$^1$H MRS and DWI for differentiation of Parkinson's disease (PD) from parkinsonian syndromes (PS)

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Purpose

Distinguish Parkinson's disease (PD) from parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) by conventional MRI is difficult in the early stages of the diseases. Parkinsonian symptoms and signs may be a prominent feature of both MSA and PSP. On the basis of symptoms at onset, MSA has been divided into two forms: MSA-C characterized by a predominance of cerebellar symptoms and MSA-P where parkinsonism is prevalent. PD and MSA are both #-synucleinopathies, and pathologically, in PD a massive loss of dopaminergic neurons in the pars of compacta of the substantia nigra and intraneuronal Lewy bodies are present. In MSA, neuronal loss and gliosis occur in the inferior olives, pons, transverse pontocerebellar fibres, cerebellum, substantia nigra, locus ceruleus, striatum, and in the intermediolateral column of the spinal cord. In MSA-P, the nigrostriatal system is the main site of pathology but less severe degeneration can be widespread and usually includes the olivopontocerebellar system.

In MSA-C, mainly the olivopontocerebellar system is involved along with loss of pontine neurons and transverse pontocerebellar fibres and atrophy of middle cerebellar peduncles (MCPs). Unlike PD, and MSA, PSP is a taupathy characterized, pathologically, by neuronal loss, granulovacuolar degeneration, gliosis and neurofibrillary tangles in the midbrain, pons and basal ganglia.

Conventional MRI has been extensively used to identify diagnostic markers for PD, MSA, and PSP. MR-images of the brain in patients with PD are generally normal, although subtle mesencephalic changes, of uncertain diagnostic value, have been reported in some cases.

In PSP, atrophy of the midbrain, third ventricle dilation and hyperintensive foci in the periaqueductal region on the T2-weighted axial MR-images are present. Moreover, a reduction of the anteroposterior diameter of the midbrain on T2-weighted axial MR-images differentiates PSP from PD. MRI is useful for distinguish the two forms of MSA: the MSA-P shows a putaminal atrophy, T2-hypointensity and "slit-like" marginal hyperintensity ("hot cross bun" sign) on T2-weighted, and proton-density-weighted MR-images.

With in vivo 1H MRS we can describe quantitatively the brain states of the patients with PD and Parkinsonian Syndromes. Moreover we put the task ourselves to make it for an individual brain to exclude statistical evaluations of the brain state of a human. To achieve such a goal we choose measured quantities, which may give us an information about the brain state and define such indicators based on the experimental data which will allow us to establish quantitative empirical laws characterizing the human brain states.
The major pathology underlying idiopathic PD is a loss of dopaminergic neurons in the substantia nigra. If NAA is a valid marker of functional neuronal integrity, than one would predict decreased NAA content in the substantia nigra in patients with PD. In contrast to the apparent lack of changes in PD, there does appear to be a significant reduction in basal ganglia NAA concentration in MSA-patients. In patient with MSA a significant reduction of the NAA/Cr has been reported in the lentiform nucleus, particularly in patients with MSA-P, suggesting that measurement of NAA concentration by MRS may be clinically useful for differentiating MSA-P from PD.

There is increasing recognition that PD is a multisystem disorder with neuronal dysfunction that is not restricted to dopaminergic pathways or to the basal ganglia. Consistent with this, a reduced NAA/Cr ratio has been reported in motor cortex, temporoparietal cortex, and in posterior cingulate cortex. There are a number of important factors that may contribute to the variability of results, and a major issue is the methodology used to quantify metabolite content. One of the standard approach used by many investigators has been to express the data as a ratio of the main cerebral metabolites and Cr that is presumed to remain constant. The results vary from patient status (early untreated patients with PD, or patients with advance disease required treatment), from echo time, etc. may lead to heterogeneous results.

In our approach we use the primary spectral parameters of three main metabolites, such as N-acetylaspartic acid (NAA) - a putative neuronal marker, total creatine (Cr), and choline (Cho).

