CALL FOR PAPERS | *Neurophysiology of Tactile Perception: A Tribute to Steven Hsiao*

Reduced GABAergic inhibition and abnormal sensory symptoms in children with Tourette syndrome

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[1]*Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland;* [2]*F. M. Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland;* [3]*Center for Neurodevelopment and Imaging Research, Kennedy Krieger Institute, Baltimore, Maryland;* [4]*Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland;* [5]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland;* and [6]*Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*

Puts NA, Harris AD, Crocetti D, Nettles C, Singer HS, Tommerdahl M, Edden RA, Mostofsky SH. Reduced GABAergic inhibition and abnormal sensory symptoms in children with Tourette syndrome. *J Neurophysiol* 114: 808–817, 2015. First published June 3, 2015; doi:10.1152/jn.00060.2015.—Tourette Syndrome (TS) is characterized by the presence of chronic tics. Individuals with TS often report difficulty with ignoring (habituating to) tactile sensations, and some patients perceive that this contributes to a "premonitory urge" to tic. While common, the physiological basis of impaired tactile processing in TS, and indeed tics themselves, remain poorly understood. It has been well established that GABAergic processing plays an important role in shaping the neurophysiological response to tactile stimulation. Furthermore, there are multiple lines of evidence suggesting that a deficit in GABAergic transmission may contribute to symptoms found in TS. In this study, GABA-edited magnetic resonance spectroscopy (MRS) was combined with a battery of vibrotactile tasks to investigate the role of GABA and atypical sensory processing in children with TS. Our results show reduced primary sensorimotor cortex (SM1) GABA concentration in children with TS compared with healthy control subjects (HC), as well as patterns of impaired performance on tactile detection and adaptation tasks, consistent with altered GABAergic function. Moreover, in children with TS SM1 GABA concentration correlated with motor tic severity, linking the core feature of TS directly to in vivo brain neurochemistry. There was an absence of the typical correlation between GABA and frequency discrimination performance in TS as was seen in HC. These data show that reduced GABA concentration in TS may contribute to both motor tics and sensory impairments in children with TS. Understanding the mechanisms of altered sensory processing in TS may provide a foundation for novel interventions to alleviate these symptoms.

Tourette syndrome; magnetic resonance spectroscopy; GABA; somatosensory function; inhibition; tactile processing

TOURETTE SYNDROME (TS) is a neurodevelopmental disorder characterized by the presence of chronic tics. However, it has long been recognized that individuals with TS often report sensory, primarily tactile, urges (e.g., itchy skin). Many patients report these as contributing to a premonitory urge to tic (Belluscio et al. 2011; Cohen and Leckman 1992; Miguel et al. 2000). Individuals with TS have reported difficulty with ignoring (habituating to) repetitive and consistent tactile stimuli (Cohen and Leckman 1992; Leckman et al. 1993) and show differences in stimulus detection threshold (Belluscio et al. 2011), suggesting impaired tactile processing. Although the link between sensory abnormalities and motor tics is recognized by many individuals with TS (Du et al. 2010; Jankovic 1997; Robertson et al. 1988), there is limited understanding of the role, scope, and mechanisms underlying sensory phenomenon in TS and its association with motor impairments.

Recent work has suggested that a deficit in cortical GABAergic inhibitory transmission may contribute to symptoms found in TS: GABA-related genes have been associated with risk for TS and with symptom severity (Fernandez et al. 2012; Tian et al. 2011); serum GABA levels are reduced in TS patients; and medication affecting the GABAergic system has been shown to reduce tics (Wang et al. 2012). Furthermore, altered GABA-A receptors and reduced density of GABAergic interneurons (Kalanithi et al. 2005; Lerner et al. 2012) have been shown in TS. GABA concentration can be measured in vivo with edited magnetic resonance spectroscopy (MRS) (Mescher et al. 1998; Puts and Edden 2012).

GABAergic processes play an important role in shaping the neuronal response to tactile stimulation. It is thought that subthreshold stimulation predominantly activates feedforward inhibitory mechanisms (Blankenburg et al. 2003; Favorov and Kursun 2011; Zhang et al. 2011). Therefore, a dynamically increasing stimulus will be perceived at a higher amplitude compared with a near-threshold stimulus that was not preceded by subthreshold stimulation (i.e., a static stimulus). We have demonstrated this task difference in healthy adults and typi-

cally developing children [but not children with autism spectrum disorder (ASD); Puts et al. 2013, 2014]. By contrasting a baseline static detection threshold to a task in which a subthreshold stimulus is applied prior to detection, specific tactile functions can be separated and feedforward inhibitory mechanisms investigated. Such mechanisms are thought to be involved in filtering of sensory input. Amplitude discrimination relies on proper separation of signals between the left index finger (LD2) and the left middle finger (LD3), a mechanism that is, in part, dependent on GABAergic lateral inhibitory connections in cortical layer III [indeed, separation of two distinct signals disappears when a GABA antagonist is applied (Whitsel et al. 1989)]. Adaptation, the process of adjusting one's senses to incoming sensory stimuli, is a short-term plasticity mechanism crucial for refining one's response to sensory stimuli. By means of adaptation (an adapting stimulus prior to one of the test stimuli), the perceived intensity of the subsequent stimulus is weakened as firing rate drops (Whitsel et al. 2003), which we would expect to make discrimination of the two test stimuli more difficult. Adaptation is an important aspect of habituation to sensory input (Tannan et al. 2006, 2007, 2008). Finally, frequency discrimination relies on correct temporal encoding of frequencies, in which GABA plays a role (Puts et al. 2011) [by gating synchronous and periodic firing (McLaughlin and Juliano 2005)]. This periodic encoding disappears when GABA antagonists are applied. Recent studies in healthy adults have shown that GABA concentration in vivo is correlated with behavioral performance on sensory tasks (Boy et al. 2010; Edden et al. 2009). Puts et al. (2011) showed that participants with higher GABA levels perform better at a tactile frequency discrimination task. Altered GABAergic function in TS may be a driving factor contributing to sensory impairments. Sensory processing, and in particular GABAergic aspects of sensory processing, in children can be probed by applying a battery of vibrotactile tasks (Puts et al. 2013).

