In vivo MRSI confirmation of post mortem results for metabolic changes in Parkinson's disease

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Introduction

Parkinson's disease (PD) is a frequent neurological disorder with increasing prevalence in the older population and the process of progressive neuron loss is not well understood yet. Discovering metabolic changes within the substantia nigra (SN) could improve the early diagnosis and help for therapeutic advances. So far, no reliable methods exist that can be used as a diagnostic tool to identify early pathological changes. Characterization of early pathology would be of utmost benefit for the diagnosis and treatment of this relentlessly progressive disorder. In our previous work we could demonstrate for the first time that it is possible to perform 3D-MRSI at 3T in the SN region in humans with good reliability and high spatial resolution (1). Moreover, we could show significant differences in the biochemical profiles of PD patients compared to normal age-matched controls as well as compared to patients with atypical and secondary Parkinsonian syndromes (2). These changes could be used for an early diagnosis when first clinical symptoms will be developed. However, it has not been elucidated yet, whether the detected significant differences were really in NAA and creatine or in metabolites or macromolecules underlying these main metabolites. Therefore, the goal of this study was to refine the analysis of obtained 3D-MRSI spectra, to give a biochemical explanation for molecular changes which could help to develop new therapy options with neuron protection.

Material and Methods

23 PD patients with disease durations between 4 and 25 years and 24 neurologically healthy controls in the same age range were examined using 3D-MRSI (2). All MR examinations were carried out on a 3T MR scanner (Magnetom Tim Trio, Siemens Healthcare, Erlangen) with a 32-channel head coil. The proton 3D-MRSI was performed using a PRESS sequence (TE/TR = 30/1350 ms) with water saturation. The volume of interest was fitted to the size of midbrain so that the SN region was located in the same voxels in all subjects. The resulting nominal voxel size was 6×6×7 mm^3 so that two enclosed voxels (rostral and caudal) defined the SN region in the sagittal direction (Fig. 1). Automatic and manual shimming procedure was performed. The total acquisition time was approximately 30 minutes. The 3D-MRSI raw data were analyzed using LCModel 6.2-2B. However, using the standardized basis data set a systematic incomplete spectrum fit with bent baseline was obtained. Therefore, a specific basis data set was calculated using VESPA 0.6.0 (3) which contains tissue-specific metabolites. Furthermore, the macromolecular baseline and the control parameters were optimized and soft constrains were adjusted according to the tissue-specific metabolite concentrations (4). To increase the signal/noise ratio, group-specific mean spectra for the rostral and the caudal voxels were calculated from the FID data using Matlab R2010b. Afterwards, these mean raw data were used for the LCModel analysis. Additionally, all individual spectra were also analyzed with the same basis data set and control parameters.

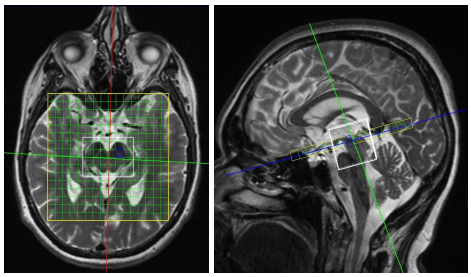

Fig. 1: *3D-MRSI voxel localization in SN region for rostral and caudal slice.*

Results

Correct spectral curve fittings with reasonable baselines could be obtained. The calculation of group-averaged spectra resulted in high signal/noise ratios between 39 and 46. The spectral quality was evaluated based on the estimated FWHM values and was similar in both groups, differences in line broadening could not be observed. The estimated concentrations for NAA, choline, creatine, myo-inositol, glutathione and dopamine are clearly decreased in PD patients compared to controls whereas glutamine + glutamate and GABA are slightly increased (Fig. 2). Furthermore, clear differences were found between the rostral and caudal SN parts in the estimated NAA, choline, glutamine + glutamate, myo-inositol, and GABA concentrations in the same manner for both groups. All results are shown in detail in Tab. 1. The individual metabolite concentrations show large standard deviations also caused by the low signal/noise ratios between 6 and 12. Therefore, only the concentrations of the three main metabolites were estimated on individual level. The decrease of NAA, choline, and creatine could be reproduced in PD patients.

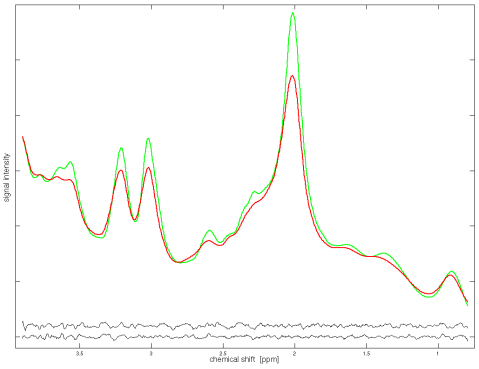

Fig. 2: *Rostral mean spectra of controls (green) and PD patients (red). The residuals of the optimized LCModel spectral curve fits are shown at the bottom.*

Tab. 1: *Metabolite concentrations [arbitrary units] of PD patients and age-matched controls estimated using the mean spectra.*

	Controls (n = 24)		PD patients (n = 23)	
	rostral	caudal	rostral	caudal
S/N	46	41	41	39
FWHM	13.2 Hz	11.7 Hz	14.7 Hz	11.7 Hz
NAA	50.2	40.7	37.8	29.5
Choline	5.4	6.3	4.7	5.4
Creatine	28.0	27.2	22.9	20.6
Glu + Gln	10.1	5.0	18.4	16.1
Myo-inositol	27.2	21.8	19.1	17.3
GABA	21.1	18.4	33.1	20.7
Glutathione	20.7	20.2	12.4	11.7
Dopamine	12.6	12.1	10.8	4.2

Discussion

Motor symptoms of PD result from progressive degeneration of dopamine-producing neurons within the SN pars compacta (5). The process of neuron loss is not well understood, yet. However, there is strong evidence that mitochondrial dysfunction and oxidative stress play a causal role in PD pathogenesis. Therefore, reduced NAA (putative marker of viable neurons), creatine (marker for impaired energy metabolism due to mitochondrial dysfunction) glutathione (marker for oxidative stress) and dopamine concentrations are expected in PD patients. In this study we could show these expected decreases of NAA, choline, creatine, myo-inositol, glutathione and dopamine in the SN region of PD patients *in vivo* for the first time. Furthermore, the slightly increase of glutamine + glutamate and GABA is in good agreement with the *post mortem* data by Gerlach et al. (4). In conclusion, the presented study provides a method by which it should be possible to monitor the disease progression and to validate biochemical explanation for molecular changes in PD which could help to understand the disease better, and to develop new therapy options with neuron protection and progression delay for a long time period.

References

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