We use Diffusion Weighted MRI (DWI) for differential diagnosis PD from MSA and PSP using of water apparent diffusion coefficients (ADC). ADC depends on the interactions between water molecules and the chemical environment as well as the structural barriers at cellular and subcellular level hindering their motion in vivo. Typically, pathological processes that modify tissue integrity, like in neurodegenerative disorders, result in an increased ADC. In our previous study we have found out, that ADC values in putamen of MSA-P may distinguish MSA-P from PD in patients with PD who demonstrated respectively high and normal putaminal ADC. In many studies have been reported abnormalities, including increased ADC values and diffusion tensor changes in putamen, caudate nucleus, and pallidus, correlating with disease severity and apparently present in early stages of MSA-P. In the our study, in order to identify objective diagnostic markers for differential diagnosis of PD, MSA-P, and PSP, we use DWI to assess the ADC values in the brainstem, middle cerebral peduncles (MCPs), basal ganglia and cerebral white matter regions of the brain.
Methods and Materials

Four groups of patients are studied with 1.5T Signa Excite (GE). The PDG group includes 19 patients with PD, the MSAG group includes 16 patients with MSA, the PSPG group consists of 14 patients with PSP, and CG group includes 15 healthy volunteers. For all patients 1H spectra are obtained in basal ganglia (BG) and in MCPs with SVS-STEAM: TR/TE=1500/144,164,184,204ms. From the echo-time dependence of AM (where AM are the peak areas of the signals from Cho, Cr and NAA the T2M are calculated.

DWI was performed with # = 90°, TR = 10 s, TE = 100 ms, an in-plane resolution of 2.5 mm and phase encoding in anterior-posterior direction. The diffusion-weighted gradients were applied on each of the three physical axes x, y, z in separate scans. Three different gradient strengths were chosen corresponding to b-factor values = 300,600,900s/mm². From DWI the ADC coefficients are determined in all above mentioned regions of the brain.
Results

The peak areas of MR signals are the primary quantities in our approach to the quantitative description of the brain metabolism. We define two observed quantities: the metabolite content as the peak area $A_i$ and the metabolite concentration $C_i = A_i/S$, here the superscript $i$ numerates metabolites, $S$ is the sum of three peak areas:

$$S = A_{\text{Cho}} + A_{\text{Cr}} + A_{\text{NAA}}.$$ The sum $S$ we call the total metabolite content.

We consider the content and concentration as functions of $S$ and analyze how these functions change with the DOI location, state and age of different subjects. We have found out a fine structure of the average content and concentration. This structure corresponds to the different configuration of a spectrum or to the different sets of the relative values of peak areas. To describe this fine structure we introduce in each DOI the triad $T^* = \{A_{\text{Cho}}, A_{\text{Cr}}, A_{\text{NAA}}\}$, where $A_{\text{Cho}}$, $A_{\text{Cr}}$, and $A_{\text{NAA}}$ are the peak areas of the signals from Cho, Cr and NAA, respectively. We believe that each of the three peak areas takes three values: 1, 2 and 3, to represent symbolically six possible spectral configurations: $T = \{1^*, 2^*, \ldots, 6^*\}$.

One can graphically imagine a triad like a three-peak spectrum which characterizes a corresponding local metabolic state of the brain.

All experimental peak areas for controls and patients are divided into the sets of data points in a correspondence with the spectral configurations. For each of these sets we plot metabolite content and concentration data points as a function of total content $S$.

We also do a linear fit to all peak area sets

$$A_i^f = a_i^f + C_i^f S$$

and a hyperbolic fit $C_i^f = c_i^H + b_i^H S$ to all sets of the concentration data points. The mean values of $C_i$ are under $\langle C_i \rangle = (1/n) \sum A_i^f / S_k$ calculated. Here $n$ is the number of spectra for each spectral configuration. In the experiment the total content of metabolites $S >> 1$. In many cases $a_i^f \ll 1$, and $b_i^H \# 1$. The tangents of slope angles for the linear fits and the constants for the hyperbolic fits are approximately equal to the corresponding average concentrations. The separation of the data points in accordance with triad configurations sets gives essential decrease of the dispersion (SD) for every concentration set compared to the dispersion for all concentration data points. We analyze the separated data in different ways. Figs.8-9 demonstrate the dependences of
NAA concentration as a function of total content S in basal ganglia for normal elderly people (Fig. 8) and patients with PD (Fig. 9). The thick hyperbolas are the least squares fits to the points for one subject, and the thin hyperbolas represent the least squares fits to the points for all subjects in this group. The dependences of NAA concentration as a function of total content S in MCP for patients with PD (Fig. 10) and patients with PSP and MSA (Fig. 11).

