Frequency and Intensity of Premonitory Urges-to-tic in Tourette Syndrome is associated with SMA GABA+ levels

Jason L. He¹, Mark Mikkelsen^{2,3}, David A. Huddleston⁴, Deana Crocetti⁵, Kim M. Cecil⁶, Harvey S. Singer^{7,11}, Richard A. E. Edden^{2,3}, Donald L. Gilbert³, Stewart H. Mostofsky^{7,8,9}, Nicolaas A. J. Puts^{1,10}

¹Department of Forensic and Neurodevelopmental Sciences, Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, United Kingdom

²Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, United States

³F. M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, United States

⁴Division of Neurology, Cincinnati Children's Hospital Medical Center; Department of Pediatrics, University of Cincinnati, Cincinnati, OH, USA

⁵Center for Neurocognitive and Imaging Research, Kennedy Krieger Institute, Baltimore, MD, United States

⁶Department of Radiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

⁷Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD, United States.

⁸Center for Neurodevelopmental and Imaging Research, Kennedy Krieger Institute, Baltimore, MD, USA

⁹Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, United States.

¹⁰MRC Centre for Neurodevelopmental Disorders, King's College London

¹¹Kennedy Krieger Institute, Baltimore, MD, United States

Corresponding author: Nicolaas Puts

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Abstract

Background. Individuals with Tourette syndrome (TS) often report that they express tics as a means of alleviating the experience of unpleasant sensations. These sensations are perceived as an urge-to-act and are referred to as premonitory urges. Premonitory urges have been the focus of recent efforts to develop interventions to reduce tic expression in those with TS. This study examined the contribution of brain GABA and glutamate levels of the right primary sensorimotor cortex (SM1), supplementary motor area (SMA), and insular cortex (insula) to tic and urge severity in children with TS.

Methods. Edited magnetic resonance spectroscopy was used to assess GABA+ (GABA + macromolecules) and Glx (glutamate + glutamine) of the right SM1, SMA and insula in 68 children with TS ($M_{Age} = 10.59$, $SD_{Age} = 1.33$) and 41 typically developing controls ($M_{Age} = 10.26$, $SD_{Age} = 2.21$). We first compared GABA+ and Glx levels of these brain regions between groups. We then explored the association between regional GABA+ and Glx levels with urge and tic severity.

Results. GABA+ and Glx of the right SM1, SMA and insula were comparable between the children with TS and typically developing controls. In children with TS, lower levels of SMA GABA+ was associated with more severe and more frequent premonitory urges. Neither GABA+ nor Glx levels were associated with tic severity.

Conclusions. These results broadly support the role of GABAergic neurotransmission within the SMA in the experience of premonitory urges in children with TS.

Introduction

Individuals with Tourette syndrome (TS) report that their tics are often preceded by a feeling of mounting inner tension that can only be relieved through the expression of a tic¹. This sensory phenomenon is referred to as a “premonitory urge”. Premonitory urges are experienced as either generalized or localized tension, and are sometimes described as a tactile sensation or a ‘tickle’^{2,3}. Estimates of how many individuals with TS experience premonitory urges varies with age, being lower in younger children (~24% of children aged 8-10 years⁴) and higher in adolescents (57% in those aged 15-19⁴). By adulthood, up to 98% individuals with TS report experiencing premonitory urges⁵⁻⁷. It has been suggested that lower reporting of premonitory urges in children with TS may be due to the sensation being difficult to describe at an early age⁸. Given that premonitory urges generally appear to precede and potentially cause tics, understanding the underlying neurobiology of premonitory urges may help inform the development of interventions for alleviating tics in TS.

Much of the existing work towards understanding the neurobiology of premonitory urges has come from functional neuroimaging studies⁸. Functional magnetic resonance imaging (fMRI) studies have shown that prior to the expression of tics, and concurrent with the experience of a premonitory urge, there is an increase in the activation of the anterior cingulate cortex, primary sensorimotor cortex (SM1), supplementary motor area (SMA), insular cortex (insula), and parietal operculum in individuals with TS⁹⁻¹³. When taken together with similar findings from studies using other functional neuroimaging modalities such as magnetoencephalography^{14,15} and position emission topography^{16,17}, there is now a converging evidence pointing towards the neurobiological signature of premonitory urges having origins in these neocortical and paralimbic brain regions.

