Diffusion tensor imaging of the extracortical network in the brains of patients with Wilson disease

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Abstract

Objective: To evaluate damage to the extracortical tract in Wilson disease (WD) patients using diffusion tensor imaging (DTI).

Methods: 70 patients with WD, including 50 with cerebral type and 20 with hepatic type, and 20 age-matched healthy controls were enrolled. Neurological symptoms were scored using the modified Young Scale. Patients with cerebral type WD were divided into four subgroups: those with (1) hypokinesia, (2) parkinsonism, (3) mouth and throat dystonia, and (4) psychiatric symptoms. All study subjects underwent DTI of the brain. Five regions of interest (ROIs) were chosen. Fractional anisotropy (FA) and fiber volumes between ROIs were determined, and the relationships between DTI metrics and clinical status were evaluated.

Results: FA values and fiber volumes between subcortical nuclei were lower in WD patients. Fiber volumes between the putamen (PU) and the globus pallidus (GP), substantia nigra (SN), and thalamus (TH); between the head of the caudate nucleus (CA) and the GP and TH; and between the TH and cerebellum were lower in group 1 than in the other groups of WD patients. Fiber volumes between the GP and the SN and TH were lower in group 2, and fiber volumes between the SN and TH were lower in group 3. DTI metrics differed between patients with the cerebral and hepatic types of WD.

Conclusions: DTI can reconstruct the network of the extracortical tract. Fiber projection between subcortical nuclei was abnormal in WD patients. Damage to fiber connections may correlate with neurological symptoms in WD patients.

Keywords: Wilson disease; diffusion tensor imaging; extracortical tract; network

Abbreviations: WD= Wilson disease; DTI= diffusion tensor imaging; MRI = magnetic resonance imaging ; ROIs= regions of interest; FA= fractional anisotropy; PU= putamen; GP= globus pallidus; SN= substantia nigra; TH= thalamus; CA= caudate nucleus; VOL= volumes

1. Introduction

Wilson disease (WD) is an autosomal recessive inherited disorder of copper metabolism, characterized by excessive copper deposition, especially in the liver and brain. Patients with WD have many clinical manifestations and changes on magnetic resonance imaging (MRI), and show varied responses to treatment. Conventional MRI usually shows signal abnormalities in the subcortical nuclei, including the mesencephalon, thalamus and basal ganglia regions^[1]. Neurological symptoms in WD patients may be caused by damage to both the subcortical nuclei and the fiber projections between them^[1,2,3,4]. However, it is difficult to evaluate damage to the network in the brains of WD patients.

Neurodegenerative diseases are frequently characterized by less efficient organization of the white matter^[7]. Memory and executive functioning are affected by damage to the local network of the brain^[2]. White matter disruption results in prominent motor features in dementia with Lewy bodies (DLB)^[5] and may be a sensitive marker and a prominent feature of Parkinson's disease^[6,7,8,9,10]. To our knowledge, however, damage to cerebral networks has not been examined in patients with WD.

Diffusion tensor imaging (DTI) has been used to detect changes in white matter integrity^[11]. DTI can identify and quantify microstructural damage in the brain, while providing directional information on the random movement of water molecules^[12,13]. DTI metrics include fractional anisotropy (FA), radial diffusivity and axial diffusivity^[13]. DTI fiber tracking (FT) can show individual fiber tracts of the brain because of the anisotropy of water diffusion in central nervous system tissue^[3,14]. Moreover, DTI can be used to trace subcortical gray matter connections. This study therefore utilized DTI to evaluate fiber tracts abnormalities in patients with WD and to correlate clinical characteristics with damage to the network of the brain.

2. Materials and methods

2.1. Participants

The study enrolled 70 WD patients (38 males and 32 females, mean age 21 ± 4 years) evaluated at the First Affiliated Hospital, Sun Yat-Sen University, between July 2007 and October 2013. Patients were categorized as having cerebral type WD, presenting mainly with psychiatric and/or neurological symptoms, or hepatic type WD, presenting mainly with hepatic symptoms. The diagnosis of each patient was based on a combination of clinical symptoms and laboratory tests. Clinical indications included decreased serum ceruloplasmin concentration, low serum copper concentration, elevated 24 h urinary copper excretion and the presence of Kayser–Fleischer (K–F)

