ON-LINE APPENDIX

Materials and Methods

MR Imaging Acquisition. DTI data from all subjects were acquired on a 3T Achieva MR imaging scanner (Version 2.1.3.2; Philips Healthcare, Best, the Netherlands) at our institution, by using a dedicated imaging protocol including sensitivity encoding single-shot EPI (TE = 60 ms, TR = 8166 ms, section thickness = 2 mm, voxel dimensions = 1.75 × 1.75 × 2 mm, FOV = 100 mm, image dimensions = 128 × 128 × 60, acquisition matrix = 112, number of sections = 1020), 15 distributed orientations for the diffusion gradients, b-value = 800 s/mm^2, and a first T2 volume without diffusion-weighting.

Statistical Analysis. Comparison of demographic and clinical variables among groups was done by using SPSS, Version 20 (IBM, Armonk, New York), a 2-sample *t* test, or ANOVA with a Tukey post hoc for quantitative variables and a χ^2 test for categoric variables. The significance level was set at $P < .05$.

For the comparison between patients with CS and controls, a whole-brain voxelwise analysis with a randomized tool (included in fMRI of the Brain Software Library, Version 4.1.4),[1] and a standard general linear model design (2 groups, 2 contrasts, between-group comparisons) were used. To investigate the influence of hypercortisolism on WM integrity, we applied a design with 4 groups and 12 contrasts. For both analyses, clinical variables that differed among groups (hypertension, hypertriglyceridemia, central obesity, and body mass index) were included as covariates to control for potential influences on WM analysis. All FA skeleton data were projected on the mean FA skeleton mask by 5000 permutations at $P < .05$, with a family-wise error correction for multiple comparisons and the threshold-free cluster enhancement technique, the highest sensitive and interpretable methodology.[2] MD, AD, and RD maps also followed this statistical approach. In addition, we performed correlation analysis ($P < .05$, family-wise error correction for threshold-free cluster enhancement), searching for potential relationships among 24-hour UFC levels, disease duration, and DTI values (FA, MD, AD, and RD maps).

REFERENCES

1. Nichols TE, Holmes AP. **Nonparametric permutation tests for functional neuroimaging: a primer with examples.** *Hum Brain Mapp* 2002;15:1–25
2. Smith SM, Nichols TE. **Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localization in cluster inference.** *Neuroimage* 2009;44:83–98

On-line Table 1: Between-group differences in DTI maps (healthy controls vs all CS)

Principal Cluster Differences		X	Y	Z	Size (mm^2)	P	t	r	JHU White Matter Tractography Atlas
Healthy controls > all CS	FA	12.00	40.00	−16.00	50536	<.001	3.107	0.353	5% Forceps minor
Healthy controls < all CS	MD	−41.00	−13.00	−20.00	51424	.001	2.748	0.316	37% Inferior longitudinal fasciculus L
Healthy controls < all CS	AD	−36.00	−39.00	15.00	9817	.005	3.62	0.402	No label found
Healthy controls < all CS	RD	11.00	36.00	−16.00	61673	.001	2.3	0.268	No label found

Note:—JHU indicates Johns Hopkins University; L, left.

On-line Table 2: Between-group differences in DTI maps (healthy controls vs active CS)

Principal Cluster Differences		X	Y	Z	Size (mm^2)	P	t	r	JHU White Matter Tractography Atlas
Healthy controls > active CS	FA	−16.00	37.00	−1.00	5146	.025	3.047	0.429	87% Forceps minor, 3% uncinate fasciculus L, 3% inferior fronto-occipital fasciculus L, 3% cingulum (cingulate gyrus) L, 3% anterior thalamic radiation L
Healthy controls < active CS	MD	29.00	−65.00	16.00	45876	.002	5.501	0.652	24% Forceps major, 16% inferior fronto-occipital fasciculus R, 3% inferior longitudinal fasciculus R
Healthy controls < active CS	AD	17.00	−31.00	6.00	26844	<.001	3.053	0.430	No label found
Healthy controls < active CS	RD	19.00	37.00	2.00	39603	.004	4.524	0.577	39% Forceps minor, 16% anterior thalamic radiation R, 8% inferior fronto-occipital fasciculus R

Note:—JHU indicates Johns Hopkins University; L, left; R, right.