While functional neuroimaging studies can localize the brain regions likely to be involved in the experience of premonitory urges, a deeper mechanistic understanding of how

these brain regions contribute to the experience of premonitory urges and tics requires the consideration of metabolite profiles and neurotransmission. Historically, investigations into the pathophysiology of TS have focused on the dopaminergic system¹⁸. Despite there being many individual accounts of altered dopaminergic functioning in TS, the evidence in support of dopamine hypothesis of TS is mixed¹⁹. An alternative hypothesis proposes that the symptoms of TS may be explained by an imbalance of inhibitory and excitatory neurotransmission. Specifically, altered phasic GABAergic neurotransmission and/or reduced tonic levels of GABA in higher-order motor areas has been suggested to result in a failure of control over the gain of motor excitability and tic expression in TS²⁰. In support of this alternative hypothesis, reduced short-interval intracortical inhibition (a marker of inhibitory motor control and GABA_Aergic neurotransmission) in left motor cortex (M1) has been identified in both children and adults with TS through paired-pulse transcranial magnetic stimulation (TMS) studies, although the stronger associations in children are with co-occurring ADHD^{21–24}. A recent pilot study using double-coil-TMS reported adolescents with TS have diminished inhibitory signalling from right SMA to left M1²⁵. Reduced SM1²⁶ and ACC²⁷ GABA levels has also been identified in individuals with TS through the application of magnetic resonance spectroscopy (MRS). These findings align well with the body of animal studies showing that striatal injection of GABA_A antagonists such as bicuculine and picrotoxin can produce tic-like behaviors in both rodents^{28,29} and primates³⁰. Interestingly, reducing glutamatergic striatal innervation appears to reduce tic-like behaviors in rodents²⁹, supporting the idea that the symptoms of TS may manifest out of an imbalance of excitatory and inhibitory signalling.

In the current study, we used edited proton MRS to measure and compare both GABA and Glx (the combination of glutamate + glutamine since glutamate cannot be fully resolved at 3 Tesla (T)) levels as markers of inhibition and excitation in right SMA, right SM1, and

right insula in children with and without TS. These three brain regions were selected based on their associations in prior TS imaging research with urges and tics. Concurrent with the time period in which the present study took place, other investigators have published studies GABA and glutamate, with heterogeneous findings (see Mahone and colleagues³¹). Our specific objective was to characterize group differences in neurotransmitter levels in affected children and to quantify associations with tic and premonitory urge severity.

Methods

Participants

Children between the age of 8 and 12 years were recruited from the Johns Hopkins Hospital, Kennedy Krieger Institute and the Pediatric Neurology Movement Disorders Clinic at Cincinnati Children's Hospital Medical Center. There were 50 children recruited from Kennedy Krieger Institute and 72 children recruited from Cincinnati Children's Hospital Medical Center. The final sample consisted of 122 children with 68 children in the TS group and 41 children in the TDC group. There was no difference in age between the TS ($M = 10.59$, $SD = 1.33$) and TDC ($M = 10.26$, $SD = 2.21$) groups (Welch's $t(58.96) = -0.90$, $p = 0.374$). There was also no difference in handedness between TS ($R:L = 64:4$) and TDC ($R:L = 40:1$) groups ($\chi^2(1) = 0.13$, $p = 0.719$). There were more females in the TDC ($M:F = 26:15$) group compared to the TS ($M:F = 59:9$) group ($\chi^2(1) = 6.81$, $p = 0.009$).

