Pathological glutamatergic neurotransmission in Gilles de la Tourette syndrome

Ahmad Seif Kanaan[1,2], Sarah Gerasch[2], Isabel Garcia Garcia[1], Leonie Lampe[1], André Pampel [1], Alfred Anwander[1], Jamie Near[3], Kirsten Müller-Vahl[2], Harald E. Möller [1]

[1]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2]Department of Psychiatry, Social Psychiatry and Psychotherpay, Hannover Medical School, Hannover, Germany
[3]Douglas Mental Health University Institute and Department of Psychiatry, McGill University, Montreal, QC, Canada

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Introduction

- Gilles de la Tourette syndrome (GTS) is a neuropsychiatric movement disorder characterized by tics with reported abnormalities in the neurotransmission of dopamine and γ-aminobutyric acid (GABA) [1].
- Spatially focalized alterations in excitatory, inhibitory and modulatory neurochemical ratios within specfic functional subdivisions of the basal ganglia, may lead to the expression of diverse motor and non-motor features as manifested in GTS [2].
- Current treatment strategies are often unsatisfactory thus provoking the need for further elucidation of the underlying pathophysiology.
- In view of (a) the close synergy exhibited by excitatory, inhibitory and modulatory neurotransmitter systems; (b) the crucial role played by glutamate (Glu) in tonic/phasic dopaminergic signalling [3]; and (c) the interdependent metabolic relationship exhibited between Glu and GABA via glutamine (Gln) [4]; we postulated that glutamatergic signalling is related to the pathophysiology of GTS.
- We examined the neurochemical profile of cortico-striato-thalamo-cortical regions in healthy controls and a well-characterized, drug-free adult patient sample at baseline and following treatment with the antipsyhotic aripiprazole.

Methods

Population Sampling

- **Healthy Controls:** *36 test subjects (7 female, age 38.4 ± 11.1) and 23 re-test subjects for reliability measurements.*
- **Gilles de la Tourette syndrome:** *37 patients at baseline (6 female, age 38.3 ± 11.1) & 15 patients following a 4-week treatment with aripiprazole.*
- **Clinical assessment:** *Yale global tic severity scale (YGTSS) and Rush video-based tic rating scale (RVTRS) for tics. Premonitory Urge for Tics Scale (PUTS) for urges. Yale-Brown obsessive compulsive scale (YBOCS) for OCD. Conners' Adult ADHD Rating Scales (CAARS) for ADHD.*

MR Data Acquisition and Absolute Quantiation

- **System:** *Siemens 3T MAGNETOM Verio, 32-channel head coil.*
- **Scout:** *Auto-Align Head (AAH) scout for automatic and accurate re-localiztion of voxel position within and between sessions.*
- **MP2RAGE:** *TR=5s, TE=3.93ms, T_1=0.7/2.5s; sagittal slab orientation, 256x256 acq. matrix, and 1.0mm^3 isotropic.*
- **^{1}H-MRS:** *PRESS TE= 30ms, TR=3s, 1024 time-domain data points; 6 unsuppressed acq., FASTESTMAP shimming [5,6], AutoAlignHead repositioning [7].*
  - ***Ant. Mid-Cingulate Cortex (aMCC):*** *25×16×16mm^3, 80 supp acq.*
  - ***Bi-lateral Thlamaus (THA):*** *28×16×16mm^3, 80 supp acq.*
  - ***Corpus Striatum (STR):*** *20×15×20 mm^3, 128 supp acq.*
- **Spectral Preprocessing:** *Time-domain frequency and phase drift correction to a limited frequency range (Fig. 1) [8,9].*
- **Absolute metabolite quantiation:** *LCModel fitting [10] and partial-volume correction with respect to voxel compartmentation according to Eq.1 [11].*

$$C_{Met} = \frac{I_{Met}}{I_{H2O}} \cdot \frac{2}{N^{1H}_{Met}} \cdot C^{0}_{H2O} \cdot \frac{f_{GM} \cdot R_{H2O} \cdot \alpha_{GM} + f_{WM} \cdot R_{H2O} \cdot \alpha_{WM} + f_{CSF} \cdot R_{H2O} \cdot \alpha_{CSF}}{f_{GM} \cdot R_{GM} + f_{WM} \cdot R_{WM}} \quad (1)$$

$$\text{where} \quad R(TR, TE) = \left(1 - e^{-\frac{TR}{T1}}\right) \cdot e^{\frac{-TE}{T2}}$$

$$\text{and} \quad \alpha_{GM} = 0.81 \; ; \; \alpha_{WM} = 0.71 \; ; \; \alpha_{CSF} = 1.0$$