On-line Table 3: Between-group differences in DTI maps (healthy controls vs remitted CS)

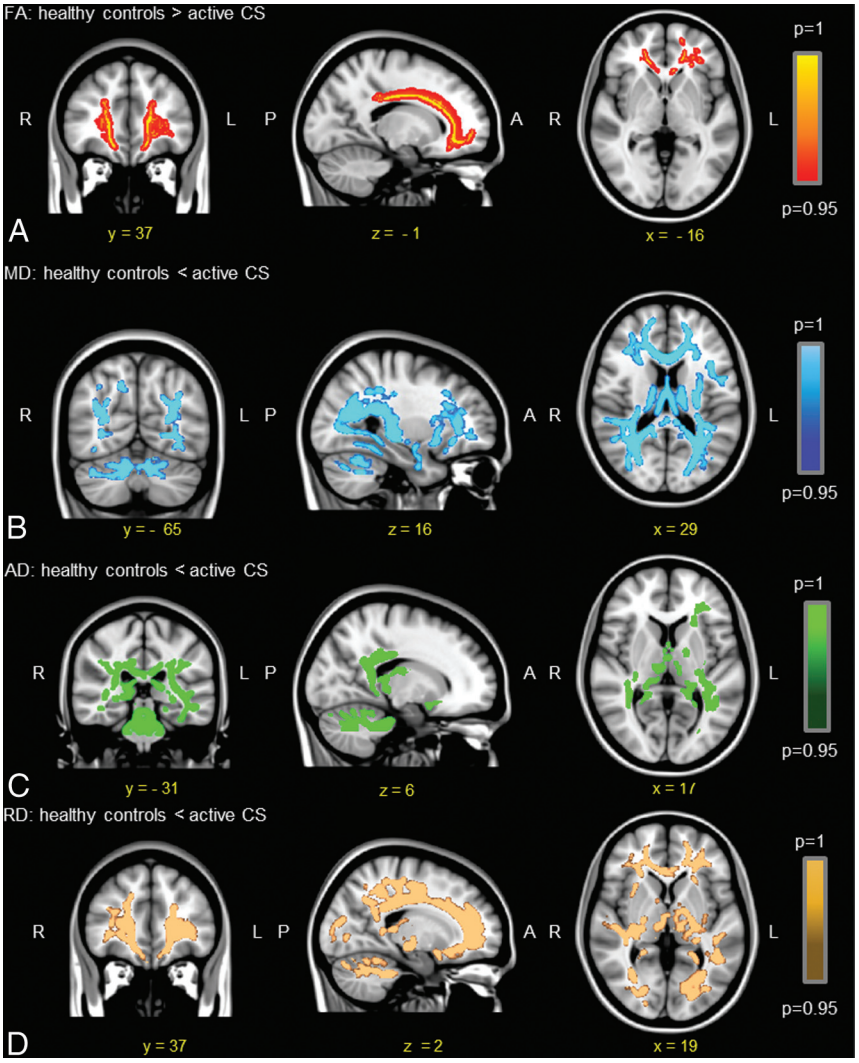
Principal Cluster Differences		X	Y	Z	Size (mm^2)	P	t	r	JHU White Matter Tractography Atlas
Healthy controls > remitted	FA	−18.00	−32.00	32.00	4933	.032	3.369	0.470	3% Anterior thalamic radiation L
Healthy controls < remitted	MD	−40.00	−16.00	−12.00	34112	.004	4.335	0.565	42% Inferior fronto-occipital fasciculus L, 8% inferior longitudinal fasciculus L, 3% superior longitudinal fasciculus (temporal part) L, 3% superior longitudinal fasciculus L
Healthy controls < remitted	RD	−16.00	−28.00	30.00	35024	.009	3.825	0.517	No label found

Note:—JHU indicates Johns Hopkins University; L, left.