Diagnosis of TS followed the guidelines set forth by the Tourette Syndrome Association (TSA) Genetics Consortium and was confirmed by two neurologists (SM and DG), who both have extensive clinical and research experience in diagnosing TS. Tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS)³², and premonitory urge severity was assessed with the Individualized Premonitory Urge for Tic Scales (PUTS)³³. Participants were excluded if they had a presence or history of a) a neurological disorder

other than TS, including seizures, tumor, head injury or stroke, b) a severe chronic medical disorder or c) presence of a major visual impairment. Participants with TS must also not have had a) a history of substance abuse or dependency or b) a history of autism. Finally, children within both groups must have had a full-scale IQ (FSIQ) of > 80 as measured by the Weschler Intelligence Scale for Children – IV (WISC-IV).

MRS

Prior to MRI scanning, children underwent a mock scan with a research assistant in order to improve their comfort and decrease their anxiety. To motivate children to lie still during the scan, the children were allowed to watch movies during the acquisition and received ‘points’ for lying still. These points could be exchanged for prizes after the scan. MRI and MRS scans were conducted using Phillips 3T Achieva scanners (Best, The Netherlands; 32-channel head coil for receive and body coil for transmit) at both sites using identical exam cards for the pulse sequences. One person (NP) travelled to both sites to ensure cross-site consistency and train in voxel placement. For voxel placement and segmentation, a 1-mm³ isotropic T1-weighted image (MP-RAGE) was first acquired (TR = 7.99 ms, TE = 3.76 ms, flip angle = 8°). $3 \times 3 \times 3$ cm³ voxels were then positioned in three regions of interest (ROIs): The right SMA, right SM1 and right insula. See Fig. 1. We chose to examine right hemisphere voxels due to previous work having suggested that the right rather than left insula was specifically involved in the experience of the premonitory urge-to-tic and to correspond with a separate study of tactile function, which has traditionally been examined in the left hand. Full details of the MRS data acquisition, including results of analyses comparing quality assurance metrics between groups and sites can be found in Supplementary Materials.

Figure 1. Voxel placement and resultant spectra. (a) Voxel placement in SM1 and (b) accompanying spectra. (c) Voxel placement in SMA and (d) accompanying spectra. (e) Voxel placement in insula and (f) accompanying spectra. *SM1* = *primary sensorimotor cortex*, *SMA* = *supplementary motor area*, *Insula* = *insular cortex*. *GABA+* = *GABA* + *macromolecules*, *Glx* = *glutamate* + *glutamine*

Statistical analyses. All statistical analyses were conducted using the R programming language (v4.0.3) in RStudio (v1.3.1093). The code used to generate the results and figures of this manuscript are available online through the Open Science Framework (<https://osf.io/e7yw9/>). The alpha level for all analyses was set to 0.05. For group comparisons using analysis of variance (ANOVA), partial eta-squared (η^2_p) was estimated using the ‘effect size’ package⁴³ and Bayes factors were estimated using the ‘BayesFactor’ package⁴⁴. BF_{10} was estimated for each variable of interest by comparing the BF_{10} of the model with the variable of interest included against the model without the variable of interest included. Similarly, to determine the BF_{10} of interaction effects, the BF_{10} of the model with

the interaction term included was compared against the model without the interaction term included.

First, after controlling for age, a 3×2 ANOVA was conducted to determine whether there were differences with regard to GABA+ and Glx levels between our ROIs (SMA, SM1 and insula), and Groups (TS and TDC). Where there was evidence of an interaction effect, which was determined through joint consideration of p-values, η^2_p and Bayes factors, simple main effect analyses were conducted. If there was evidence of a main effect, post-hoc comparisons were conducted, and Tukey's HSD was used to control for inflation of Type I Error. Second, to determine whether individual differences in GABA+ and Glx levels were related to urge and tic severity, Pearson's correlation analyses were conducted between metabolite concentration levels of each ROI and scores on the PUTS and YGTSS. Due to the large number correlations being conducted here, the more conservative Bonferroni's method was used to correct for inflation of Type I error.

Results

There were no significant group differences in any of the quality assurance metrics (see Supplementary Materials – Table 1). Descriptive statistics for scores on the PUTS, YGTSS, GABA+ and Glx levels for each of the regions of interest are available in Table 1.

