Voxel-based Relaxometry in Autistic Disorder

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INTRODUCTION: Autism is a severe neurodevelopmental disorder with a spectrum of symptoms and ranging severity. Despite the heterogeneity of the disorder, the symptom triad of social deficits, impaired communication, and restricted and repetitive patterns of behavior are consistently observed. While there is strong evidence suggesting that autism has a neurobiological basis, the anatomical extent and timing of the biological abnormalities involved in the disorder remain unknown. It has been hypothesized that autism is associated with neural underconnectivity[1], suggesting that underdeveloped connective circuitry results in deficient information integration in autism. Transverse relaxation time (T2) imaging provides the opportunity to examine tissue abnormalities *in vivo*, with increased T2 reflecting increased tissue water and therefore reduced density. In this study, we used whole-brain voxel-based relaxometry to investigate potential tissue density abnormalities, which may be associated with underconnectivity in autism. We hypothesized that patients would have higher T2 values in white matter compared to controls.

METHODS: Nineteen males with autism (age: 9.2±3.0 years) and 20 male controls (age: 10.7±2.8 years) participated in this study. The diagnosis of autism was made according to DSM-IV criteria using the Autism Diagnostic Interview – Revised and the Autism Diagnostic Observation Schedule. All patients had a non-verbal intelligence greater than 70. All controls were screened using the K-SADS to exclude psychiatric disorders. The groups did not differ significantly in age, sex, race, or non-verbal intelligence, although controls did have higher verbal and full-scale IQ. Consistent with other studies, more patients than controls were not right-handed (6/19 vs. 0/20). Ten patients were medication-naïve at the time of their scan, while three other patients had discontinued their psychotropic medication. The other patients were being treated with stimulants (n=4), antipsychotics (n=3), and antidepressants (n=2). Fifteen patients required sedation with oral midazolam in order to complete the scan; no control subjects were sedated.

Imaging experiments were performed with a 3.0 T head-only magnetic resonance scanner with a quadrature head coil (IMRIS). Magnetic resonance images were acquired using a **G**radient-**E**cho **S**ampling of the **F**ree **I**nduction **D**ecay and **E**cho (GESFIDE) sequence[4,5]. Imaging parameters included a 192 x 256 matrix size, FOV = 220 mm, bandwidth = 50kHz, 4 mm slice thickness, slice spacing = 6mm, TR = 2500 msec and a total imaging time of 8 minutes. For our study, five gradient echoes were acquired prior to the 180º radio frequency (rf) pulse, with a first-echo time of 9 msec and an inter-echo spacing of 8.70 msec. Six gradient echoes were acquired after the 180º rf pulse, each spaced by 8.78 msec. The k-space data was then reconstructed into $R2^*$ and $R2^-$ maps by performing a voxel-by-voxel least-squares fit of the natural logarithm of the signal amplitude versus echo time. R2 maps (1/T2 maps) were calculated from $R2 = (R2^* + R2^-)/2$.

The R2 maps were analyzed using statistical parametric mapping (SPM) methods. The maps were warped to a template brain specifically created for this study, smoothed, and statistically compared using Analysis of Covariance (ANCOVA) with age as the covariate. The results were thresholded at $p < 0.001$ (uncorrected).

RESULTS: Compared with controls, patients with autism had widespread regions of increased T2, particularly in frontal and occipital white matter and parietal gray matter. The few regions where patients had a reduction in T2 were largely cortical gray matter regions (see table 1 and figure 1).

DISCUSSION: The widespread increases in white matter T2 suggest reduced tissue density and are consistent with the theory that autism is associated with cortical underconnectivity. While the results of this study, the first to specifically examine whole-brain T2 in autism, are intriguing, the findings should be interpreted cautiously in light of several limitations: small sample size, lack of female subjects and possible medication effects.

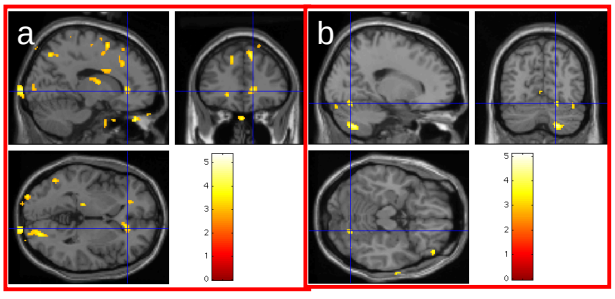

Figure 1. Regions of significantly (a) increased and (b) decreased transverse relaxation times (T2), overlaid on three orthogonal planes of a normalized brain.