In this study, GABA-edited MRS was combined with vibrotactile psychophysics to investigate atypical sensory processing in children with TS. Given the importance of GABA in tactile perception, and the theory that the GABAergic system is affected in TS, we hypothesized that, compared with healthy control children (HC), children with TS show lower brain GABA concentration. Furthermore, we expected GABA concentration to correlate with symptom severity, and that children with TS would show an anomalous profile of tactile discrimination and adaptation, supported by impaired cortical GABAergic inhibition, in particular reduced feedforward inhibition and reduced adaptive modulation of amplitude discrimination. The investigation of tactile and related GABAergic dysfunction in TS allows for a deeper understanding of the neurophysiological mechanisms and scope of tactile dysfunction in TS.

METHODS

Participants

Two groups of children aged 8–12 yr were tested on a tactile battery consisting of eight tasks: 67 healthy children (HC; age 10.08 ± 1.28 yr; 13 girls, 54 boys) and 23 children with Tourette syndrome (TS; age 10.60 ± 0.89 yr; 1 girl, 22 boys). Age was not significantly different between groups ($P = 0.17$). A subset of these children [25 HC (1 girl, 24 boys) and 19 TS (1 girl, 18 boys)] underwent GABA-edited MRS (HC: average age 9.96 ± 1.25 yr, TS: average age

10.47 ± 0.88 yr; age t-test $P = 0.2$). A subset (32) of the HC children were included in a previous study testing the validity of the behavioral tasks between healthy adults and HC (Puts et al. 2013). Informed consent was obtained from a parent of each child, and children assented to testing themselves, under protocols reviewed and approved by the Kennedy Krieger Institute and Johns Hopkins School of Medicine Institutional Review Boards.

Inclusion and Exclusion Criteria

Diagnosis of TS was based on methods used successfully by the TSA Genetics Consortium, i.e., subject self-report measures supplemented by examination and review by an experienced clinician (H. S. Singer or S. H. Mostofsky). Self-report on the Yale Global Tic Severity Scale (YGTSS) required at least moderate tic severity determined by a minimum total score of ≥14 for both motor and vocal tics or ≥10 if motor or vocal tics only and was acquired in the week prior to the visit. For the TS group, mean Yale tic severity scores were 13 (motor) and 6.64 (vocal) and 37.28 for global tic severity.

None of the participants had *1*) a history of neurological disorders other than TS, *2*) presence of a severe chronic medical disorder, *3*) presence of visual impairment, *4*) history of alcohol or substance abuse, or *5*) history of autism. Children with conduct disorder, childhood schizophrenia or psychosis, major depression, or bipolar disorder were excluded. The Diagnostic Interview for Children and Adolescents—Fourth Edition (DICA-IV) was used to confirm comorbid diagnoses of attention-deficit/hyperactivity disorder (ADHD; 48%), obsessive compulsive disorder (28%), specific phobia (20%), generalized anxiety disorder (8%), and oppositional defiant disorder (8%) among the TS cohort (Reich 2000). Psychotropic medication was allowed, and children who were prescribed stimulant medication (24%) were allowed to take their medication as prescribed. Current medications for the TS cohort included stimulant medication ($n = 6$), guanfacine ($n = 1$), alprazolam ($n = 1$), and sertraline ($n = 1$). All children in the HC cohort were free of criteria for psychiatric disorders as assessed with the DICA-IV, and none of the children in the HC cohort was prescribed psychoactive medications. Standard intellectual functioning was assessed with the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) (Wechsler 2003). Children with full-scale IQ scores below 80 were excluded from participation. Handedness was evaluated with the Edinburgh Handedness Inventory (Oldfield 1971); 1 of 23 TS and 5 of 67 HC were left-handed.

Behavioral

All children performed a battery of vibrotactile tasks outside the scanner. The procedures have been described in greater detail and visually elsewhere (Puts et al. 2013). This battery has been shown to be suitable for children and was acquired in 30–40 min (with a break half-way).

A CM4 four-digit tactile stimulator (Cortical Metrics) was used for vibrotactile stimulation (Holden et al. 2012). Stimuli were delivered to the glabrous skin of LD2 and LD3, and all stimuli were presented within the flutter range (0–50 Hz) with sinusoidal stimuli. Visual feedback, task responses, and data collection were performed on an Acer Onebook Netbook computer running Cortical Metrics software (Holden et al. 2012). The vibrotactile testing battery consisted of eight tests divided into four tasks each with two conditions.

Simple and choice reaction time. In these tasks, participants were asked to press a button as soon as they felt a suprathreshold vibrotactile stimulus (25 Hz, 300 μm, 40 ms); in the choice task, they had to indicate stimulus location as well [intertrial interval (ITI) 3 s; 20 trials]. These tasks were performed to judge attention and task compliance. For each participant, reaction times were sorted (correct trials only in the choice condition) and a truncated mean was calculated by averaging the median six values (to exclude the effect of extreme outliers on mean reaction time).

Static and dynamic detection threshold. In the static task, in each trial a weak stimulus (starting amplitude 25 μm, 25 Hz, 500 ms) was applied to either LD3 or LD3, and participants were asked to indicate on which finger the stimulus was applied (ITI = 5 s; 24 trials). Stimulus level was decreased for the next trial when a correct answer was given and increased when a wrong answer was given, using stepwise tracking (details can be found in Puts et al. 2013, 2014). In the dynamic task, stimulus amplitude started at zero after a variable delay (0–2,500 ms) and increased with 2 μm/s (ITI 10 s; 7 trials). Participants were asked to press a button when the stimulus was perceived. Feedforward inhibition is crucial in sensory perception, and by contrasting static and dynamic detection threshold the extent of feedforward inhibition can be probed.