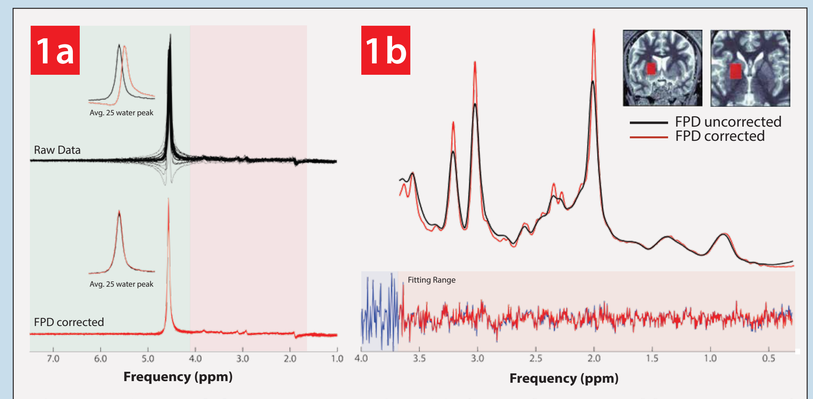

Figure 1. Spectral data pre-processing. (a) The performance of frequency- and phase-drift (FPD) correction is clearly visible on the data acquired from a striatal voxel of a GTS patient. For high SNR spectra (aMCC), spectral fitting was conducted in the 1.8-4.2 ppm range (red shaded area). For low SNR spectra, the strength of the water signal was utilized for spectral registration (~4.2-7.5ppm, green shaded area). (b) LCModel fits exhibited increased SNR and decreased linewidth. Fitting was conducted in the 0.2-3.67 ppm range to circumvent potential biases that may result due to spurious signals observed above 3.7 ppm.

