

Original article

## Magnetic resonance relaxometry in monozygotic twins discordant and concordant for schizophrenia

Filip Spaniel<sup>a,c,\*</sup>, Vit Herynek<sup>b,1</sup>, Tomas Hajek<sup>a,c</sup>, Monika Dezortova<sup>b</sup>, Jiri Horacek<sup>a,c</sup>,  
Milan Hajek<sup>b</sup>, Jiri Kozeny<sup>a</sup>, Colleen Dockery<sup>a</sup>, Cyril Höschl<sup>a,c</sup>

<sup>a</sup> Psychiatric Center Prague, Ustavni 91, 181 03 Prague 8, Bohnice, Czech Republic

<sup>b</sup> MR Unit, Department of Radiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

<sup>c</sup> 3rd School of Medicine, Charles University, Prague, Czech Republic

Received 11 June 2004; accepted 1 November 2004

Available online 13 December 2004

### Abstract

T1 and T2 relaxation times were examined in four pairs of monozygotic (MZ) twins discordant and concordant for schizophrenia with low and high genetic loading for the illness and five healthy control MZ twin pairs. Patients with schizophrenia ( $n = 11$ ) showed significant prolongation in T1 relaxation times in the globus pallidus (GP) bilaterally ( $P < 0.005$ , Bonferroni corrected) when compared to 14 healthy MZ twins.

© 2004 Elsevier SAS. All rights reserved.

**Keywords:** MR relaxometry; T1 relaxation times; T2 relaxation times; Monozygotic twins; Schizophrenia; Globus pallidus

### 1. Introduction

In order to assess physical and chemical deviations in the brain tissue in schizophrenia, we examined T1 and T2 relaxation times within the caudate nucleus, globus pallidus (GP), thalamus, and frontal white matter in a group of monozygotic (MZ) twins concordant and discordant for schizophrenia with presence and absence of familial loading of the illness and healthy controls. The study subjects were recruited as representative of high and low risk subjects in terms of their genetic preponderance towards schizophrenia. Our initial intention was to explore possible differences in brain metabolic changes between sporadic and more “genetic” subjects.

### 2. Methods

#### 2.1. Subjects

The study sample consisted of 13 MZ twin pairs. Four MZ pairs were discordant and four were concordant for schizo-

phrenia while five were healthy twin pairs without personal or psychiatric history. Valid data were obtained from three affected subjects and four healthy of their healthy co-twins of the four discordant pairs. None of the discordant pairs had a family history of schizophrenia or other major psychiatric disorder. Of the four concordant MZ twin pairs, three of them had a family history of schizophrenia or schizophrenia spectrum disorder in their first-degree relatives. Discordant affected twins and concordant twins thus represented groups with lower and higher genetic loading for schizophrenia. All twin pairs were reared together. Relevant clinical data are summarized in [Table 1](#).

Schizophrenic subjects were stabilized on their medication for at least 20 months prior to the study. None of the subjects received medical treatment that might affect T1 and T2 (e.g. diuretics) during the study procedure.

The study was approved by the Ethics Committee of the Prague Psychiatric Center. The procedure was fully explained to participants and written consent was obtained. Diagnosis of schizophrenia was made by two experienced psychiatrists according to the Structured Clinical Interview for DSM-III-R. Monozygosity was confirmed with genetic analysis (the concordance in 16 short tandem repeats markers) (PowerPlex® 16 System, Promega, Madison, USA [10]).

\* Corresponding author.

E-mail address: [spaniel@pcp.lf3.cuni.cz](mailto:spaniel@pcp.lf3.cuni.cz) (F. Spaniel).

<sup>1</sup> These authors contributed equally to this paper.