Amplitude discrimination without adaptation ("baseline") and with single-site adaptation. In the baseline condition, two stimuli (both 25 Hz; 500 ms; standard stimulus amplitude: 100 μm; initial comparison stimulus amplitude: 200 μm; ITI 5 s; 20 trials) were applied on LD2 and LD3 simultaneously, and participants were asked to judge which of the two stimuli had higher amplitude. The difference between the two stimuli was decreased for the next trial when a correct answer was given and increased when a wrong answer was given, using stepwise tracking. In the adaptation task, one of the two test stimuli was preceded by a 1-s-long "adapting" stimulus (Puts et al. 2013) (amplitude 100 μm), which participants were told to ignore. The effect of adaption was calculated as the percent difference between the threshold in the single-site adaptation task and the baseline no-adaptation task [(Adapt − Base)/Base × 100].

Sequential and simultaneous frequency discrimination. In these tasks, two stimuli with the same amplitude but varying frequency (both 500 ms; 200 μm; standard stimulus frequency 30 Hz; comparison stimulus starting frequency 40 Hz) were applied (either sequentially or simultaneously) on LD2 and LD3 (ITI 5 s; 20 trials). Participants were asked to judge which of the two stimuli had higher frequency. The frequency difference between the two stimuli was decreased for the next trial when a correct answer was given and increased when a wrong answer was given, using stepwise tracking.

MRI Acquisition

On the same day, for each participant, GABA-edited MRS data, with a Philips 3T Achieva MRI scanner (Best, The Netherlands; 32-channel head coil for receive and body coil for transmit), were acquired from a voxel (3 cm)^3 placed on the right sensorimotor cortex (SM1; as tactile stimulation was performed on the left hand) and was centered on the central sulcus posterior to the hand knob (Yousry et al. 1997) in the axial plane (Fig. 1A). The voxel was rotated to align with the cortical surface by rotating in the coronal slice and subsequently in the sagittal slice, as shown in Fig. 1A and previously described (Puts et al. 2011). Prior to voxel placement, a 1-mm^3 isotropic T1-weighted image (MP-RAGE) was acquired for voxel localization (TR = 7.99 ms, TE = 3.76 ms, flip angle = 8°). GABA-edited MEGA-PRESS scans were acquired with the following parameters: TE = 68 ms, 14-ms editing pulses at 7.46 ppm (edit-OFF) and 1.9 ppm (edit-ON), TR = 2 s, 40 blocks of 8-step phase cycles in a ~10-min acquisition, 2,048 data points, 2-kHz spectral width, VAPOR water suppression. An unsuppressed water scan with the same parameters was acquired for quantification. All scanning was performed on the same day as the vibrotactile testing.

Analysis

Behavioral data were visually inspected prior to analysis. Data for individual tasks were excluded when it was observed by the experimenter that the participant was unable to execute the task properly (e.g., random button presses) or when inspection of the tracking profile showed that deviations in stimulus value over the last five trials were greater than four times the starting value, divided by the number
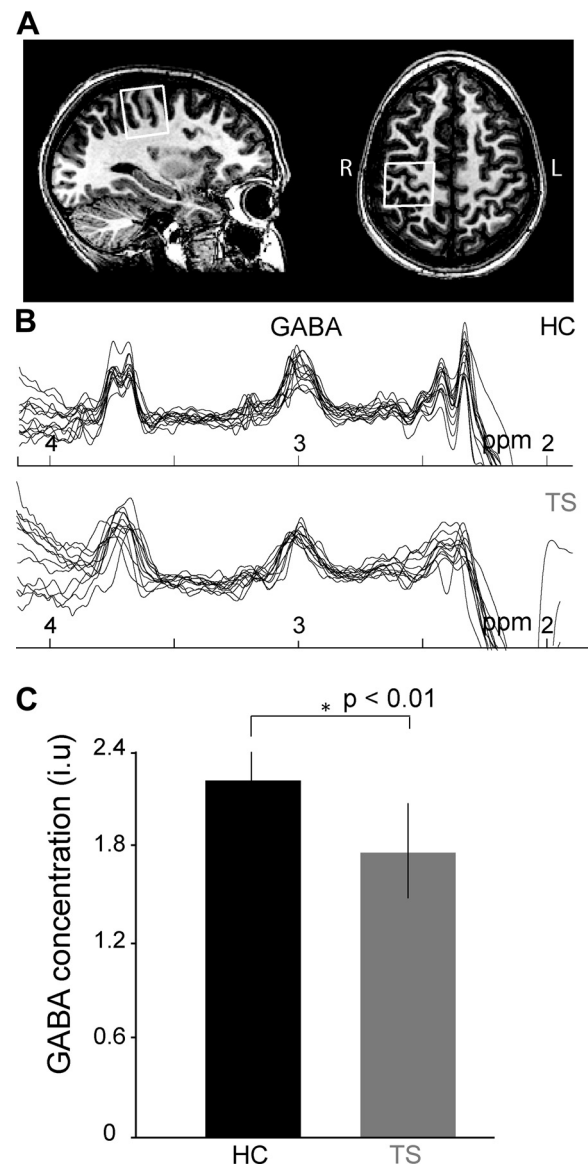

Fig. 1. Edited magnetic resonance spectroscopy (MRS) of GABA. A: example voxel location for the sensorimotor region. The voxel was centered on the hand knob and rotated to align with the edge of the brain. B: example spectra from healthy control subjects (HC) and subjects with Tourette syndrome (TS); 6 TS and 1 HC were excluded because of excessive motion. There were no significant differences in spectral quality between cohorts for data included in the quantitative analysis. C: GABA concentration [institutional units (iu)] over sensorimotor cortex is significantly reduced in TS.