Table 1. Descriptive statistics

Variable	TS					TDC				
	N	Mean	St. Dev.	Min	Max	N	Mean	St. Dev.	Min	Max
Premonitory Urge to Tic Scale (PUTS)										
Number of Tics	59	7.19	5.82	1	26	-	-	-	-	-
Number of Urges	59	4.37	5.34	0	25	-	-	-	-	-
Urge Frequency	59	11.56	14.94	0	70	-	-	-	-	-
Urge Intensity	59	10.69	14.37	0	80	-	-	-	-	-
Yale Global Tic Severity Scale (YGTSS)										
Total Motor Tics	59	2.63	0.98	0	5	-	-	-	-	-
Total Phonic Tics	54	1.78	1.22	0	5	-	-	-	-	-
Total Impairment	59	14.1	13.07	0	40	-	-	-	-	-
Global Severity	59	35.1	20.13	7	90	-	-	-	-	-
Magnetic Resonance Spectroscopy (MRS) of GABA and Glx										
SM GABA (IU)	68	2.76	0.43	1.02	3.92	39	2.78	0.31	1.99	3.61
SMA GABA (IU)	68	2.49	0.39	1.07	3.37	41	2.57	0.46	1.45	3.88
Insula GABA (IU)	62	2.62	0.49	0.9	4.07	41	2.65	0.57	1.66	4.53
SM Glx (IU)	68	5.97	1.54	2.44	9.58	39	5.83	1.63	2.93	10.72
SMA Glx (IU)	68	6.45	1.98	1.81	10.91	41	6.4	1.76	2.54	11.35
Insula Glx (IU)	62	6.67	1.95	2.72	11.58	41	6.64	2.01	2.85	15.45
SM GABA / Cr	68	0.1	0.01	0.04	0.13	39	0.1	0.01	0.07	0.14
SMA GABA / Cr	68	0.1	0.02	0.04	0.14	41	0.1	0.02	0.06	0.15
Insula GABA / Cr	62	0.1	0.02	0.04	0.14	41	0.1	0.02	0.07	0.16
SM Glx / Cr	68	0.06	0.02	0.03	0.09	39	0.06	0.02	0.03	0.1
SMA Glx / Cr	68	0.07	0.02	0.02	0.11	41	0.07	0.02	0.03	0.12
Insula Glx / Cr	62	0.07	0.02	0.03	0.11	41	0.08	0.02	0.03	0.14

GABA+ = GABA + macromolecules, Glx = glutamate + glutamine, PUTS = premonitory urge to tic scale,

YGTSS = yale's global tic severity scale, SM1 = primary sensorimotor cortex, SMA = supplementary

motor area, Insula = insular cortex, TDC = typically developing controls, TS = Tourette Syndrome, IU = institutional units

GABA+ and Glx in SM, SMA and Insula was comparable between children with TS and TDC.

After controlling for age ($F(1, 312) = 0.38, p = 0.540; \eta_p^2 = 0.00; BF_{10} = 0.15$), there was a significant main effect of Region ($F(2, 312) = 8.39, p < 0.001; \eta_p^2 = 0.05; BF_{10} = 70.89$) but not Group on GABA+ levels ($F(1, 312) = 0.17, p = 0.362; \eta_p^2 = 0.00; BF_{10} = 0.18$). There was no significant Region by Group interaction effect ($F(2, 312) = 0.171, p = 0.843; \eta_p^2 = 0.00; BF_{10} = 0.08$). When taken together, the results of these analyses suggests that while GABA+ was different across the three regions, GABA+ across these regions was comparable between children in the TS and TDC groups. Subsequent post hoc comparisons revealed that GABA+ was higher in the SM than SMA ($p_{\text{Tukey}} = 0.0016$) and that GABA+ was otherwise comparable between SM and insula ($p_{\text{Tukey}} = 0.0715$), and SMA and insula ($p_{\text{Tukey}} = 0.1600$). See Fig. 2a. A slightly different pattern of effect was observed when GABA+ was referenced to creatine, see Supplementary Material. While there was no significant main effect of Group, we visualized the post hoc group comparisons across the regions in Fig. 2b to d.

