

[1] Tic severity reported as total YGTSS scores (/100) instead of total tic severity scores (/50).

[2] Premonitory urges presented as percentages of tics associated with urge.

Abbreviations: ADHD, Attention-Deficit and Hyperactivity Disorder; CTD, Chronic Tic Disorder; DSM-IV-TR, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision; GABA, Gamma Aminobutyric Acid; MEG, Magnetoencephalography; MRI, Magnetic Resonance Imaging; MRS, Magnetic Resonance Spectroscopy; NA, Not Available; OCD, Obsessive-Compulsive Disorder; PET, Positron Emission Tomography; PUTS, Premonitory Urge for Tics Scale; VBM, Voxel-Based Morphometry; YGTSS, Yale Global Tic Severity Scale.