1 rings on slit lamp examination. As a control group, 20 age- and sex-matched healthy individuals were recruited
2 from the hospital. Informed consent was obtained from all participants prior to enrollment.
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4 The severity of neurological symptoms was assessed using the modified Young Scale^[15]. This scale consists
5 of items evaluating dysarthria, dysphagia, rigidity, ataxia, tremor, choreic movement, gait abnormality and
6 psychogenia. Based on their neurological symptoms, patients with cerebral type WD were divided into four
7 subgroups: those with (1) hypokinesia (tremor, choreic movement, ataxia), (2) parkinsonism (rigidity and gait
8 abnormality), (3) mouth and throat dystonia (dysarthria and dysphagia), and (4) psychiatric symptoms. Copper
9 concentrations in serum and cerebrospinal fluid (CSF) and 24 h urinary copper excretion were measured before
10 treatment.
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18 **2.2. MRI protocol**

19 All participants underwent DTI tests of the brain before treatment. All MRI data were obtained using a 1.5 T
20 scanner (Achieva Nova Dual; Philips Healthcare, Best, The Netherlands), equipped with eight-channel,
21 phase-array head coils. Conventional MRI sequences included spin-echo (SE) T1-weighted images [488 ms
22 repetition time (TR), 15 ms echo time (TE)] obtained in the axial and sagittal planes, with an acquisition time of 2
23 min, matrix of 256×256, and a 250 mm field of view (FOV). Axial T2-weighted images were also acquired (3600
24 ms TR, 100 ms TE). The section thickness was 5 mm. DTI was performed using SE echo-planar imaging (EPI)
25 (9500 ms TR, 70 ms TE, 256×256 matrix size, 250 mm field of view, 2 mm section thickness with no gaps).
26 Images were obtained with 32-direction diffusion-encoding ($b = 1000 \text{ s/mm}^2$ for each direction) and without
27 diffusion encoding ($b = 0 \text{ s/mm}^2$) and were corrected for head and cardiac motion artifacts.
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40 **2.3. Image processing**

41 All DTI data were transferred to a workstation (Philips extended MR workspace 2.6.3.2, Philips Medical
42 Systems) and processed using DTI fiber-tracking software for DTI quantitative analysis. Regions of interest (ROIs)
43 were drawn according to anatomical structures, including the globus pallidus (GP), head of the caudate nucleus
44 (CA), putamen (PU), thalamus (TH), substantia nigra (SN), and cerebellum. Fiber tracts were reconstructed using
45 the fiber assignment continuous tracking (FACT) method. DTI fibers were counted, and FA values along the tracts
46 were determined. Two neuroradiologists separately and independently drew all ROIs on tensor color maps and
47 measured FA and DTI fiber counts. To reduce random variability in the measurements, each value was an average
48 of three different measurements. The reported values are the mean of the two observers.
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58 **2.4. Statistical analysis**

59 Results are presented as mean±SEM. All statistical analyses were performed using SPSS 13.0. (SPSS Inc.,
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Chicago, Illinois, USA). DTI parameters of WD patients and controls were compared using independent-sample t-tests. One-way analysis of variance (ANOVA) and least significance difference (LSD) tests were used to compare the DTI parameters of each group. Pearson's correlation analysis was used to assess the correlations of DTI parameters with copper and iron parameters and modified Young Scale scores. A P value < 0.05 was considered statistically significant.

3 Results

3.1. Demographic and clinical characteristics of each group

Gender distribution and age were similar in WD patients and healthy volunteers (Table 1).

3.2. DTI parameters of fibers in ROIs

FA values and fiber volumes in ROIs of WD patients and healthy controls are shown in Table 2.

FA values of fibers were significantly lower ($P=0.011$) in the PU of WD patients than in healthy controls. FA values were lower in the CA ($P=0.029$) and TH ($P=0.044$) of WD patients than in controls. In addition, fiber volumes in the CA ($P=0.033$), TH ($P=0.027$), SN ($P=0.033$) and cerebellum ($P=0.027$) were lower in WD patients than in controls. FA values of fibers were lower in the CA than in the other regions. In addition, the volumes of fibers in the CA ($P=0.041$), TH ($P=0.022$), SN ($P=0.035$), and cerebellum ($P=0.042$) differed on the left and right sides in WD patients.

3.3. DTI parameters of fibers between ROIs

FA values and the volume of fibers between ROIs of WD patients and healthy controls are shown in Table 3.