As with GABA, after controlling for age ($F(1, 312) = 9.59, p = 0.002; \eta_p^2 = 0.03; BF_{10} = 10.85$), there was a significant main effect of Region ($F(2, 312) = 4.76, p = 0.009; \eta_p^2 = 0.03; BF_{10} = 2.64$), but no significant main effect of Group on Glx levels ($F(1, 312) = 0.00, p = 0.981; \eta_p^2 = 0.00; BF_{10} = 0.122$). There was no significant Region by Group interaction either ($F(2, 312) = 0.03, p = 0.970; \eta_p^2 = 0.00; BF_{10} = 0.07$). Post hoc comparison revealed that Glx levels were higher in SMA than in SM1, though this effect fell shy of significance ($p_{\text{Tukey}} = 0.09$). There were no significant differences in Glx levels between insula and SMA ($p_{\text{Tukey}} = 0.630$), but was Glx was higher in insula than SM ($p_{\text{Tukey}} = 0.008$). See Fig. 2e. A similar pattern of effect was observed when Glx was referenced to creatine, again, suggesting that this pattern of effect was due to the metabolite rather than the reference variable. Again,

while there was no significant main effect of Group, we visualized the post hoc group comparisons across the regions in Fig. 2g to h.

Figure 2. Comparing GABA+ and Glx Across Regions and Between Groups. The top row depicts analyses conducted on GABA+, while the bottom row depicts analyses conducted on Glx. (a). Group x Region on GABA+ analysis. There were differences in GABA+ between regions, but no differences of GABA+ between groups. The latter was confirmed by subsequent post hoc comparisons showing comparable GABA+ between TDC and TS in the (b) SM1, (c) SMA and (d) Insula. (d) Group x Region on Glx analysis. For Glx, again, there were significant differences between the regions (e), but no significant differences between the groups in terms of (f) SM1, (g) SMA and (h) Insula Glx. *GABA+* = *GABA* + *macromolecules*, *Glx* = *glutamate* + *glutamine*, *SM1* = *primary sensorimotor cortex*, *SMA* = *supplementary motor area*, *Insula* = *insular cortex*, *TDC* = *typically developing controls*, *TS* = *Tourette Syndrome*, *IU* = *institutional units*. Error bars in panels (a) and (e) represent standard error of the mean.

Individual differences in GABA+ predict urge but not tic severity in children with TS.

A heatmap of the associations between GABA+ with urge and tic severity is presented in Fig. 3a. The associations which survived correction for multiple comparisons are presented as

scatterplots in Fig. 3b–d. Among children with TS, there were no significant associations between SM GABA+ with urge (all $p_{\text{Bonferroni}} > 0.999$) or tic (all $p_{\text{Bonferroni}} > 0.184$) severity, as measured by the PUTS and YGTSS respectively. Lower levels of SMA GABA+ was related to a higher number of urges ($r = -0.38$, $p_{\text{Bonferroni}} = 0.024$; Fig. 3b), more frequent urges ($r = -0.39$, $p_{\text{Bonferroni}} = 0.018$; Fig. 3c) and more intense urges ($r = -0.42$, $p_{\text{Bonferroni}} = 0.008$; Fig. 3d) on the PUTS. There was, however, no significant association between SMA GABA+ with the number of tics on the PUTS ($r = -0.16$, $p_{\text{Bonferroni}} > 0.999$), or any of the tic severity measures on the YGTSS (all $p_{\text{Bonferroni}} > 0.999$). GABA+ levels in the insula were not related to either urge severity as measured by the PUTS (all $p_{\text{Bonferroni}} > 0.999$) or tic severity as measured by the YGTSS (all $p_{\text{Bonferroni}} > 0.380$).

There were no significant associations between levels of Glx in any of the regions of interest with any of the measures from either the YGTSS (all $p_{\text{Bonferroni}} > 0.640$) or the PUTS (all $p_{\text{Bonferroni}} > 0.052$).

