

Correlation of GABA Levels and Motor Performance in Parkinson's disease

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Purpose: Dopamine loss in the striatal neurons leads to simultaneous increased inhibition of the indirect pathway and decreased excitation of the direct pathway of the basal ganglia in Parkinson's disease (PD). PD is a progressive neurodegenerative disorder and while treatments with dopamine precursors alleviate symptoms, they do not prevent disease progression. For the development of treatments to slow the disease progression, a biomarker is needed to detect the changes in brain function which are more subtle than those detected by a clinical examination alone. Gamma-aminobutyric acid (GABA) and glutamate (Glu) are the main inhibitory and excitatory neurotransmitters of the basal ganglia, which are deregulated in the absence of dopamine. The aim of this study was to determine the impact of PD on these metabolite levels using magnetic resonance spectroscopy (MRS) in relation to disease severity as measured with motor tests.

Methods: Fifteen PD patients (age: 59±8 y, no dementia, right handed) underwent single voxel MRS on a 3 T Philips Achieva scanner. Short TE PRESS (TE/TR=30/2000 ms) and MEGA-PRESS GABA (TE/TR=68/2000 ms, 256 averages) spectra were acquired from 30×30×25 mm³ volumes of interest (VOIs) placed in the left and right striatum (Str_L and Str_R) and thalamus (Th_L and Th_R) (fig. 1). A reference scan without water suppression was acquired for frequency and phase correction. LCModel (v6.2-0R) was used for quantification of glutamate+glutamine (Glx) from PRESS spectra and for quantification of GABA from MEGA-PRESS

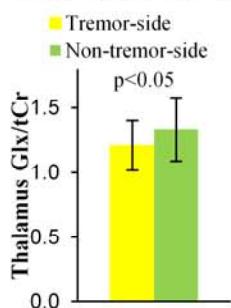


Fig 2. Glx/tCr tremor vs non-tremor side

spectra. Metabolite levels are reported as ratios to total creatine (tCr) to minimize partial volume effects. All subjects were tested for fine-motor skills on both sides, which included a steadiness test for tremor and a tapping test for motor speed. The steadiness test consisted of holding a pen in a 4.8 mm hole without touching the floor or edge while the tapping test involved tapping with a pen for 32 seconds as often as possible. Higher scores on the steadiness test and lower scores on the tapping test are indicative of worse performance. A clinical evaluation of motor skills was also performed for all subjects using the Unified Parkinson's Disease Rating Scale (UPDRS)-III. Two-sided paired t-tests were used to test for laterality and tremor-side effects. Spearman's partial correlation coefficients (r_s) controlled for age were calculated for the associations between motor tests and metabolite levels.

Results: Thalamic Glx levels were significantly lower ($p=0.04$) on the tremor-side (1.21 ± 0.2) compared to the non-tremor side (1.33 ± 0.25) of PD patients (fig. 2). Significant correlations were observed between thalamic GABA and increasing UPDRS-III scores (indicating worse motor performance), steadiness test scores and tapping scores (fig 3 a,b,c). Additionally, right striatal Glx levels were correlated with non-tremor side steadiness scores ($r_s=-0.55$, $p=0.05$).

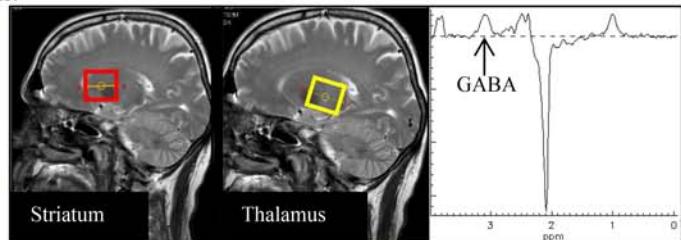


Fig 1. Representative left striatum and thalamus VOI and MEGA-edited GABA spectra.

Str_L	Str_R	Th_L	Th_R
0.24 ± 0.05	0.26 ± 0.05	0.28 ± 0.08	0.27 ± 0.07

Table 1. GABA/tCr levels (mean±sd) in all VOIs

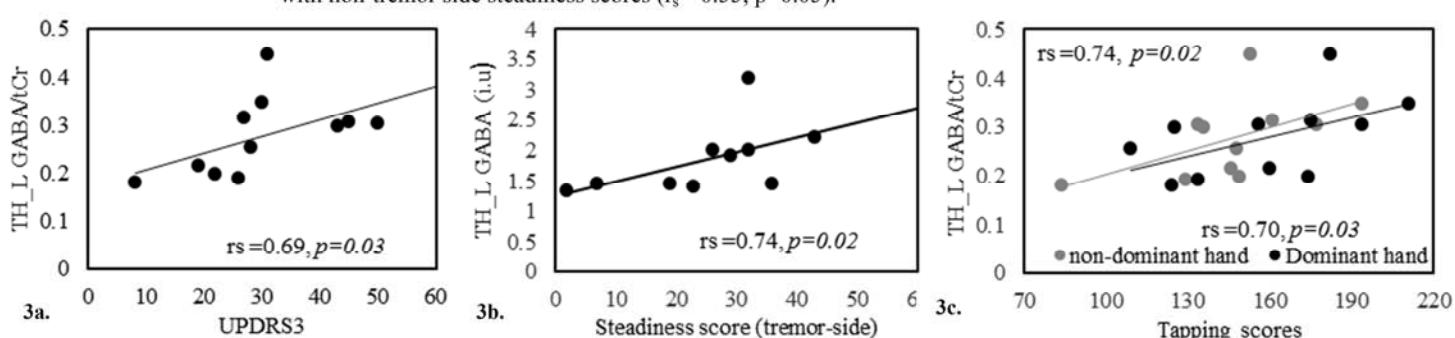


Fig 3. Significant correlations between thalamic GABA and motor tests in PD patients

Discussion and Conclusion: Tapping and steadiness are two measures of different functions of the motor system. Tapping is very rhythmic and neurophysiologically requires quick opening and closing of thalamo-cortical gates, regulated by GABA. In contrast steadiness requires the thalamo-cortical gates to remain closed in order to allow for a steady posture. Our results of increasing thalamic GABA being associated with worse steadiness (more tremor), better tapping and worse motor performance therefore seem coherent. While this study still requires a larger sample size, our results indicate that GABA and Glx levels in the thalamus might serve as marker of disease progression with respect to motor dysfunction.

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