FA values of the fibers between the GP and the PU, the GP and the TH, the left GP and the CA, the left SN and the TH, and the left PU and the CA were significantly lower in WD patients than in healthy controls ($P=0.037, 0.042, 0.035, 0.032, 0.035, 0.027, 0.019$). The volumes of fibers between the right GP and the SN, the GP and the PU, the GP and the TH, the left GP and the CA, the right PU and the SN, the SN and the TH, the right CA and the SN, the SN and the cerebellum, the left PU and the TH, and the left TH and the cerebellum were also significantly lower in WD patients than in healthy controls ($P=0.021, 0.021, 0.034, 0.031, 0.024, 0.034, 0.033, 0.022, 0.024, 0.044, 0.042, 0.046, 0.023, 0.03, 0.019, 0.020$). No fibers were observed between the cerebellum and the PU, GP, and CA.

In patients with WD, the left and right fibers between the GP and the SN ($P=0.043$), the GP and the PU ($P=0.035$), the PU and the SN ($P=0.044$), the SN and the TH ($P=0.046$), the SN and the cerebellum ($P=0.049$), the CA and the SN ($P=0.023$), the PU and the CA ($P=0.016$), the CA and the TH ($P=0.037$), and the TH and the

cerebellum ($P=0.041$) differed significantly.

FA values were lower for the fibers between the GP and the PU than for fibers between other regions, whereas the volume of fibers between the PU and SN was lower than between other regions.

3.4 Differences in DTI parameters among subgroups of WD patients

Patients with WD were divided into four subgroups: those with (1) hypokinesia, (2) parkinsonism, (3) mouth and throat dystonia, and (4) psychiatric symptoms. Figure 1 shows FA values and the volumes of fibers in ROIs of these subgroups and healthy controls.

FA values and the volumes of fibers were lower in the TH, CA and cerebellum of WD patients with hypokinesia than in the other subgroups. FA values of fibers in the GP and SN were lower in WD patients with parkinsonism than in the other subgroups, whereas FA values of fibers in the PU were lower in WD patients with mouth and throat dystonia than in the other subgroups of WD patients.

FA values and the volumes of fibers between ROIs of WD patients and healthy controls are shown in Figure 2. The volumes of fibers between the PU and the GP, SN, and TH; between the CA and the GP and TH; and between the TH and cerebellum were lower in WD patients with hypokinesia than in the other subgroups of WD patients (Fig 3). The volumes of fibers between the GP and the SN and TH were lower in WD patients with parkinsonism than in the other subgroups; and the volume of fibers between the SN and TH was lower in patients with mouth and throat dystonia than in the other subgroups of SD patients. In addition, the volume of fibers between the PU and TH was lower in WD patients with psychiatric symptoms than in patients with parkinsonism and mouth and throat dystonia.

3.5 Differences in DTI parameters between hepatic and cerebral type of WD patients

FA values of fibers in the left ($P=0.044$) and right ($P=0.013$) GP, left CA ($P=0.004$), and right TH ($P=0.038$) were significantly lower in patients with cerebral type than hepatic type WD. The volume of fibers in the cerebellum ($P=0.048$) was lower in patients with cerebral than hepatic type WD.

The volumes of fibers between the GP and PU ($P=0.047$) and TH ($P=0.007$), and between the cerebellum and SN ($P=0.041$), GP ($P=0.033$), and TH ($P=0.049$) were lower in patients with cerebral type than hepatic type WD.

3.6 Correlations between DTI parameters and clinical parameters in patients with WD

DTI values were unrelated to Child-Pugh liver grade or disease duration. The metal parameters of WD patients and healthy controls are shown in Table 4. Copper concentration in the CSF and urinary copper content were significantly higher, and serum copper concentrations significantly lower, in WD patients than in normal controls. DTI metrics did not correlate with serum or CSF copper concentration or urinary copper content.

3.7 The extracortical tract network in the brains of WD patients

Figure 4 shows the extracortical tract networks in the brains of WD patients.

4. Discussion

Neurodegenerative diseases are due to damage to the microstructural white matter connections in the brain. Functional imaging has indicated that cognitive dysfunction and movement disorders are predominantly caused by neuronal synaptic dysfunction^[2,5,6]. Neurological symptoms of WD may also be secondary to damage to networks of the extracortical tract, which includes both nuclei and fiber projections. Conventional MRI can show lesions to nuclei involving the GP, PU, TH, mesencephalon, pons, and cerebellum^[16, 17,18,19], but is less effective at evaluating damage to fiber tracks.