of trials (see Puts et al. 2013, 2014 for details). For each task a univariate model analysis was performed with condition as dependent measure (e.g., simple reaction time and choice reaction time) and diagnosis as between-subjects factor with SPSS 17 (SPSS, Chicago, IL). Main effects of task and diagnosis, as well as interactions, are reported. Further post hoc testing was performed to determine differences in individual tasks between the two cohorts. Reported *P* values are not corrected for multiple comparisons. This is a preliminary study on a relatively small cohort, with analyses based on a priori hypotheses. Independence between measures needs further inquiry. Gannet (Edden et al. 2014) was used for analysis of the MRS spectra, and GABA concentrations were calculated relative to the unsuppressed water signal from the same region. All of the time domain data were frequency- and phase-corrected with spectral registration (Near et al. 2014), filtered with a 3-Hz exponential line broadening, and zero-

filled by a factor of 16. GABA concentration was estimated with a single Gaussian peak with a five-parameter Gaussian model, fitting between 2.79 and 3.55 ppm. The GABA signal is quantified relative to the unsuppressed water signal (fit with a Gaussian-Lorentzian model) in institutional units (iu); secondary quantification is performed relative to the creatine (Cr) peak (from the Cr integral of a two-Lorentzian model of Cr and choline in the OFF spectrum). To account for potential differences in variability in GABA levels, statistical group differences in GABA concentration were additionally tested with a nonparametric Mann-Whitney U-test. It is a concern that children with TS might move more during scans, and motion-related subtraction errors may lead to underestimation of the GABA concentration (Harris et al. 2013). Therefore, the standard deviation of the frequency drift of the water signal across the scan (Harris et al. 2013) and GABA signal fit errors (Evans et al. 2013) were used as a metric for data quality. Scans where no clear GABA signal could be identified or where Gannet fitting failed were excluded. Pearson correlations were used to examine whether GABA concentration was correlated with behavioral frequency discrimination threshold [as shown previously (Puts et al. 2011)] and tactile adaptation (for those children with good-quality data for MRS and both amplitude discrimination tasks), as well as with disease severity.

RESULTS

Behavioral

Table 1 shows group average thresholds for each group and statistical analysis between conditions within a task and between cohorts. As some participants were excluded because of poor compliance or poor task comprehension, participant numbers are also shown.

There was no effect of diagnosis on reaction time and no significant difference for both simple and choice reaction time between HC and TS. Across both diagnostic groups, there was a significant effect of condition, with choice reaction time being significantly slower for both cohorts ($P < 0.001$; Fig. 2A).

For the detection threshold tasks there was a significant effect of diagnosis ($P < 0.05$), a near significant effect of condition ($P = 0.06$), but no significant interaction of diagnosis and condition ($P = 0.4$). Post hoc analysis showed that, as has been found in healthy populations of adults and children (Puts et al. 2013; Zhang et al. 2011), for the HC group dynamic detection threshold was significantly higher compared with

static detection threshold ($P < 0.001$); however, no such effect was observed in children with TS ($P = 0.35$). Static detection threshold was significantly higher for TS than for HC ($P < 0.05$), but there were no significant differences in dynamic detection ($P = 0.31$; Fig. 2B). Consequently, the percent change between the static and dynamic conditions was significantly higher in HC than in children with TS ($P < 0.001$).

For the amplitude discrimination tasks there was a significant effect of diagnosis ($P < 0.05$), a near significant effect of condition ($P = 0.07$), and a near significant interaction between diagnosis and condition ($P = 0.08$). Post hoc analysis showed that, as has been found in healthy populations of adults and children (Puts et al. 2013; Tannan et al. 2007), for HC group discrimination threshold was significantly higher during the adaptation condition compared with the "baseline" amplitude discrimination condition ($P < 0.001$); however, no such effect was observed in children with TS ($P = 0.78$; Fig. 2C). There were no significant differences in baseline amplitude discrimination threshold between HC and TS, but threshold in the adaptation condition was higher in HC than in TS ($P = 0.012$).

For the frequency discrimination tasks, there was a significant effect of diagnosis ($P = 0.017$) but no effect of condition ($P > 0.5$) and no significant interaction between diagnosis and condition ($P = 0.4$). Post hoc analysis did not show significant differences between groups in either condition. However, whereas for the HC there was no significant difference in discrimination threshold for the simultaneous and sequential conditions ($P = 0.07$), the TS children showed significantly lower threshold in the sequential condition compared with the simultaneous condition ($P = 0.02$; Fig. 2D).

Given the high comorbidity for ADHD, preliminary analyses were also performed between those TS subjects with (11 children) and without (12 children) ADHD with Student's t-tests. No significant differences were found for any of the tasks.

GABA MRS

Data for 6 of 19 TS (including 1 girl) participants and 1 HC participant were excluded because of excessive motion, and no GABA peak could be identified. Figure 1B shows spectra from all HC and 13 TS participants. GABA concentration relative to

Table 1. *Behavioral analysis*

Task Group	Condition	Participants		Average ± SD HC	Average ± SD TS	Main Effects		Task × Diagnosis Interaction, P	Post Hoc Between Tasks-Within Cohort, P		Post Hoc Within Task-Between Cohorts, P
		HC	TS			Condition	Diagnosis		HC	TS	
Reaction time, ms	SRT	67	22	310.79 ± 89.47	309.22 ± 115.73	<0.001	0.6	0.772	<0.001	<0.001	0.6
	CRT	66	22	644.13 ± 179.32	639.55 ± 139.82						0.7
Detection threshold, μm	sD	67	23	6.59 ± 2.81	8.24 ± 2.95	0.06	<0.05	0.4	<0.001	>0.3	<0.05
	dD-RT	64	21	8.13 ± 3.77	8.83 ± 3.91						0.31
Amplitude discrimination, μm	nAD	66	23	49.05 ± 28.34	46.26 ± 28.38	0.07	<0.05	0.08	<0.001	>0.7	0.68
	sAD	62	20	68.90 ± 36.63	46.6 ± 29.15						<0.02
Frequency discrimination, Hz	sqFD	66	22	8.83 ± 4.2	7.22 ± 3.41	>0.5	<0.02	0.4	0.07	0.02	0.11
	smFD	66	22	10.08 ± 3.82	10.01 ± 4.23						0.81

Group average thresholds are shown for each group, with statistical analysis between conditions within a task and between cohorts. As some participants were excluded because of poor compliance or poor task comprehension, participant numbers are also shown. TS, Tourette syndrome subjects; HC, healthy control subjects; SRT, simple reaction time; CRT, choice reaction time; sD, static detection threshold; dD-RT, dynamic detection threshold-reaction time corrected; nAD, amplitude discrimination-no adaptation; sAD, amplitude discrimination-single-site adaptation; sqFD, sequential frequency discrimination; smFD, simultaneous frequency discrimination.