**Relaxation Time Configurations (RTC)**

The intensity of signals in the MR spectra, obtained with spin-echo method, depends on delay intervals of the pulse sequence (TE) and the relaxation times $T_1$ and $T_2$ of protons of main cerebral metabolites. In this work we consider the relaxation times of metabolites as the quantities of interest and as complimentary quantities to spectral configurations. Relationship between $T_2^i$, where $i = \text{Cho, Cr and NAA}$, gives us dependence of spectral configuration from TE. Thus, to spectral configuration for some value of TE we add the relaxation times set for Cho, Cr and NAA. This relaxation time configuration characterizes how stable the spectral configuration under varying of TE is. According to the Hahn spin-echo theory, the amplitude of stimulated echo signal at the time $t$ is calculated under Eq. (4):

$$V_i(T_{SE}) = V_0^i \exp\{-\left(\frac{T_M}{T_1^i}\right) - \left(\frac{T_E}{T_2^i}\right)\}, \quad (4)$$

Here $T_M$ is the mixing time ($T_M = 10 - 30 \text{ ms}$), $T_{SE} = T_E + T_M$ is the stimulated echo time, $i$ numerates metabolites. From measurement $V_i$ for various $T_E$ and $T_M$ the $T_1$ and $T_2$ from Eq.(4) are calculated. As usual, $T_M \ll T_1$, and $T_E$ is of order $T_2$, than intensity of signals depend on $T_E$. These dependences, or other words, spin-spin relaxation times $T_2^i$ obtain spectral configuration $T^*$ for each $T_E$. The value of $T_2$ is calculated under Eq.(5).

$$A_i(T_E) = A_0^i \exp\{-\frac{T_E}{T_2^i}\} \quad (5)$$

From measurement of $T_2$ we obtain, that relationship between $T_2^i$ may be different. Configurations of relaxation times (RTC) must be add to spectral configurations $T^*$ for some value of $T_E$, for example, for $T_E = 0$. Extrapolation of $T^*$ to $T_E = 0$ is the case of small $T_E$. The time $T_2$ is defined as the inverse tangent of the slope angle of the linear fit to the $\ln A_i$ versus the echo-time $T_E$: $\ln A_i = \text{const} - \frac{t}{T_2}$. $A_0^i$ #is the value of $A_i$ extrapolated from $T_E$ to zero.

The three-dimensional graph in Fig. 18 demonstrate the distribution of RTC $T_2$ for Cho, Cr and NAA for patients of all groups in MCPs.

DWI data processing and data evaluation:
In our study the distortions of DWI EPI images due to eddy currents gradients suffer from large gradients applied for diffusion weighting were corrected by slice-wise registration of the DW images onto the T2-weighted EPI images using FLIRT-method.

Attenuation depending mono-exponentially on the b-value, the ADC of each direction was determined pixel-wise using a least-squares fit. By calculating the mean of the three directions, the ADC trace map was generated. In order to avoid contamination of the ADC values for grey and white matter by the much higher values of CSF during further evaluation, CSF was removed from the ADC map. This was accomplished using the algorithm for a two-class segmentation based on corresponding T2-weighted EPI images. ADC maps do not show clearly brain structures for the presence of intrinsic low contrast differences. Therefore, the ROIs were initially selected on the T1-weighted images, then checked on the T2-weighted EPI-images which has the same distortions from field inhomogeneities as the diffusion images, and than transferred to ADC maps for determination of the mean values in each ROI. The main ROIs localization are the following: left and right nucleus caudatus, putamen, pallidus, thalamus, prefrontal and precentral white matter, and MCPs. We select the dimensions of each ROI to minimize partial volume effects. In the basal ganglia and in thalamus ADC are calculated by including in the ROI the whole individual brain structure. The spatial resolution of standard DWI does not allow a reliable measurement of ADC values in the cerebral cortex and other structure like superior cerebellar peduncles (SCP) as partial volume effects cannot be avoided.

Conventional MRI and DWI data discussion:

Typical abnormalities for MSA-P obtained on the T2-weighted and PD-weighted images include hyperintense putaminal rim, putaminal hyperintensity and atrophy of the dentate nucleus, but MSA-C patients may show a signal increase in the cerebellum, MCPs, and a cruciform hyperintensity in the pons (hot-cross bun). In patients with PSP common MRI-abnormalities comprise a reduction of the anteroposterior diameter < 14mm, signal increase in midbrain, atrophy or signal increase of the red nucleus, frontal or temporal lobe atrophy.