Figure 3. Associations of Urge and Tic with Metabolite Levels (a) Heatmap depicting the associations between GABA+ and Glx across the ROIs on the x-axis, with urge and tic severity on the y-axis. Scatterplots depicting the associations between SMA GABA+ (IU) and the number (b), frequency (c) and intensity (d) of urges as assessed by the PUTS. Note that while we corrected for multiple comparisons using the Bonferroni method in the main text, the p-values presented in panels b to d are uncorrected. *GABA+* = *GABA* + *macromolecules*, *Glx* = *glutamate* + *glutamine*, *PUTS* = *premonitory urge to tic scale*, *YGTSS* = *yale's global tic severity scale*, *SM1* = *primary sensorimotor cortex*, *SMA* = *supplementary motor area*, *Insula* = *insular cortex*, *IU* = *institutional units*

A similar but slightly different pattern of associations was identified when GABA+ was referenced to creatine. Generally, the associations were in the same direction and slightly stronger for creatine-referenced GABA+ and Glx. For example, the Pearson's *r* value for the

associations between GABA⁺ and the Number of Urges ($r = -0.46$, $p_{\text{Bonferroni}} < 0.001$), Urge Frequency ($r = -0.50$, $p_{\text{Bonferroni}} = 0.001$) and Urge Intensity ($r = -0.48$, $p_{\text{Bonferroni}} = 0.001$) were ~10-20% stronger than those shown in Fig. 3a (see Supplementary Fig. 2). Interestingly, when referenced to creatine, insula GABA⁺ levels also showed significant associations with Urge Intensity ($r = -0.48$, $p_{\text{Bonferroni}} = 0.003$), Urge Frequency ($r = -0.50$, $p_{\text{Bonferroni}} = 0.002$) and the Number of Urges ($r = -0.46$, $p = 0.005$). Given that the associations between SMA GABA⁺ and urge severity remained significant across reference variables while insula GABA⁺ did not, these results suggest that the SMA GABA⁺ associations are not being driven by the reference variable (and are hence reliable) while the insula GABA⁺ associations might be spurious. We discuss these reference variable discrepancies and the robustness of our correlations in more detail in Supplementary Materials.

Discussion

We measured, in 8 to 12 year old children with TS and TDC, GABA⁺ and Glx in right SM1, SMA, and insula. We found that although both groups have comparable GABA and Glx profiles, lower SMA GABA⁺ levels were associated with more frequent and more intense premonitory urges to tic in TS. In contrast, GABA⁺ of SM1 and insula did not show any significant association to urge severity. GABA⁺ was also not associated with tic severity. We also did not identify any associations between Glx and urge or tic symptom severity.

SMA GABA⁺ levels are associated with premonitory urge to tic severity in children with TS.

Our most consistent finding were the associations between SMA GABA⁺ levels with urge severity, which were present regardless of whether GABA⁺ was referenced to water or creatine. Based on the putative role of the insula (e.g., its role in interoceptive awareness⁴⁵ and awareness of the urge-for-action in other behavioral domains⁴⁶), it is likely that

premonitory urges do have their origins in the insula (specifically the anterior-dorsal region of the right Ins, which has been demonstrated to be positively associated with premonitory urge scores but uncorrelated with motor tic severity⁴⁶). However, since the posterior insular is anatomo-functionally connected to the middle cingulate around the area of the SMA⁴⁷, we speculate that although premonitory urges may be initially generated within the insula, the conscious experience of these urges may be mediated by tonic GABA levels of the SMA. This would explain our results showing that children with TS who had lower SMA GABA+ levels reported more urges, more frequent urges, and more severe urges. In support of our suggestion, Tinaz and colleagues had also previously demonstrated that functional connectivity between the right dorsal anterior insula and bilateral SMA was positively associated with urge severity¹³.

Draper and colleagues⁴⁸ had previously reported higher GABA levels in SMA in TS ($N = 8$, $M_{Age} = 18.30$, $SD_{Age} = 2.7$) compared to TDC ($N = 9$, $M_{Age} = 17.20$, $SD_{Age} = 3.30$). GABA levels in the SMA also predicted the amount of change in blood-oxygen level dependent (BOLD) activity in the same voxel prior to voluntary action, with an increase in SMA GABA being interpreted as a possible mechanism by which tic suppression is gained with increasing age²⁰. While we did not identify increased SMA GABA+ levels in our sample, our sample contained an appreciably younger sample than that of Draper and colleagues, thus the results are not necessarily in conflict. However, since our results suggest that GABA+ levels of the SMA mediates urge rather than tic severity in younger children with TS, it is possible that the mechanism of gaining control over tics first occurs through the suppression of urges, rather than simply through control over tics.