Results

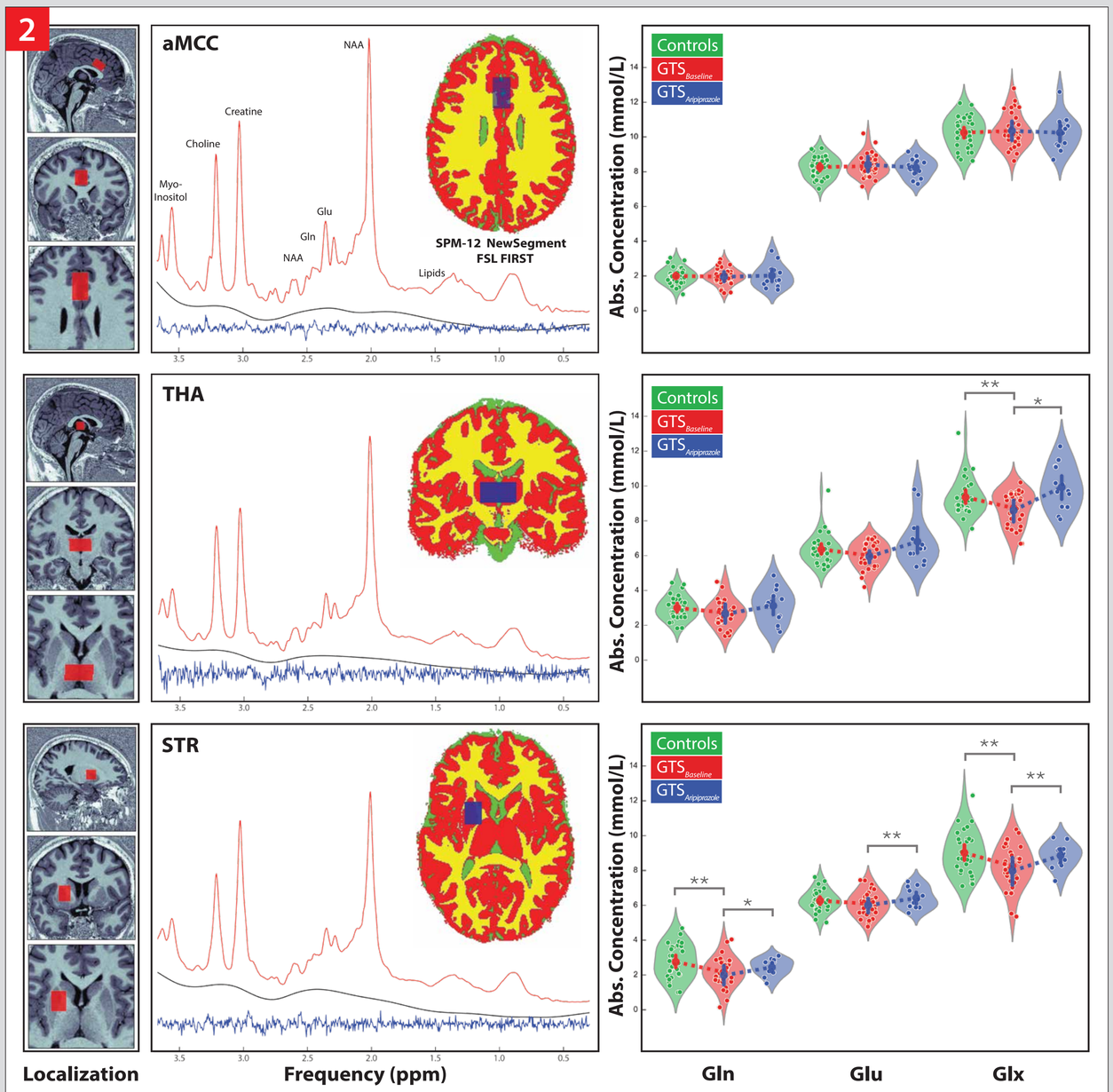

Figure 2 Spectral localization, fitting and statistical analysis. *Left-panel*: Sagittal, coronal and axial images illustrating the localization of the cingular, thalamic and striatal regions of interest. The reconstructed masks were generated based on geometric information extracted from the raw file header. *Mid panel*: Exemplary spectra illustrating LCModel fits, baselines and residual signals of frequency- and phase-drift-corrected data. The inset images demonstrate the location of voxels with respects to the GM, WM and CSF compartments, which were used to calculate within-voxel tissue proportions for absolute quantitation. A combination of segmentation outputs from SPM12 and FSL-FIRST was used for accurate masking of subcortical nuclei. *Right panel*: Plots illustrating the distribution of Gln, Glu and Glu + Gln (Glx) concentrations in controls (green), GTS patients (red) and GTS patients following treatment with aripiprazole (blue); ** denotes significance at p<0.05; * denotes a trend for significance (p<0.1).

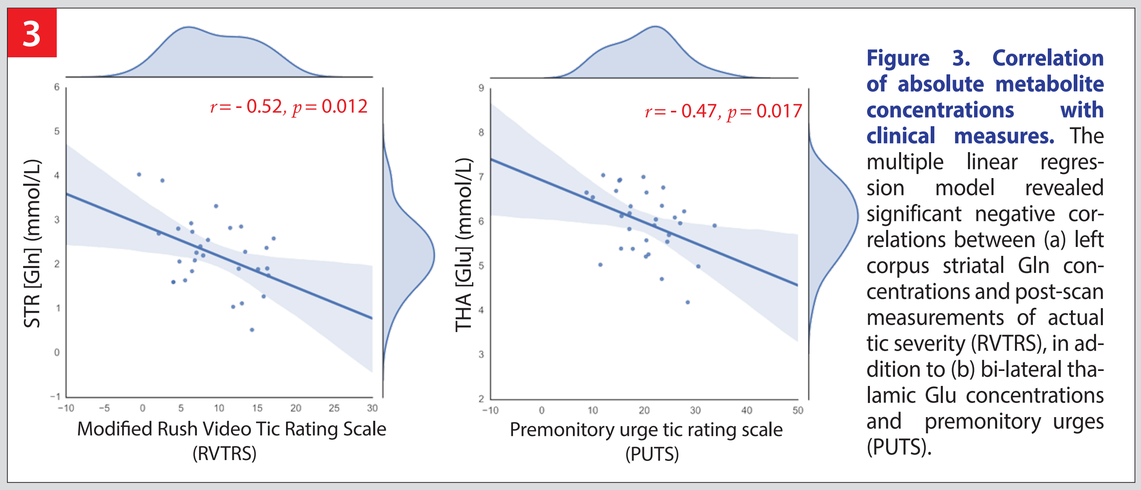

Figure 3. Correlation of absolute metabolite concentrations with clinical measures. The multiple linear regression model revealed significant negative correlations between (a) left corpus striatal Gln concentrations and post-scan measurements of actual tic severity (RVTRS), in addition to (b) bi-lateral thalamic Glu concentrations and premonitory urges (PUTS).