Fig. 2. Behavioral data (mean and SE for each group and condition). *A*: there were no differences in reaction time between cohorts. *B*: static detection threshold was higher in TS, and TS did not show an effect of a dynamic subthreshold on static detection threshold, whereas HC did. *C*: there were no differences in baseline amplitude discrimination between HC and TS. An adapting stimulus makes HC significantly worse, but this effect is absent in TS. Amplitude discrimination after adaptation was significantly worse for HC. *D*: there were no main effects in frequency discrimination between TS and HC, but TS were significantly better at sequential frequency discrimination compared with simultaneous frequency discrimination, whereas this effect was nonsignificant (although trended) in HC.
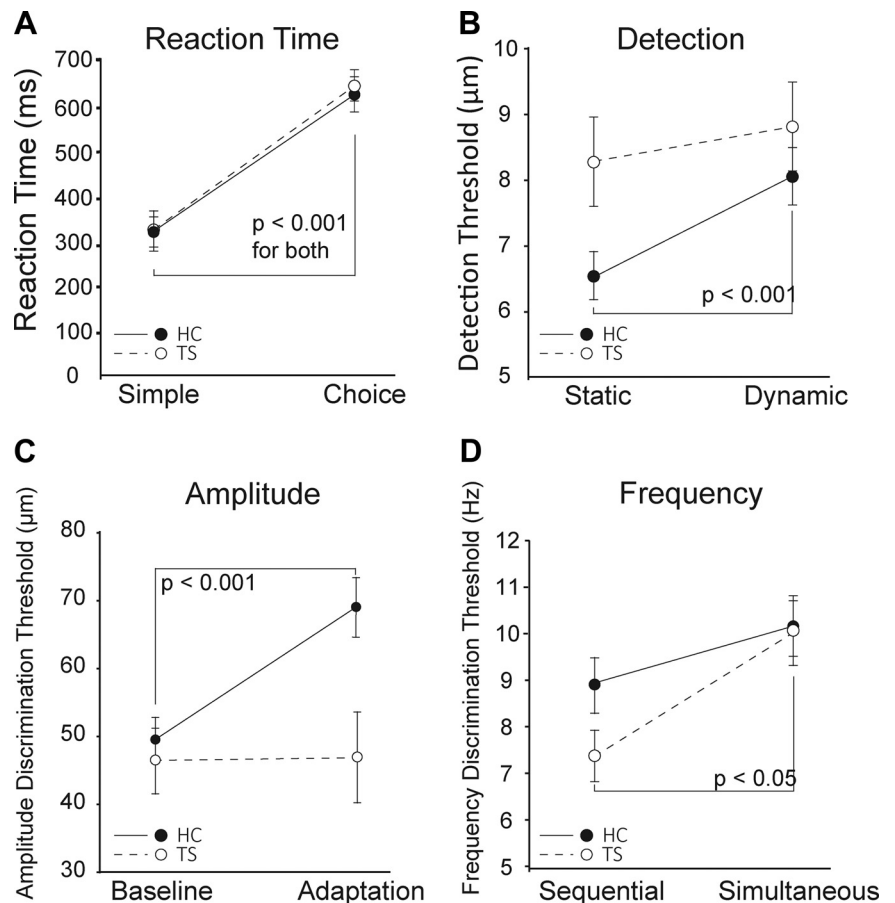
the unsuppressed water signal in the right sensorimotor cortex in children with TS was significantly lower than for HC (Fig. 1*C*; TS = 1.79 ± 0.36 iu, HC = 2.12 ± 0.25 iu; $t = -2.69$, $P < 0.01$).

To exclude the possibility that reduced GABA concentration in TS is driven by excessive frequency drift (an indication of motion), fit errors (HC 8.33 ± 3.48, TS 7.1 ± 2.98) and water frequency drift (an indication of motion; HC 3.27 ± 2.4, TS 5.22 ± 2.63) were compared between TS and HC, were within the expected range, and were not found to be significantly different between groups. Furthermore, GABA concentration did not correlate significantly with water frequency drift in TS ($R = -0.15$, $P = 0.60$). Analysis of the first half of transients for each participant (to reduce the potential for motion-related artifacts later in the scan) showed that GABA levels in TS remained lower compared with HC ($P = 0.04$). To ensure that the decreased GABA concentration was not due to a net decrease across all metabolites, GABA levels across all transients were also expressed against creatine; findings remained consistent, with a significant effect of diagnosis (HC GABA/Cr = 0.13 ± 0.019, TS GABA/Cr = 0.12 ± 0.018; $P = 0.025$). Nonparametric testing of group differences to account for difference in variability between groups also showed a significant reduction in TS for GABA quantified to unsuppressed water ($Z = -3.209$, $P = 0.0014$) and GABA quantified against creatine ($Z = -2.048$, $P = 0.041$). Finally, secondary analysis on only those TS participants not on medication (to exclude an effect of medication) also revealed reduced GABA levels compared with HC ($P < 0.0001$).

Correlation of MRS GABA with Diagnostic/Behavioral Measures

In children with TS, right SM1 GABA concentration correlated strongly and significantly ($r = -0.55$, $P = 0.011$) with motor tic severity (but not vocal or global tic severity), with lower GABA concentration associated with greater motor tic severity (Fig. 3*A*). Motor tic severity correlated with vocal ($R = 0.41$) and overall ($R = 0.5$) tic severity. In HC, right hemisphere SM1 GABA concentration correlated significantly with sequential frequency discrimination performed on the left hand [$r = -0.58$, $P < 0.01$, replicating the results seen previously (Puts et al. 2011)]. In HC SM1 GABA concentration also correlated with the effect of adaptation (as expressed as % difference between "baseline" amplitude discrimination and adaptation; $r = -0.44$, $P = 0.03$). This means that higher GABA concentration is associated with better frequency discrimination but with a smaller effect of adaptation. These correlations were absent in children with TS (Fig. 3, *B* and *C*).