DTI, a method of visualizing white matter fibers in vivo, has applications in neurodegeneration^[8,20]. This study showed that DTI characterization of the networks of the extracortical tract can provide insights into how changes in brain white matter connectivity affect neurological function in patients with WD. The direct loops of the extracortical tract, including the cortex-PU-GP-TH-cortex, cortex-PU-SN-TH-cortex, cortex-CA-GP-TH-cortex and cortex-CA-SN-TH-cortex loops, were reconstructed in this study. Fiber tracts between other subcortical nuclei were also reconstructed. Animal experiments have shown that FA values may reflect the integrity of myelin and neuraxons^[13,20]. Decreased FA values in the cerebellar hemispheres, SN and circuits, including the nigrostriatal, corticostriatal, and thalamocortical projections, have been observed in PD patients^[10,21]. FA values were also reduced in bilateral temporal lobes of patients with Alzheimer's disease (AD)^[2]. We found that FA values and the volumes of fibers between subcortical nuclei were significantly lower in WD patients than in healthy controls, indicating that the brains of these patients had sustained damage to the nuclei and to the integrity of the fiber tract. Network-based analysis of extracortical tract connections may reveal the structural basis of WD.

The neurological symptoms of WD patients are not symmetrical. Conventional MRI is inadequate in showing differences between the left and right sides of the subcortical nuclei. Using DTI, however, we observed differences between the left and right sides in WD patients, indicating that damage to the extracortical network was not symmetrical. The asymmetry of neurological symptoms may result from the asymmetry of damage to fiber connections. DTI values in different fiber projections also differed, indicating differences in the extent of damage in different regions of the network. Damage to the fiber tract between the GP and PU may be the most obvious in WD patients.

1 Disease severity showed a fair correlation with DTI metrics. The cerebello-thalamo-cortical-cerebellar and
2 cortico-thalamo-cortical loops are regarded as being involved in tremor activity and whole-body ataxia^[22]. Part of
3 the cerebello-thalamo-cortical network, the dentato-rubro-thalamic tract (DRT), has been associated with tremor
4 control^[14,22]. Cognitive dysfunction was found to correlate with fiber tract changes in patients with AD dementia,^[2]
5 and the UPDRS-III was found to correlate with reduced FA in white matter tracts of the motor areas in DLB^[5]. In
6 addition, FA values were shown to negatively correlate with clinical scores of WD patients^[13]. In agreement with
7 these findings, we observed correlations between DTI metrics and type of WD and that tremor was associated with
8 the cerebello-thalamo-cortical network. In addition, we found that the inflow path of the GP was associated with
9 hypokinesia including tremor, choreic movement and ataxia. Our results indicate that damage to the outflow path
10 of the GP and SN may be an important cause of hypermyotonia and that fiber projection may be important in the
11 pathogenesis of psychiatric symptoms. We also observed differences in DTI parameters between patients with
12 cerebral type and hepatic type WD, indicating that damage to the extracortical network was greater in the
13 cerebral type. DTI may therefore provide new insights into the mechanisms underlying neurological symptoms in
14 WD.

31 Limitations

32 This study had several limitations. First, as ROIs were drawn by radiologists relative to anatomical structures,
33 there may have been random variability in the measurements. To reduce this variability, all measurements were
34 made by two neuroradiologists independently, with the value for each being an average of three different
35 measurements. Furthermore, fiber tracts were reconstructed using the fiber assignment continuous tracking (FACT)
36 method, which can reconstruct fiber projections between pairs of ROIs, but cannot distinguish between outflow
37 and inflow fiber tracts. This made it difficult to define the network path in the brain using DTI. Third, DTI was not
38 performed in these patients after treatment with copper chelators, so treatment-associated changes in fiber
39 projection of the brain could not be determined. Additional studies are needed to evaluate treatment outcomes in
40 these patients.

54 Conclusion

55 DTI can reconstruct the network of the extracortical tract. Abnormal fiber projection between
56 subcortical nuclei was observed in the brains of WD patients. Damage to the extracortical network was not
57 symmetrical. Damage to the fiber tract between the GP and PU may be the most evident in WD patients. Damage

to fiber connections may correlate with neurological symptoms in patients with WD.

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Table 1 Clinical and demographic characteristics of patients and controls.

	Subgroup	Subgroup	Subgroup	Subgroup	Hepatic	Controls	P
	1	2	3	4	type WD		
Number	12	10	15	13	20	20	
Gender (M/F)	6/6	4/6	8/7	6/7	10/10	9/11	0.072
Age (years)	20±3	23±2	21±3	20±2	18±5	22±3	0.068
Duration	20±8	17±4	19±3	22±6	25±7	0	0.013
(months)							
Modified	16.35 ±	23.09 ±	17.12 ±	6.33 ± 3.01	0	0	0.006
Young Scale	5.02	4.24	5.16				
scores							

Data are shown as number or mean±standard deviation.