DWI show overlapping abnormalities in patients with MSA and PSP. The results of rADC values at the next Table are presented.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>PD</th>
<th>PSP</th>
<th>MSA-P</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>0.86</td>
<td>0.936</td>
<td>0.973</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>(0.81 - 0.93)</td>
<td>(0.89 - 1.02)</td>
<td>(0.96-1.03)</td>
<td>(0.81 - 0.95)</td>
</tr>
<tr>
<td>Nucleus caudatus</td>
<td>0.85</td>
<td>0.921</td>
<td>0.91</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>(0.82 - 0.93)</td>
<td>(0.85 - 1.1)</td>
<td>(0.80 - 0.98)</td>
<td>(0.80 - 0.90)</td>
</tr>
<tr>
<td>Region</td>
<td>ADC (mean value ·10⁻³ mm²/s (range))</td>
<td>ADC (mean value ·10⁻³ mm²/s (range))</td>
<td>ADC (mean value ·10⁻³ mm²/s (range))</td>
<td>ADC (mean value ·10⁻³ mm²/s (range))</td>
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<td>-----------------------------</td>
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</tr>
<tr>
<td>Globus pallidus</td>
<td>0.87 (0.81 - 0.92)</td>
<td>0.94 (0.91 - 0.96)</td>
<td>0.92 (0.85 - 1.01)</td>
<td>0.87 (0.83 - 0.92)</td>
</tr>
<tr>
<td>Talamus</td>
<td>0.89 (0.84 - 0.99)</td>
<td>0.953 (0.89 - 1.02)</td>
<td>0.913 (0.88 - 0.98)</td>
<td>0.89 (0.82 - 0.91)</td>
</tr>
<tr>
<td>Middle cerebellar peduncles</td>
<td>0.79 (0.73 - 0.85)</td>
<td>0.831 (0.73 - 0.84)</td>
<td>0.93 (0.89 - 1.03)</td>
<td>0.81 (0.68 - 0.83)</td>
</tr>
<tr>
<td>Prefrontal white matter</td>
<td>0.90 (0.84 - 0.97)</td>
<td>0.96 (0.89 - 1.06)</td>
<td>0.91 (0.85 - 0.97)</td>
<td>0.79 (0.81 - 0.88)</td>
</tr>
<tr>
<td>Precentral white matter</td>
<td>0.88 (0.80 - 0.94)</td>
<td>0.951 (0.83 - 1.02)</td>
<td>0.90 (0.82 - 1.01)</td>
<td>0.82 (0.75 - 0.87)</td>
</tr>
<tr>
<td>Pons</td>
<td>0.89 (0.79 - 0.95)</td>
<td>0.95 (0.81 - 1.03)</td>
<td>0.97 (0.86 - 1.28)</td>
<td>0.86 (0.72 - 0.89)</td>
</tr>
</tbody>
</table>

ADC (mean value ·10⁻³ mm²/s (range)) for differentiation of patients with PD, PSP, MSA-P and controls
Images for this section:

**Fig. 1:** 6 possible spectral configurations

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Fig. 2

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Fig. 4

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Fig. 5

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**Fig. 6:** For Figs. 2-7: In vivo spectra and ROI localization for ADC calculation in patient with PD (Figs. 2,3,5,6), in patient with PSP (Fig.4) and in patient with MSA-P (Fig.7).

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Fig. 7

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Fig. 8

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Fig. 9: The NAA concentration CNAA as a function of S in basal ganglia of the normal elderly people (Fig. 8) and in patients with PD (Fig. 9). Comment: The dependences of CNAA as a function of S in basal ganglia of patients with PD and in normal elderly people are the similar.

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Fig. 10

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Fig. 11: The NAA concentration CNAA as a function of S in MCP of the patients with PD (Fig. 10) and in patients with PSP and MSA (Fig. 11). In MCP of patients with MSA and PSP the concentrations of NAA demonstrate the greater reduction, than in white matter.