Table 1  
Clinical description of the groups of schizophrenic patients and controls

	MZ twins			
	Discordant unaffected mean (S.D.)	Discordant affected mean (S.D.)	Concordant mean (S.D.)	Controls mean (S.D.)
Subjects	<i>n</i> = 4	<i>n</i> = 3	<i>n</i> = 8	<i>n</i> = 10
Gender male/female	2/2	2/1	4/4	4/6
Age	32.7 (11.8)	32.7 (11.8)	30.3 (6.5)	30.2 (4.0)
Schizophrenia subtype		Three paranoid type in remission	Six paranoid type (five chronic, one in remission) two residual type	
Handedness	0 left	0 left	0 left	1 left
Education (years)	13.2 (2.2)	12.2 (0.4)	10.0 (1.5)	13.0 (1.4)
Duration of illness (years)		8.1 (5.3)	8.1 (4.3)	
PANSS (P)		11.5 (1.8)	12.2 (3.9)	
PANSS (N)		20.0 (10.6)	25.4 (5.5)	
PANSS (G)		33.5 (11.9)	44.0 (13.2)	
Type of medication		Two risperidone, flupenthixol	Two olanzapine, two clozapine, two haloperidol, thioridazine, fluphenazine	
PANSS (total)		65.0 (23.8)	81.6 (21.5)	
Current antipsychotic exposure (years)	Typicals	7.0 (1.0)	15.2 (3.3)	
	Atypicals	2.1 (0.4)	5.7 (0.2)	
Total antipsychotic exposure (years)		7.7 (4.4)	10.8 (5.3)	

## 2.2. T1 and T2 measurement

We used a 1.5 T whole body imager Siemens Magnetom-Vision (Siemens, Erlangen, Germany) equipped with a commercially available CP head coil. After a standard localization procedure by turbo spin echo sequences (5-mm transversal and coronal slices: repetition time TR = 5.4 s, echo time TE = 99 ms, flip angle = 180°, field of view FOV = 300 × 300 mm, matrix size: 154 × 256; 5-mm sagittal slices: TR = 700 ms, TE = 12 ms, flip angle = 180°, FOV = 260 × 260 mm, matrix size: 216 × 256) a 5-mm thick tilt-corrected axial slice at the level of the basal ganglia was measured using the following sequences:

- For T<sub>1</sub> measurement a series of T<sub>1</sub> weighted images (saturation recovery) with repetition time TR varying from 100, 200, 400, 600, 800, 1000 and 1500 ms, and an echo time TE = 22 ms were used with a field of view FOV 195 × 260 mm and a matrix 154 × 256.
- For T<sub>2</sub> measurement a standard 16-echo CPMG sequence with TR = 3 s and echo spacing TE = 22.5 ms was used, with field of view and matrix size the same as in T<sub>1</sub> measurement.

T<sub>1</sub> and T<sub>2</sub> maps were obtained by a three-parameter fitting for each image pixel by an in-house software [7]. Values of T<sub>1</sub> and T<sub>2</sub> were obtained from regions of interest (ROI) selected in the caudate nucleus, putamen, GP, thalamus and frontal white matter bilaterally. The sizes of the ROI were approximately: caudate nucleus – 100 mm<sup>2</sup>, putamen – 190 mm<sup>2</sup>, GP – 90 mm<sup>2</sup>, thalamus – 240 mm<sup>2</sup>, frontal white matter – 280 mm<sup>2</sup>.

Reproducibility of the relaxation time measurements was ensured by regularly performed quality control [5]. The control was performed using gelatine phantoms both for T<sub>1</sub> and T<sub>2</sub> measurements. Long-term reproducibility of the average values of the relaxation time T<sub>2</sub> obtained by a standard 16-echo CPMG pulse sequence on gelatine phantoms (with T<sub>2</sub> values close to those found in the brain, i.e. approximately 80 ms) is represented by a standard deviation below 10%. Similar results were obtained for reproducibility of T<sub>1</sub>. The dispersion of in vivo T<sub>1</sub> data may be slightly higher because the phantoms did not have the same T<sub>1</sub> relaxation times as those found in the brain, nevertheless our quality control excludes a systematic error.