Comparable GABA and Glx levels between children with TS and TDCs

Perhaps to our surprise, we were unable to reproduce our prior finding of reduced SM1 GABA+ is reduced in children with TS²⁶. We do not believe that the discrepancy between our prior and current findings are due to the differences in MRS acquisition, as both studies utilized methods to minimize motion artifact. Similarly, the demographic characteristics of both studies were similar (children aged 8 to 12 years of age, with comparable mean age and sex ratios). Instead, we believe the discrepancy to be better explained by the larger sample size ($n = 68$ in the Tourette syndrome group for the SM1 group comparison vs. $n = 17$ in our pilot study). While small samples are not necessarily an issue in the presence of large effects, this larger study likely generated more valid and generalizable results. When taken with the work of others assessing GABA of SM1 in adolescent⁴⁸ and adult¹⁵ TS populations (which were conducted at 7T and 3T respectively), our results suggest that SM1 GABA+ levels are comparable between children with TS and TDC.

With regard to the lack of group differences and associations identified for Glx, few studies have assessed glutamate levels in TS. Of the studies which have compared Glx (or glutamate at 7T, where glutamate and glutamine can be resolved) levels between individuals with TS and TDC, the findings are mixed. At 7T, Mahone and colleagues³¹ found that glutamate levels were increased in the PMC of young children with TS (TS: $N = 32$, $M_{Age} = 9.88$, $SD_{Age} = 1.93$; TDC: $N = 43$, $M_{Age} = 8.11$, $SD_{Age} = 1.93$). For studies at 3T, Naaijen and colleagues found normal Glx levels in the dorsal striatum and anterior cingulate cortex of children with TS⁵¹ ($N = 15$, $M_{Age} = 10.40$, $SD_{Age} = 1.20$; TDC: $N = 53$, $M_{Age} = 10.00$, $SD_{Age} = 1.00$) and TS+ADHD ($N = 28$, $M_{Age} = 10.70$, $SD_{Age} = 1.60$). Kanaan and colleagues⁵² found reduced striatal and thalamic Glx in adults with TS ($N = 37$, $M_{Age} = 38.30$, $SD_{Age} = 11.10$; TDC: $N = 36$, $M_{Age} = 38.40$, $SD_{Age} = 11.10$). Given the variability in the sample size,

MRS acquisition and ROIs across these studies, it is perhaps too premature to try and draw any firm conclusions regarding the status of glutamate levels in TS based on these studies.

Future Directions

If SMA GABA levels mediates the conscious experience of premonitory urges generated by the insula, it follows that targeting SMA GABA levels (or GABAergic functioning within the SMA) may be a plausible way of treating the symptoms of TS. Suppression of the SMA using high-frequency repetitive TMS has already been shown to temporarily reduce tic severity in individuals with TS, though the findings have been mixed^{55–57}. Increasing tonic GABA levels or improving GABAergic functioning in the right dorsal anterior insula may also help dampen the limbic drive it imposes on the SMA. However, there have only been a few studies that have demonstrated direct stimulation of the insula with TMS^{58,59}, with some questioning its feasibility⁵⁹. Further discussion of future directions, limitations of the current study and additional considerations of our interpretation of the results can be found in Supplementary Materials.

Conclusion

Using edited MRS, we found that although children with TS had comparable GABA+ and Glx levels as their typically developing peers, SMA GABA+ levels were specifically associated with the number, frequency and intensity of premonitory urges in children with TS. That is, the children with TS who had higher SMA GABA+ levels were also those who had less severe premonitory urges. When taken with existing work, our results suggest that targeting SMA GABA levels may reduce both urge and, thereby, tic severity in children with TS.

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