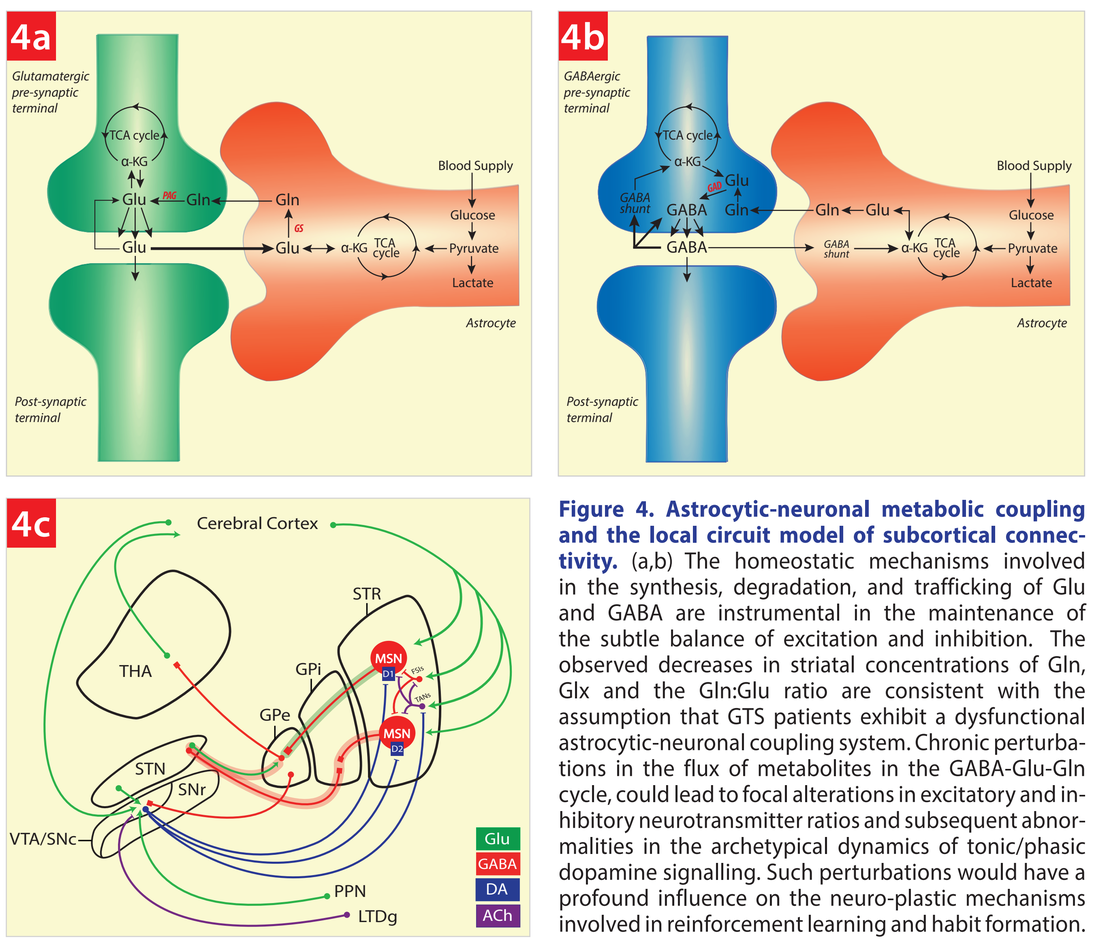

Figure 4. Astrocytic-neuronal metabolic coupling and the local circuit model of subcortical connectivity. (a,b) The homeostatic mechanisms involved in the synthesis, degradation, and trafficking of Glu and GABA are instrumental in the maintenance of the subtle balance of excitation and inhibition. The observed decreases in striatal concentrations of Gln, Glx and the Gln:Glu ratio are consistent with the assumption that GTS patients exhibit a dysfunctional astrocytic-neuronal coupling system. Chronic perturbations in the flux of metabolites in the GABA-Glu-Gln cycle, could lead to focal alterations in excitatory and inhibitory neurotransmitter ratios and subsequent abnormalities in the archetypical dynamics of tonic/phasic dopamine signalling. Such perturbations would have a profound influence on the neuro-plastic mechanisms involved in reinforcement learning and habit formation.

Discussion

- In this work, we investigated the neurochemical profiles of a well-characterized sample of adult patients with GTS at baseline and following a four-week treatment with the antipsychotic aripiprazole using 1H-MRS at 3T.
- To obtain spectra of sufficient precision to identify rather subtle metabolic changes, we applied an automated voxel (re-)localization technique, frequency and phase error correction, absolute metabolite quantitation with the consideration of within voxel compartmentation and a careful quality assessment protocol.
- Our results implicate altered flux of metabolites in the GABA-Glu-Gln cycle, thus implying perturbations in subcortical astrocytic-neuronal coupling systems that maintain the subtle balance between excitatory and inhibitory neurotransmission.
- Such perturbations may ultimately lead to spatially focalized alterations in excitatory, inhibitory and modulatory neurotransmitter ratios in functionally distinct striatal subdivisions, thus leading to the diverse symptomatology associated with GTS.

References

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