Table 2 FA values and fiber volumes in ROIs of WD patients and healthy controls

		FA		VOL	
		Left	right	left	right
PU	WD	0.47 ± 0.03^a	0.45 ± 0.02^a	304 ± 44	308 ± 20
	Controls	0.59 ± 0.06	0.57 ± 0.03	329 ± 15	358 ± 55
GP	WD	0.51 ± 0.04	0.49 ± 0.04	449 ± 16	400 ± 34
	Controls	0.53 ± 0.04	0.52 ± 0.03	469 ± 82	447 ± 75
CA	WD	0.41 ± 0.07^a	0.43 ± 0.04^a	115 ± 24^{ab}	70 ± 17^a
	Controls	0.48 ± 0.10	0.47 ± 0.08	245 ± 21	276 ± 34
TH	WD	0.48 ± 0.04^a	0.48 ± 0.03^a	1192 ± 114^{ab}	844 ± 49^a
	Controls	0.58 ± 0.10	0.53 ± 0.07	1443 ± 239	1203 ± 113
SN	WD	0.55 ± 0.05	0.57 ± 0.02	386 ± 52^b	227 ± 42^a
	Controls	0.57 ± 0.09	0.59 ± 0.09	397 ± 44	396 ± 78
cerebellum	WD	0.44 ± 0.05	0.42 ± 0.04	2189 ± 123^{ab}	1511 ± 27^a
	Controls	0.48 ± 0.13	0.47 ± 0.13	2261 ± 213	2225 ± 113

Abbreviations: PU, putamen; GP, globus pallidus; CA, head of the caudate nucleus; TH, thalamus; SN, substantia nigra,

Results reported as mean $\pm$ SEM. a: $P \leq 0.05$ compared with healthy controls. b: $P \leq 0.05$ compared with the right side.

Table 3. FA values and fiber volumes between ROIs of WD patients and healthy controls

		FA		VOL	
		left	right	left	right
GP-SN	WD	0.56±0.09	0.56±0.11	230±44 ^b	180±20 ^a
	Controls	0.51±0.06	0.56±0.03	258±25	240±41
GP-PU	WD	0.43±0.06 ^a	0.43±0.04 ^a	303±56 ^{a,b}	239±44 ^a
	Controls	0.52±0.04	0.51±0.03	336±92	327±55
GP-TH	WD	0.50±0.06 ^a	0.47±0.04 ^a	140±24 ^a	119±15 ^a
	Controls	0.57±0.10 ^a	0.58±0.08 ^a	208±29	187±37
GP-CA	WD	0.41±0.09 ^a	0.46±0.02	332±84 ^a	354±45
	Controls	0.55±0.10	0.54±0.07	395±59	388±73
SN-PU	WD	0.50±0.04	0.52±0.02	72±23 ^b	59±22 ^a
	Controls	0.47±0.09	0.48±0.09	84±44	95±28
SN-TH	WD	0.50±0.08 ^a	0.51±0.07	607±115 ^{a,b}	485±49 ^a
	Controls	0.56±0.17	0.55±0.11	815±93	835±53
SN-CA	WD	0.60±0.17 ^b	0.50±0.01	140±35	114±49 ^a
	Controls	0.62±0.13	0.59±0.04	155±25	144±47
SN-cerebellum	WD	0.55±0.04	0.54±0.03	516±75 ^{a,b}	399±69 ^a
	Controls	0.58±0.03	0.59±0.11	638±113	609±110
PU-TH	WD	0.49±0.05	0.49±0.06	281±75 ^a	274±49 ^a
	Controls	0.53±0.20	0.58±0.13	339±73	325±43
PU-CA	WD	0.15±0.08 ^{a,b}	0.44±0.02	237±65	245±49
	Controls	0.46±0.07	0.49±0.03	261±43	265±37
TH-CA	WD	0.40±0.05	0.45±0.04	206±65 ^b	286±49
	Controls	0.45±0.11	0.41±0.09	257±33	225±53
TH- cerebellum	WD	0.53±0.08	0.50±0.04	261±49 ^b	173±38 ^a
	Controls	0.53±0.15	0.55±0.10	249±43	225±63

Abbreviations: PU, putamen; GP, globus pallidus; CA, head of the caudate nucleus; TH, thalamus; SN, substantia nigra,

Results reported as mean±SEM. a: P≤0.05 compared with healthy controls. b: P≤0.05 compared with the right side.