Table 1. Areas of significantly (i) increased and (ii) decreased T2 in Autism (white matter regions in **bold**)

Cortical Regions	Cluster Size	Z score	p	T-stat	Talairach coordinates		
					x	y	z
(i)							
R Superior Frontal Gyrus (WM)	29	-3.81	0.11	4.26	11.9	35.2	44.3
R Superior Frontal Gyrus (WM)	33	-3.77	0.09	4.21	21.8	29.8	51.9
R Occipital Lobe - Cuneus (WM)	49	-3.68	0.04	4.09	17.8	-88.9	8.1
R Middle Frontal Gyrus (WM)	32	-3.84	0.09	4.30	19.8	12.8	62.0
R Limbic Lobe - cingulate gyrus (WM)	18	-3.61	0.19	4.00	9.9	11.1	27.1
R Frontal Lobe- Sub-Gyral (WM)	31	-3.74	0.10	4.17	37.6	20.2	15.6
R Frontal Lobe- Sub-Gyral (WM)	23	-3.50	0.15	3.85	15.8	33.0	0.2
L Parietal Lobe - Sub-Gyral (WM)	40	-3.82	0.06	4.28	-17.8	-59.0	25.1
L Parietal Lobe - Sub-Gyral (WM)	15	-3.74	0.23	4.17	-25.7	-45.7	57.6
L Parietal Lobe - Postcenral Gyrus (WM)	84	-4.56	0.01	5.35	-15.8	-41.3	66.5
L Occipital Lobe - Cuneus (WM)	15	-3.76	0.23	4.20	-15.8	-79.1	11.3
L Frontal Lobe - Sub-Gyral (WM)	33	-3.65	0.09	4.04	-19.8	36.6	-5.2
Frontal Lobe - Orbital Gyrus (WM)	40	-4.4	0.06	5.1	-15.8	43.1	-30.8
L Superior Frontal Gyrus (GM)	11	-3.52	0.31	3.88	-17.8	20.6	61.6
R Superior Frontal Gyrus - Brod area 8	9	-3.24	0.36	3.52	5.9	19.9	48.7
R Parietal Lobe- Postcentral Gyrus - Brod area 5	58	-4.08	0.03	4.64	23.8	-43.4	64.8
R Parietal Lobe - Precuneus GM - Brod area 7	11	-3.52	0.31	3.87	13.9	-65.5	49.3
R Parietal Lobe - Precuneus	13	-3.66	0.27	4.07	27.7	-63.9	41.9
L Superior Frontal Gyrus	7	-3.34	0.42	3.64	-2.0	14.8	61.9
L Middle Occipital Gyrus	27	-3.95	0.12	4.46	-29.7	-99.0	1.6
L Middle Frontal Gyrus (adjacent to Broca's)	13	-3.49	0.09	3.84	-17.8	8.9	60.4
L Inferior Frontal Gyrus [BROCA's]	17	-3.51	0.03	3.86	-57.4	11.1	27.1
L Frontal Lobe - Precentral Gyrus - Brod area 6	12	-3.43	0.29	3.77	-57.4	2.9	20.1
R Thalamus - Ventricular Ant. Nucleus	8	-3.24	0.39	3.51	11.9	-5.3	11.3
L Midbrain	10	-3.43	0.33	3.76	-13.9	-13.8	-4.4
(ii)							
R Limbic Lobe- Parahippocampal Gyrus (WM)	64	-3.72	0.022	4.14	-53.5	-1.3	-26.8
R Superior Frontal Gyrus (WM)	5	-3.54	0.498	3.26	33.7	59.8	-8.0
Inter-Hemispheric WM	14	-3.93	0.250	3.56	-47.5	-47.6	-19.5
R Inferior Frontal Gyrus - Brodman 11	6	-3.88	0.455	3.52	0.0	-69.8	3.5
L Middle Temporal Gyrus (GM) [Wernicke's]	8	-3.69	0.385	3.38	27.7	30.0	-21.7
R Cerebellum Anterior Lobe- Culmen	92	-4.44	0.008	3.94	21.8	-69.7	-35.2
R Cerebellum Posteror Lobe	59	-4.93	0.027	4.28	33.7	59.8	-8.0
L Cerebellum Anterior Lobe- Culmen of Vermis	31	-4.7	0.095	4.12	35.6	-53.4	-19.2
L Cerebellum Anterior Lobe- Culmen	4	-3.61	0.548	3.31	0.0	-69.8	3.5

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