MR spectroscopy and diffusion tensor imaging study of the impact of fluoxetine on the human brain in multiple sclerosis

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Purpose Magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) were used to assess the beneficial effects of fluoxetine treatment on the structural brain parameters of multiple sclerosis patients.

Introduction In this quantitative MR study fluoxetine, an antidepressant shown to cause an increased cerebral N-acetyl aspartate to creatine ratio (NAA/Cr) in the white matter tissue [1], was administered to 15 patients with multiple sclerosis (MS). Considering that fluoxetine stimulates astrocytic glycogenolysis, which serves as an energy source for axons, our expectation was that fluoxetine treatment would have beneficial effects on structural parameters measured by DTI and MRS (FA increase, ADC decrease, NAA increase).

Methods 15 patients (mean age 45 ± 8 years) with definite MS according to McDonald's criteria and with expended disability status scale ratings of 6 or lower, were examined by MRI and ^{1}H MRS at 1.5 Tesla using the standard head coil of a Magnetom Sonata system (Siemens AG, Erlangen, Germany). The MRI protocol included a diffusion-weighted spin-echo echo-planar imaging (SE-EPI) sequence in order to reduce motion artefacts. DTI: Diffusion weighted images were obtained in 12 independent directions with a b value of 0 to 1000 s/mm^2 and 4 mm slice thickness without gap oriented parallel to the CSI volume of interest in order to facilitate the determination of DTI parameters for the voxels defined by MRS [2]. MRS determination of water contents: PRESS 2D-CSI measurements (TR/TE 1500/135 ms) were performed without water suppression. A T2 weighted MRI series was used as guidance for defining a CSI volume of interest of 8x8 cm^2 (64 spectra) within a 16x16 cm^2 FOV (256 phase encode steps) located cranial to the ventricles, a transverse 2 cm thickness slice in that part of the brain where the white matter (WM) is most abundant, for MRS. At 1 acquisition per phase encode step the CSI measurements took 7 min. During the first week after DTI/MRS examination patients received 20 mg fluoxetine once a day and during the next week 40 mg of fluoxetine per day. The DTI/MRS examinations were repeated after the first week ("week 1") and second week of therapy ("week 2").

Results The absolute values of the DTI and MRS parameters in the group of 15 MS patients as compared with reference values are listed in Table 1. In the gray matter (GM) brain tissue, in the normal appearing white matter (NAWM) and especially in the white matter lesions (WML) of MS patients FA, Cho, Cr and NAA tend to be lower than in healthy controls and ADC higher. The changes in these parameters after fluoxetine therapy were small and therefore listed in Table 2 in per mill changes measured at week 1 (i.e. after one week of 20 mg/day fluoxetine) and week 2 (i.e. after 40 mg/day during the second week). GM Cho tended to decrease by about 5% measured at weeks 1 and 2 ($P<0.05$) and changes in NAWM were not significant. Changes in WML were significant for ADC (a minor increase at week 1 and a 3.6% decrease measured at week 2; $P<0.02$, both) and for Cho and NAA (increases by approximately 8% at week 2; $P<0.02$ and <0.001, respectively). The highly significant WML NAA increase is illustrated by Fig.1 showing the spectral maps of a MS patient before and after fluoxetine therapy projected on FLAIR images.

	FA	ADC	Cho	Cr	NAA
GM	.23(.27)	11.3(9.0)	1.3(1.5)	5.0(6.2)	8.0(10.2)
NAWM	.34(.40)	9.0(7.5)	1.4(1.7)	4.9(5.7)	9.8(12.1)
WML	.30	10.5	1.1	4.0	7.3

Table 1. Pretreatment means (healthy volunteer reference values). ADC *10^{-4}mm2/s; Cho,Cr and NAA in mM

	per mill changes	FA	ADC	Cho	Cr	NAA
GM	week 1 (week 2)	109 (18)	-24 (4)	-42 (-50)	-33 (24)	-28 (18)
NAWM	week 1 (week 2)	2 (11)	25 (0)	21 (-22)	-2 (10)	2 (12)
WML	week 1 (week 2)	47 (42)	17 (-36)	5 (76)	-16 (12)	12 (86)