DISCUSSION

To our knowledge, this is the first study to measure GABA concentration in TS in vivo and the first to apply a broad assessment of vibrotactile tasks to test the underlying neurophysiology of tactile (dys)function in children with TS.

Consistent with our hypotheses, we showed reduced SM1 GABA concentration in children with TS and, importantly, that GABA concentration in TS correlates with a measure of tic severity. Tactile testing revealed no TS-associated differences
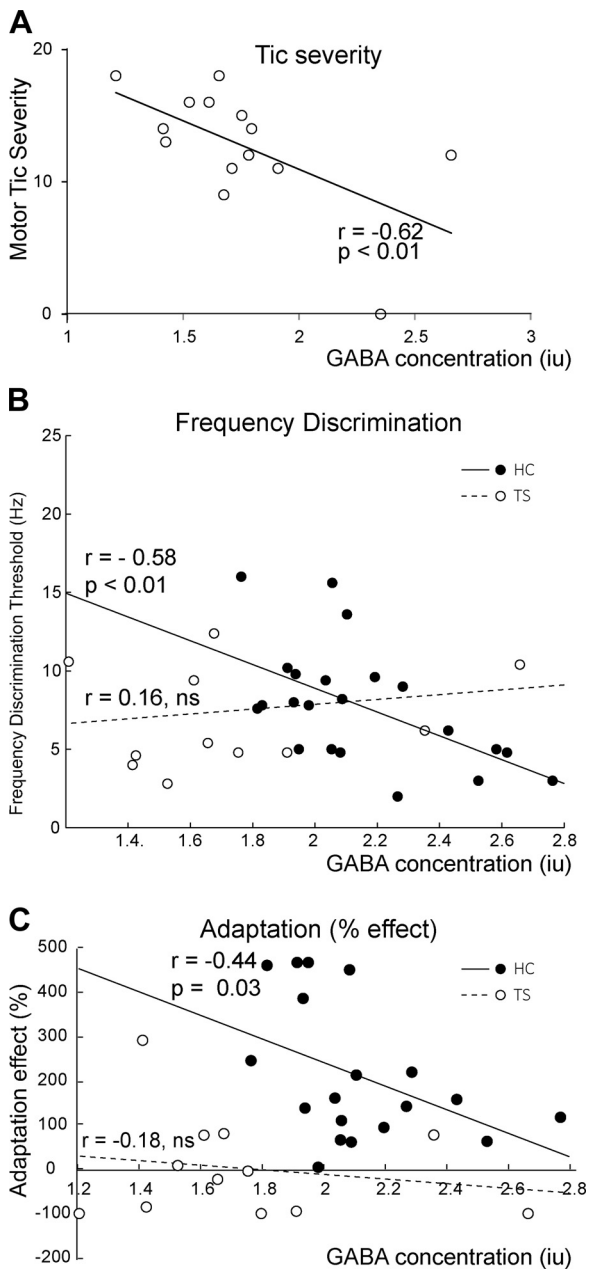
Fig. 3. GABA correlations. *A*: right sensorimotor GABA concentration correlates significantly with motor tic severity in children with TS. *B*: right sensorimotor GABA concentration correlates significantly with sequential frequency discrimination in HC but not in TS. *C*: right sensorimotor GABA concentration correlates significantly with the effect of adaptation in HC but not in TS. ns, Nonsignificant. Note that these results only show the effect for children with both good-quality GABA spectra and measurable performance on both "baseline" amplitude discrimination and single-site adaptation (19 HC and 12 TS).

seen in HC, was also absent in TS. The combined imaging and behavioral findings suggest that GABAergic function may be associated with TS and may contribute to sensory and motor impairments characteristic of TS.

Tasks of this length were well tolerated by children aged 8–12 yr. Our battery of tasks was developed to be accessible for pediatric cohorts, and thus it was decided to limit the number of trials, which necessitated enrollment of larger cohorts (particularly compared with psychophysical studies, where testing on a small number of participants, often including the authors, is normal practice).

The observed reduction in sensorimotor MRS GABA concentration is consistent with findings from other modalities suggesting disrupted GABAergic function in TS. While frequency-based indicators of motion do not significantly differ between groups, it is possible that motion contributes to and enhances the observed results. Previous studies have shown associations between GABA-related genes and risk of TS (Fernandez et al. 2012; Tian et al. 2011), GABA serum levels are reduced in TS, and medicines effective at reducing tics have been found to increase GABA serum levels in rats (Wang et al. 2012). Furthermore, using PET, investigators have found altered binding of GABA-A receptors in TS (Lerner et al. 2012), and lower densities of parvalbumin-positive GABA interneurons have been found in postmortem studies (Kalanithi et al. 2005).

While the MRS findings simply suggest that "bulk" GABA concentration is reduced in TS, the tactile behavioral data may provide some specific insight into how GABAergic mechanisms might be altered and how these alterations may contribute to core motor and sensory manifestations of the disorder.

Studies have shown that children with TS show different responses to weak stimuli compared with HC (Belluscio et al. 2011), consistent with our results showing raised static detection thresholds in TS. Reaction time appears normal in TS, suggesting normal attention. Therefore differences in threshold are unlikely due to generalized differences in task performance between cohorts (Howells et al. 1998).