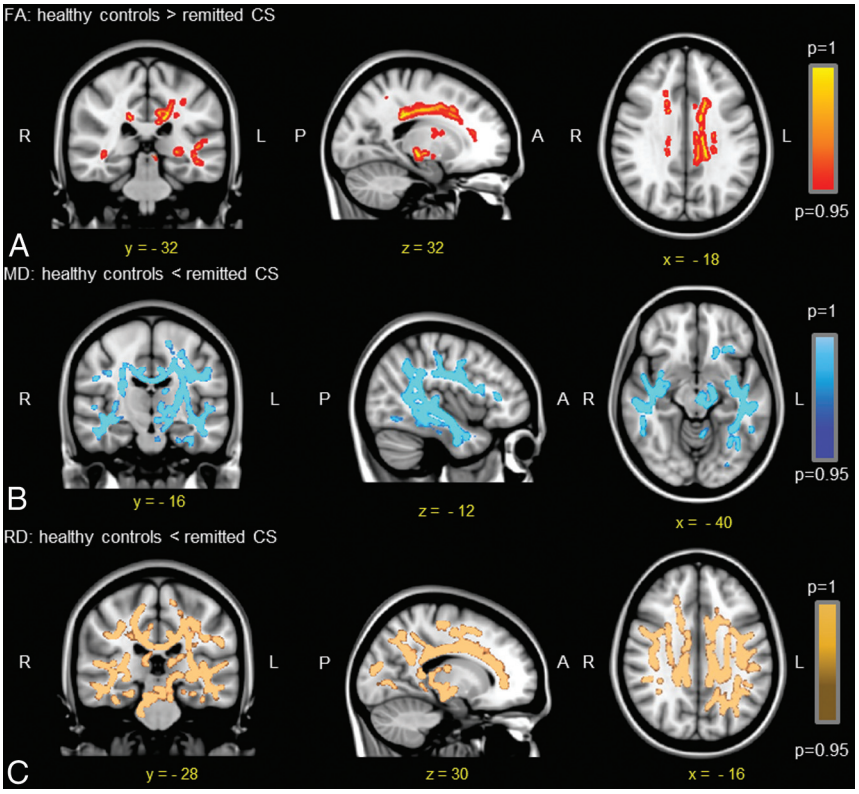
On-line Table 4: Between-group differences in DTI maps (healthy controls vs cured CS)

Principal Cluster Differences		X	Y	Z	Size (mm^2)	P	t	r	JHU White Matter Tractography Atlas
Healthy controls > cured CS	FA	41.00	−25.00	−2.00	22828	.01	5.042	0.569	21% Inferior longitudinal fasciculus R, 3% inferior fronto-occipital fasciculus R
Healthy controls < cured CS	MD	−44.00	−13.00	−19.00	55244	<.001	3.203	0.403	55% Inferior longitudinal fasciculus L, 3% inferior fronto-occipital fasciculus L
Healthy controls < cured CS	AD	−34.00	−7.00	22.00	21189	.001	2.879	0.368	26% Superior longitudinal fasciculus L, 13% superior longitudinal fasciculus (temporal part) L
Healthy controls < cured CS	RD	−42.00	−25.00	−9.00	49950	.002	3.321	0.415	42% Inferior fronto-occipital fasciculus L, 37% inferior longitudinal fasciculus L