## 2.3. Statistical analysis

Group differences in T<sub>1</sub> and T<sub>2</sub> relaxation times were tested with the Kolmogorov–Smirnov test, Monte Carlo estimation of exact  $P < 0.05$  based on 30,000 sampled tables. A Bonferroni correction was applied to take into account the large number of comparisons ( $\alpha/\text{number of ROI} = 0.05/10$ ). Therefore, T<sub>1</sub> and T<sub>2</sub> relaxation time differences were considered significant at  $P < 0.005$ . Statistical power was assessed for two-tailed Mann–Whitney test,  $P = 0.005$ , assuming normal distribution of relaxation times.

## 3. Results

No statistically significant differences were found between affected twins from discordant pairs and concordant twins.

Table 2  
Mean T1 values (ms) and standard deviations for different brain regions

		Discordant unaffected mean (S.D.)	Discordant affected mean (S.D.)	Concordant mean (S.D.)	Controls mean (S.D.)
Subjects		<i>n</i> = 4	<i>n</i> = 3	<i>n</i> = 8	<i>n</i> = 10
GP	Right	843.1 (41.3)	963.2 (77.0)	932.3 (62.4)	758.6 (83.5)
	Left	851.0 (30.0)	1001.8 (162.1)	912.5 (47.8)	768.6 (92.0)
Putamen	Right	1129.1 (55.8)	1408.2 (261.3)	1163.8 (58.9)	986.5 (130.2)
	Left	1137.7 (97.7)	1324.3 (272.7)	1150.4 (75.1)	988.8 (148.3)
Caudate nucleus	Right	1162.6 (110.3)	1449.3 (113.1)	1270.6 (153.7)	1108.6 (154.6)
	Left	1202.6 (68.5)	1500.1 (209.6)	1293.1 (83.9)	1106.1 (169.1)
Thalamus	Right	1001.6 (79.2)	1220.1 (88.0)	968.7 (62.2)	887.5 (68.6)
	Left	994.4 (104.8)	1244.6 (40.8)	1006.3 (31.4)	913.9 (77.7)
White matter	Right	735.6 (65.1)	871.6 (94.5)	769.8 (65.7)	677.3 (51.9)
	Left	739.2 (55.5)	855.5 (105.4)	749.4 (53.4)	685.1 (52.5)

GP: globus pallidus

However, given the group sample sizes of eight and three, achieved power of the study ranged from 0.6% to 26%.

Post hoc exploratory analyses showed significant bilateral prolongation in T1 relaxation times in the GP (Kolmogorov–Smirnov test, Monte Carlo estimation of exact  $P < 0.005$  based on 30,000 sampled tables, Bonferroni corrected—5% experiment-wise error rate, two-sided) in patients with schizophrenia (pooled data from affected discordant MZ twins and concordant twin pairs,  $n = 11$ ) in comparison to healthy subjects (pooled data from healthy controls and unaffected twins from discordant MZ pairs,  $n = 14$ ). Mean T1 for the right GP was 941.6 ms, S.D. 64.3, and the left GP = 939.2 ms, S.D. 96.0 in the group with schizophrenia and for the right GP 789.3 ms, S.D. 80.7, and the left GP = 798.5 ms, S.D. 84.1 in healthy subjects, respectively. Given the fact that healthy twins from discordant pairs may represent an intermediate phenotype and thus bias the results, those subjects were subsequently excluded from the analysis. Nevertheless, the results remained significant ( $P < 0.005$ , Bonferroni corrected). In this case, group sample sizes of 11 and 10 achieved power 97% for the right and 76% for the left GP, respectively.

The mean values of T1 in each ROI bilaterally are summarized in Table 2. No significant differences between the groups were found in T2 relaxation times.

#### 4. Discussion

We did not find significant differences in T1 and T2 relaxation times between the groups considered at lower and higher genetic predisposition to schizophrenia. However, the study was underpowered and the possibility of false negative results needs to be considered. Pooled data from all patients with schizophrenia, both from discordant and concordant pairs, demonstrated prolongation of the T1 relaxation time compared to healthy subjects in the GP bilaterally.