Table 4 Scores of the modified Young Scale and copper parameters of WD patients and healthy controls

	Modified Young Scale scores	CSF copper (mg/L)	Serum copper (mg/L)	Urinary copper (μ g/24h)
WD	21.33 $\pm$ 8.56 ^a	0.13 $\pm$ 0.03 ^a	0.38 $\pm$ 0.09 ^a	222 $\pm$ 56 ^a
Controls	0	0.016 $\pm$ 0.009	0.81 $\pm$ 0.10	72 $\pm$ 29

Results reported as mean $\pm$ SEM. a : P $\leq$ 0.05 compared with healthy controls

Fig. 1. FA values (A) and fibers volumes (B) in regions of interest (ROIs) in the brains of WD patients with (1) hypokinesia, (2) parkinsonism, (3) mouth and throat dystonia, and (4) psychiatric symptoms and healthy controls. Abbreviations: PU, putamen; GP, globus pallidus; CA, head of the caudate nucleus; TH, thalamus; SN, substantia nigra. * P≤0.05 compared with other groups.

Fig. 2. FA values (A, C, E) and fiber volumes(B, D, F) between regions of interest (ROIs) in the brains of WD patients with (1) hypokinesia, (2) parkinsonism, (3) mouth and throat dystonia, and (4) psychiatric symptoms and healthy controls. Abbreviations: PU, putamen; GP, globus pallidus; CA, head of the caudate nucleus; TH, thalamus; SN, substantia nigra. $*P \leq 0.05$ compared with other groups.

Fig. 3. DTI results showing the volumes of fibers between regions of interest (ROIs) in the brains of individual WD patients with hypokinesia, parkinsonism, mouth and throat dystonia, and psychiatric symptoms, healthy controls, and patients with the hepatic type of WD. The volume of fibers between the PU and GP was lower in WD patients with hypokinesia (sample 2) than in normal controls (sample 1), WD patients with parkinsonism (sample 3), mouth and throat dystonia (sample 4), and psychiatric symptoms (5), and patients with hepatic type WD (sample 6). The volume of fibers between the PU and SN was lower in WD patients with hypokinesia (sample 8) than in normal controls (sample 7), WD patients with parkinsonism (sample 9), mouth and throat dystonia (sample 10), and psychiatric symptoms (sample 11), and patients with hepatic type WD (sample 12). The volume of fibers between the CA and GP was lower in WD patients with hypokinesia (sample 14) than in normal controls (sample 13), WD patients with parkinsonism (sample 15), mouth and throat dystonia (sample 16), and psychiatric symptoms (sample 17), and patients with hepatic type WD (sample 18). The volume of fibers between the CA and TH was lower in WD patients with hypokinesia (sample 20) than in normal controls (sample 19), WD patients with parkinsonism (sample 21), mouth and throat dystonia (sample 22), and psychiatric symptoms (sample 23), and patients with hepatic type WD (sample 24). The volume of fibers between the TH and cerebellum was lower in WD patients with hypokinesia (26) than in normal controls (sample 25), WD patients with parkinsonism (sample 27), mouth and throat dystonia (sample 28), and psychiatric symptoms (sample 29), and patients with hepatic type WD (sample 30). The volume of fibers between the GP and TH was lower in WD patients with parkinsonism (sample 33) than in normal controls (sample 31), WD patients with hypokinesia (sample 32), mouth and throat dystonia (sample 34), and psychiatric symptoms (sample 35), and patients with hepatic type WD (sample 36). The volume of fibers between the SN and TH was lower in WD patients with mouth and throat dystonia (sample 40) than in normal controls (sample 37), WD patients with hypokinesia (sample 38), hypokinesia (39), and psychiatric symptoms (sample 41), and patients with hepatic type WD (sample 42). Abbreviations: PU, putamen; GP, globus pallidus; CA, head of the caudate nucleus; TH, thalamus; SN, substantia nigra.

Fig. 4. Illustration of the extracortical tract networks in the brains of WD patients. (A) cortex-PU-GP-TH-cortex loop; (B) cortex-PU-SN-TH-cortex loop; (C) cortex-CA-GP-TH-cortex loop; (D) cortex-CA-SN-TH-cortex loop. Abbreviations: PU, putamen; GP, globus pallidus; CA, head of the caudate nucleus; TH, thalamus; SN, substantia nigra.