Table 2. Mean per mill changes after 1 (and 2 weeks) of fluoxetine

Discussion We observed a single trend in gray matter brain tissue (a slight decrease of choline measured at weeks 1 and 2) and no changes at all in normal appearing brain tissue. In white matter lesions, however, ADC was increased at week 1 and decreased at week 2 ($P < 0.02$, both), whereas NAA were increased at week 2 ($P < 0.05$ and $P < 0.001$, respectively). In the white matter lesions a trend of FA increase was observed as well, both measured at weeks 1 and 2, and an increase of Cho measured at week 2 ($P < 0.02$). At week 2 after fluoxetine treatment all metabolite levels and FA are still low and ADC still high in the white matter lesions as compared with white matter tissue reference values, in other words, a partial normalization of DTI and MRS parameters was observed (compare tables 1 and 2). Our observations in white matter lesions thus provide further evidence of a neuroprotective effect of fluoxetine in multiple sclerosis by the observed partial normalization of the structure related DTI and MRS parameters (FA, ADC and NAA).

References 1. Mostert JP, Sijens PE, Oudkerk M, De keijser J. Fluoxetine increases cerebral white matter NAA/Cr ratio in patients with multiple sclerosis. Neurosci Lett 2006;402:22-24. 2. Irwan R, Sijens PE, Potze JH, Oudkerk M. Correlation of MR spectroscopy and diffusion tensor imaging. Magn Reson Imaging 2005;23:851-858.

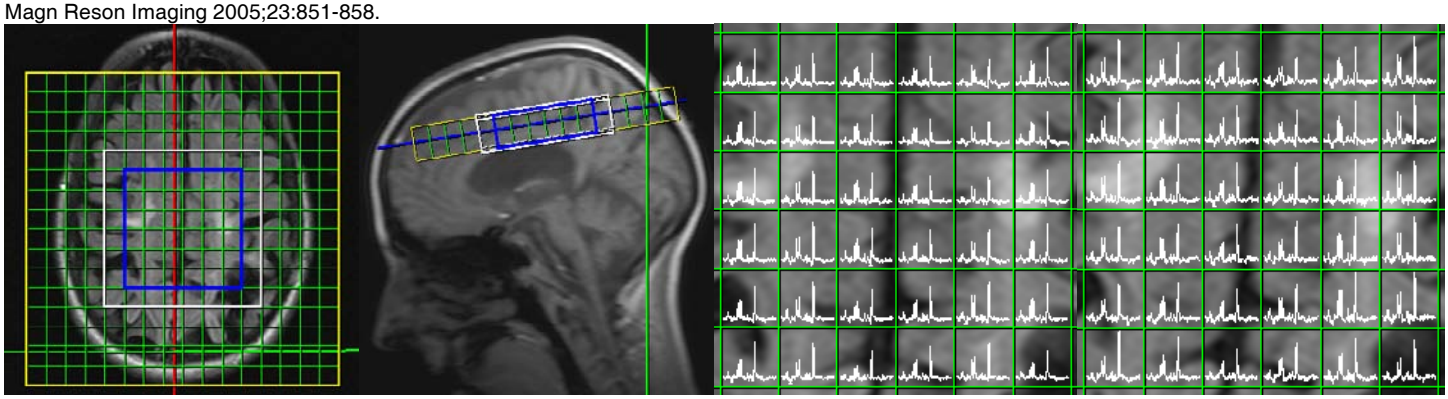

Fig.1. Chemical shift imaging results showing ^{1}H MRS (TR/TE=1500/135) spectral maps of a secondary progressive multiple sclerosis patient with white matter lesions before fluoxetine therapy and at week 2 thereafter (rightmost image). Note the NAA increases in the white matter lesions.