GABA plays a role in increasing contrast of neuronal responses to tactile stimulation (Juliano et al. 1989; Kohn and Whitsel 2002; McLaughlin and Juliano 2005). It might be expected that with altered GABAergic function the brain's responses to weak stimuli are inconsistent and noisier, raising detection threshold. Furthermore, whereas HC get worse after the application of a dynamically increasing subthreshold stimulus, children with TS are unaffected. As it is thought that a dynamic subthreshold stimulus mainly affects feedforward inhibition [important in filtering and suppression of sensory information as suggested (Blankenburg et al. 2003)], it is possible that specific modulatory feedforward mechanisms are impaired in TS. This would lead to adverse reactions to otherwise "normal" or ignored stimulation, contributing to the inability to suppress sensory information, reflected in impaired habituation in TS. This may implicate thalamo-cortical inhibitory interactions, as these circuits play an important role in filtering of sensory input (Swadlow 2003). The link between dynamic detection threshold and feedforward inhibition is based on invasive studies and modeling studies, but the link between these cellular mechanisms and the effect of a dynamically increasing subthreshold stimulus remains to be tested through pharmacological applications.

in reaction time and baseline amplitude discrimination threshold. Children with TS showed a higher static detection threshold, and while the expected detrimental effect of dynamic subthreshold stimulation was observed in HC, this effect was not seen in children with TS. Furthermore, children with TS showed impaired tactile adaptation; specifically, whereas HC showed the expected increase in discrimination threshold after a single-site adaptive stimulus, children with TS failed to show this effect. The correlation between adaptation with GABA, as

The observed abnormalities in tactile adaptation also implicate GABAergic dysfunction in TS. Whereas amplitude discrimination threshold was significantly increased in HC after application of adapting stimuli (see also Puts et al. 2013; Tannan et al. 2007, 2008), children with TS were unaffected. Lateral inhibition, mediated by GABAergic mechanisms, is thought to play an important role in amplitude discrimination and adaptation (Whitsel et al. 1989, 2003). The adapting stimulus is thought to increase amplitude discrimination threshold by reducing the perceived intensity of the subsequent test stimulus (Whitsel et al. 1989), and the reduction of the perceived intensity is thought to be primarily GABA driven. While the separation of signals through lateral inhibition appears intact in TS ("baseline" amplitude discrimination is normal), adaptive modulation of these signals is not, suggesting inflexibility of the GABAergic system to deal with adjustments to changes in ongoing sensory stimuli. Indeed, the correlation between GABA and the effect of adaptation observed in our HC cohort was absent in TS, suggesting that the role of GABA in the adjustment of the somatosensory system to ongoing stimuli is altered. This may be linked to an inability of children with TS to adapt to sensory stimulation and needs further inquiry.

Our brain-behavior correlation findings provide additional insights into how GABAergic dysfunction may contribute to the motor and sensory manifestations of TS. We found a negative correlation between SM1 GABA concentration and motor tic severity, linking the core feature of TS directly to in vivo brain neurochemistry. Previous findings have pointed to dopaminergic abnormalities and associated striatal disinhibition as one of the driving factors underlying motor tics (Bronfeld et al. 2013). While prevailing notions of TS emphasize the role of basal ganglia, tic occurrence has been shown to be closely related to activity in M1 (McCairn et al. 2013), suggesting that M1 might act as a gate for tics. Our findings suggest that GABA-mediated inhibitory processes within M1 might also play a role in the pathophysiology of tics and other clinical features of TS. Furthermore, there is a close link between GABA and dopaminergic function, with both animal and human studies showing that GABA-mediated cortical inhibition is amplified by dopamine (Marenco et al. 2010; Seamans et al. 2001). It follows that GABA and dopamine abnormalities in TS may reflect a common underlying mechanism, and it remains to be investigated whether the GABAergic dysfunction shown here is a primary or secondary effect in TS.

Interestingly, the correlation with SM1 GABA was specific to motor tic severity, as no correlations of SM1 GABA with either global or vocal tic severity were observed. This may be due to regional specificity of MRS GABA measurement, as the voxel was centered over the hand knob region and is therefore more likely to reflect limb, rather than oral/vocal, (dys)function. Follow-up studies with additional measurement from more ventral SM1, or regions such as SMA, would help address this question, as well as the localized extent of GABA abnormalities.

In HC, we found correlations between GABA and frequency discrimination and between GABA and the effect of adaptation, which are absent in children with TS. The absence of these correlations indicates that the tactile system is anomalous in TS. It is possible that children with TS use different strategies for tactile discrimination that may be less reliant on GABA-driven frequency encoding. These results do follow the pattern predicted by reduced GABA. However, it would be naive to assume that our measurements of GABA using MRS reflect a simple up- and downregulation of all GABAergic function. These differences in GABAergic function might relate to discrete genetic or receptor changes that may lead to up- or downregulation of normal GABAergic processes. Behaviorally, tasks that are most closely related to the deficient GABAergic process will show reduced performance, whereas GABA-targeted tasks more closely related to the upregulated accommodating process might show increased performance. Thus mixed observations of decreases and increases in GABA-related task outcomes can both support abnormal GABAergic processing in TS.

While lateral inhibitory connections appear intact in TS, the absence of a correlation between GABA and adaptation suggests that GABA-driven adjustments in cortical processing due to changes in sensation are impaired. The latter may be closely linked to poor habituation in TS. Interestingly, GABA is negatively associated with adaptation effects in HC, which may be counterintuitive, especially considering that TS do not show adaptation yet have lower GABA levels. These data in healthy brains suggests that more GABA leads to less flexibility of a system to alter its response. It is thought that long-term cortical plasticity (on the order of minutes to days) requires a reduction in the stabilizing effect of GABAergic processes, and that temporal changes in cortical processing occur as a result of a period of reduced GABAergic control. In the context of this picture, the extent to which discrimination performance is impacted by a prior adapting stimulus might be either negatively correlated with the strength of GABAergic control in place or positively correlated with the dynamic potential for relaxation of that control. Our results in HC are consistent with the former. It is thought that GABAergic processing plays an important role in somatosensory adaptation. However, the relationship among HC that links GABA-MRS and adaptation performance cannot simply be unidimensionally extrapolated to explain the abnormalities seen in TS—GABAergic differences in TS may be functionally distinct from the variance seen within the normal range.

It is possible that the vibrotactile differences we see in TS occur independent from the GABA changes we observe. However, given the strong focus on GABAergic function in both MRS and behavioral measurements, we maintain that, as a whole, the presented results are consistent with the hypothesis that abnormal GABAergic inhibition leads to abnormal somatosensory processing in TS. Such observations unfortunately cannot demonstrate a causative link, and individually not all results are consistent with a unified downregulation of all GABAergic processes. Further work is needed to assess specific aspects of these abnormalities.