The finding suggest a relatively increased amount of weakly bound water in patients with schizophrenia within this subregion of the basal ganglia compared to healthy subjects. As all patients were receiving antipsychotic treatment it is unclear whether the observed prolongation of T1 value was

associated with antipsychotic medication or with the pathophysiology of schizophrenia. Both neuroimaging and histological studies have repeatedly shown that antipsychotics affect the basal ganglia. It is hypothesized that a volume increase in basal ganglia nuclei observed in antipsychotic-treated patients [4,9] together with aberrant histological findings within the area [8] are mediated through sustained D2 receptor antagonism [2].

The impact of antipsychotics on relaxation times remains unresolved. One animal study that initially suggested that haloperidol may prolong T1 relaxation time [3] was not proved replicable and have subsequent studies have failed to find any effect of antipsychotics on relaxation times [6]. Several studies examined relaxation times in the basal ganglia of patients with schizophrenia in relation to the presence or absence of tardive dyskinesia following long-term antipsychotic treatment. However, the results have been inconclusive [1].

#### 5. Conclusion

We found prolonged T1 relaxation times in the GP of patients with schizophrenia compared to healthy controls. This is probably due to the effect of antipsychotics although the precise nature of the changes in brain tissue characteristics of the patients cannot be specifically inferred from our data. To examine whether prolongation of the T1 relaxation time reflects specific tissue changes attributable to the long-term antipsychotic medication requires further studies using MR relaxometry in both medicated and unmedicated schizophrenia patients.

#### Acknowledgements

This study was supported by grants GACR 309/97/K04, IKEM 906, MSMT LN00B122 (CNS), and IGA MZ NF/6033-3, Czech Republic.

## References

- [1] Buckley P, Ocallaghan E, Mulvany F, Larkin C, Stack JP, Redmond O, et al. Basal ganglia T-2 relaxation-times in schizophrenia—a quantitative magnetic-resonance-imaging study in relation to tardive-dyskinesia. *Psychiatry Res* 1995;61(2):95–102.
- [2] Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogerts B, et al. Increase in caudate nuclei volumes of first-episode schizophrenic-patients taking antipsychotic-drugs. *Am J Psychiatry* 1994;151(10):1430–6.
- [3] Fujimoto T, Nakano T, Fujii M, Okada A, Harada K, Yokoyama Y, et al. Changes in proton-T1 in dog brains due to the administration of haloperidol. *Magn Reson Imaging* 1987;5(6):469–74.
- [4] Gur RE, Maany V, Mozley D, Swanson C, Bilker W, Gur RC. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *Am J Psychiatry* 1998;155(12):1711–7.
- [5] Hajek M, Babis M, Herynek V. MR relaxometry on a whole-body imager: quality control. *Magn Reson Imaging* 1999;17(7):1087–92.
- [6] Harvey I, Ron MA, Murray R, Lewis S, Barker G, Mcmanus D. MRI in schizophrenia—basal ganglia and white matter T1-times. *Psychol Med* 1991;21(3):587–98.
- [7] Herynek V, Babiš M, Trunečka P, Filip K, Vymazal J, Dezortová M, et al. Chronic liver disease: relaxometry in the brain after liver transplantation. *Magma* 2001;12(1):10–5.
- [8] Jellinger K. Neuropathologic findings after neuroleptic long-term therapy. In: Roizin L, Shiraki H, Grsevic N, editors. *Neurotoxicology*. New York: Raven Press; 1977. p. 25–41.
- [9] Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW. Changes in caudate volume with neuroleptic treatment. *Lancet* 1994;344(8934):1434.
- [10] Thomson JA, Ayres KL, Pilotti V, Barrett MN, Walker JIH, Debenham PG. Analysis of disputed single-parent/child and sibling relationships using 16 STR loci. *Int J Legal Med* 2001;115(3):128–34.