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**Fig. 13:** Echo-time dependence of the lnAi versus TE, here i = Cho (blue), Cr (red) and NAA (green) in white matter of patient with PD (m, 43 y.o., 4 y. of disease duration). T2Cho = 67 ms, T2Cr = 59 ms, T2NAA = 207.5 ms.

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**Fig. 12:** Echo-time dependence of the lnAi versus TE, here i = Cho (blue), Cr (red) and NAA (green) in white matter of patient with PSP (m, 62 y.o., 6 y. of disease duration). T2Cho = 145 ms, T2Cr = 40.5 ms, T2NAA = 98.6 ms.

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Fig. 14: Echo-time dependence of the lnAi versus TE, here i = Cho (blue), Cr (red) and NAA (green) in the basal ganglia with PD (m, 43 y.o., 4 y. of disease duration). T2Cho = 210 ms, T2Cr = 185 ms, T2NAA = 263 ms.

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Fig. 15: Echo-time dependence of the lnAi versus TE, here i = Cho (blue), Cr (red) and NAA (green) in basal ganglia of patient with PSP (m, 62 y.o., 6 y. of disease duration). T2Cho = 134 ms, T2Cr = 151 ms, T2NAA = 133 ms.
**Fig. 16:** Echo-time dependence of the lnAi versus TE, here i = Cho (blue), Cr (red) and NAA (green) in the MCPs of patient with MSA (m, 65 y.o.). T2Cho = 204 ms, T2Cr = 198 ms, T2NAA = 331 ms.
**Fig. 17:** Echo-time dependence of the lnAi versus TE, here $i = \text{Cho}$ (blue), Cr (red) and NAA (green) in the MCPs of patient with PSP (m, 65 y.o.) $T2_{\text{Cho}} = 215$ ms, $T2_{\text{Cr}} = 114$ ms, $T2_{\text{NAA}} = 321$ ms.

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**Fig. 18:** Each RTC in voxel in the spectral matrix is represented by point with coordinates $T_{ci} = (T_{2i} / \#i T_{2i})^{1/2}$, here $i = \text{Cho}, \text{Cr}$ and NAA. Colors correspond to RTC's: 1* - green, 2* - red, 3* - orange, 4* - blue, 5* - crimson, and 6* - lilac.

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Conclusion

From comparison of $T_2^M$ values in basal ganglia for patients of four groups the shortening of the $T_2^M$ for patients are found. The mean $T_2^M$ values ($M = \text{Cho, Cr, NAA}$) in basal ganglia are the following: in PDG (67.1, 40.5, 98.6 ms), in MSAG (145.2, 59.3, 207.5 ms), in PSPG (210.1, 185.3, 263.4ms), in CG (204.2, 198.0, 331.2 ms). These $T_2^M$ differences allow us to distinguish subjects of CG from patients of MSAG, PDG, and PSPG, but they are not specific for differentiation of MSA from other diseases. The mean $T_2^M$ values in MCP are the following: in PDG (63.3, 56.5, 90.2 ms), in MSAG (58.2, 49.0, 101.8 ms), in PSPG (134.1, 152.3, 233.1ms), in CG (215.0, 114.0, 320.1ms). The shortening of $T_2^M$ in MCP for patients of MSAG is extremely specific. From analysis of DWI the ADC coefficients (in mm$^2$/s) for patients of PDG, MSAG, PSPG, and CG in the region of BG are obtain: (0.65x10^{-3}), (0.54x10^{-3}), (0.64x10^{-3}), and (0.44x10^{-3}). More pronounce are differences of ADC in MCP: (0.82x10^{-3}), (0.96x10^{-3}), (0.79x10^{-3}), and (0.81x10^{-3}) in PDG, MSAG, PSPG, CG, respectively. Increasing of ADC coefficients in MCP for patients of the MSAG allows us differentiate MSA from PSP and PD with high sensitivity. Detected in MCP significantly higher ADC, and also lower $T_2^M$ in patients with MSA in comparison with patient with PD and PSP are in vivo diagnostic markers of MSA. The DWI and relaxometry measurements in the BG allow us to discriminate patients from subjects of the CG, but did not differentiate patients of MSAG from PDG, and PSPG. Detected in MCP significantly higher ADC, and also lower $T_2^M$ in patients with MSA in comparison with patient with PD and PSP are in vivo diagnostic markers of MSA.
References

N/A