MRS of GABA is limited by low signal-to-noise ratio (Mullins et al. 2014), so that a single measurement of total GABA is acquired from a large region that includes M1 and S1. Although an experiment that separates motor from somatosensory GABA would clearly be desirable, MRS voxels are cuboidal and large and a voxel that contains hand M1 and no S1 (or vice versa) is not possible, given the curvature of the central sulcus, and voxels that would contain "just" M1 or S1 would include regions that are neither primary somatosensory

nor primary motor. The sensorimotor GABA signal is the sum of motor and somatosensory GABA signals. Variance in both motor and somatosensory GABA concentration will contribute to variance in the total MRS GABA measurement. It is likely that motor and somatosensory GABA covary to some degree (for example, because of genetic variance), while maintaining some degree of independence (for example, due to experience/training effects and local epigenetic differences). Within the constraints of the MRS measure of total sensorimotor GABA, it is reasonable to test for correlations with statistically independent measures of abnormal motor and somatosensory behavior. Increases in field, such as 7T, would also allow for more regionally specific GABA measurements. While the difference in GABA levels between TS and HC are subtle, both GABA levels quantified relative to the unsuppressed water signal as well as GABA-to-Cr ratios are significantly different between groups and the range in GABA levels seen in TS relates to functional impairment as expressed by tic severity. The sample size used in the present study is relatively small, and further studies with larger sample sizes are required to test the robustness of this group difference, as well as broadening the finding to a wider range of subjects with TS through recruitment criteria that are less restrictive with respect to symptom severity and medication.

Despite these methodological limitations, it proved possible to observe significant correlations between GABA and somatosensory function in HC and between GABA and tic severity in TS. However, the total GABA measurement is the sum of M1 and S1 GABA, and it is not clear to what extent these are independent variables, either in HC or in TS. The absence of a correlation between total GABA and somatosensory function in TS may reflect increased motor GABA variance (which drives a correlation with tic severity) that masks a somatosensory correlation. For children with TS, tic severity did not correlate with our measures of somatosensory function, and there is behavioral evidence of somatosensory inhibitory dysfunction, suggesting a separation between motor and somatosensory abnormalities in TS.

A further limitation of the study is that the GABA signal measured is contaminated to the order of 50% by macromolecular signal (MM) (Mescher et al. 1998) and is often referred to as GABA+. We recently published on a technique that removes MM signal from the GABA spectra. However, MM-suppressed editing of GABA is more susceptible to frequency drift and motion than the GABA+ method applied here, and was used for this study of TS.

Two common concerns in studies of pediatric neurodevelopmental cohorts are the effects of comorbid diagnoses and medication. The sample size of this present study is insufficient for meaningful analyses of these effects, but recognizing the impact on statistical power, analysis on only those TS participants without medication still revealed reduced GABA levels and those TS participants on medication did not appear to be distinct from those not on medication.

The most common comorbid diagnosis in this cohort is ADHD (48% of TS participants). It has previously been shown that children with ADHD also show reduced GABA (Edden et al. 2012), highlighting the limited specificity of GABA MRS as a marker of inhibitory processes. With the additional discriminatory power of the vibrotactile battery, it can be seen that this TS cohort do not show typical "ADHD-like" outcomes [e.g.,

increased reaction times linked to the attention deficit (Karalunas et al. 2014)], nor does preliminary analysis reveal differences between TS children with and without comorbid ADHD. So while it is unlikely that comorbid ADHD is the primary driver of the findings reported, better-powered future analyses may provide valuable information on TS and ADHD as separate, overlapping entities. In addition, one female participant was recruited. While there are weak sex effects on MRS GABA measurements (Gao et al. 2013; O'Gorman et al. 2011), it remains unclear whether this affects female participants prior to menarche. Recruitment for this study was open to both male and female participants, with our cohort reflecting the higher prevalence of TS in males than females.

In summary, we have shown that in vivo GABA concentration over the sensorimotor cortex of children with TS is reduced compared with HC. This measurement seems to reflect inhibitory dysfunction of both somatosensory and motor cortex: children with TS show impaired performance on tactile tasks probing inhibitory drive, and the GABA measurement is strongly correlated with tic severity. Tasks targeting filtering and adaptation to touch appear specifically altered in TS, and children with TS possibly apply different strategies to sensory perception compared with HC, given the absence of a correlation between GABA and tactile behavior. Finally, the correlation between GABA concentration and motor tic severity in TS indicates a specific and regional sensorimotor dysfunction, rather than broad pervasive impairments due to disrupted sensorimotor GABAergic function. This novel approach of targeting both tactile and related GABAergic dysfunction allows for a better understanding of the underlying neurophysiological mechanisms and scope of tactile dysfunction in TS, and provides an opportunity to identify specific patterns of inhibitory function. This may lead to novel therapeutic interventions to alleviate tics and premonitory urges. The MRS GABA and tactile measures may also prove to be useful biomarkers of treatment response. For instance, they may help to identify those individuals most likely to respond to specific medications as well as to behavioral interventions, such as cognitive behavioral intervention for tics (CBIT) (Woods et al. 2011).

DISCLOSURES

M. Tommerdahl is co-owner of Cortical Metrics, which builds the tactile stimulator used. He has no financial interests in this study.

AUTHOR CONTRIBUTIONS

Author contributions: N.A.J.P., M.T., R.A.E.E., and S.H.M. conception and design of research; N.A.J.P., D.C., and C.N. performed experiments; N.A.J.P., A.D.H., C.N., and R.A.E.E. analyzed data; N.A.J.P., A.D.H., D.C., H.S.S., M.T., R.A.E.E., and S.H.M. interpreted results of experiments; N.A.J.P. prepared figures; N.A.J.P. drafted manuscript; N.A.J.P., A.D.H., D.C., C.N., H.S.S., M.T., R.A.E.E., and S.H.M. edited and revised manuscript; N.A.J.P.,

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