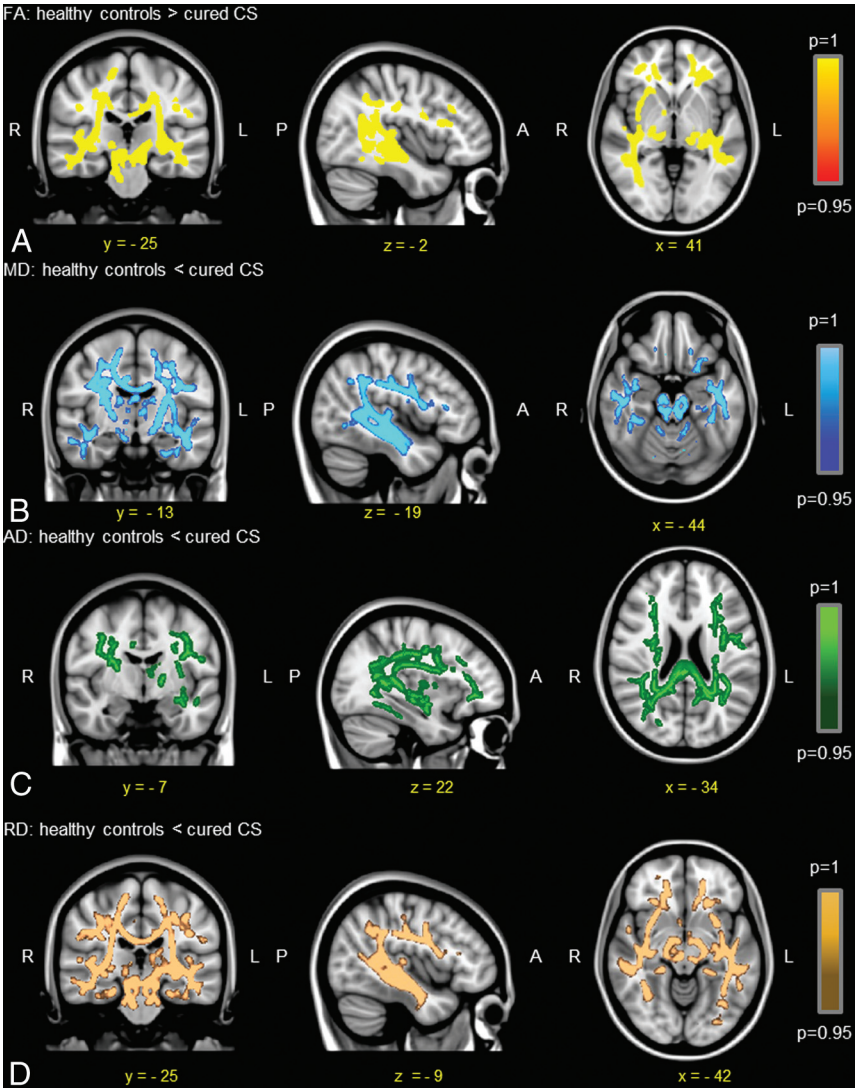
Note:—JHU indicates Johns Hopkins University; L, left; R, right.



ON-LINE FIG 1. Differences ($P < .05$) in DTI maps in patients with active hypercortisolism and CS compared with controls, with hypertension, hypertriglyceridemia, central obesity, and body mass index as covariates. *A*, Red-yellow voxels/regions have FA decreases. *B*, Blue–light-blue voxels/regions have MD increases. *C*, Green voxels/regions have AD increases. *D*, Brown–light-brown voxels/regions have RD increases. Rows show selected coronal, sagittal, and axial maximum differences ($P < .05$) on a Montreal Neurological Institute 152 brain template image (Montreal Neurological Institute coordinates).



ON-LINE-FIG 2. Differences ($P < .05$) in DTI maps in patients with hypercortisolism and remitted CS compared with controls, with hypertension, hypertriglyceridemia, central obesity, and body mass index as covariates. *A*, Red-yellow voxels/ regions have FA decreases. *B*, Blue–light-blue voxels/regions have MD increases. *C*, Brown–light-brown voxels/regions have RD increases. Rows show selected coronal, sagittal, and axial maximum differences ($P < .05$) on a Montreal Neurological Institute 152 brain template image (Montreal Neurological Institute coordinates).



ON-LINE-FIG 3. Differences ($P < .05$) in DTI maps in patients with cured CS compared with controls, with hypertension, hypertriglyceridemia, central obesity, and body mass index as covariates. *A*, Yellow voxels/regions have FA decreases. *B*, Blue–light-blue voxels/regions have MD increases. *C*, Green–light-green voxels/regions have AD increases. *D*, Brown–light-brown voxels/regions have RD increases. Rows show selected coronal, sagittal, and axial maximum differences ($P < .05$) on a Montreal Neurological Institute 152 brain template image (Montreal Neurological Institute coordinates).