ARTICLE

Patterns of motor recovery and structural neuroplasticity after basal ganglia infarcts

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Abstract

Objective

To elucidate the timeframe and spatial patterns of cortical reorganization after different stroke-induced basal ganglia lesions, we measured cortical thickness at 5 time points over a 6-month period. We hypothesized that cortical reorganization would occur very early and that, along with motor recovery, it would vary based on the stroke lesion site.

Methods

Thirty-three patients with unilateral basal ganglia stroke and 23 healthy control participants underwent MRI scanning and behavioral testing. To further decrease heterogeneity, we split patients into 2 groups according to whether or not the lesions mainly affect the striatal motor network as defined by resting-state functional connectivity. A priori measures included cortical thickness and motor outcome, as assessed with the Fugl-Meyer scale.

Results

Within 14 days poststroke, cortical thickness already increased in widespread brain areas (p = 0.001), mostly in the frontal and temporal cortices rather than in the motor cortex. Critically, the 2 groups differed in the severity of motor symptoms (p = 0.03) as well as in the cerebral reorganization they exhibited over a period of 6 months (Dice overlap index = 0.16). Specifically, the frontal and temporal regions demonstrating cortical thickening showed minimal overlap between these 2 groups, indicating different patterns of reorganization.

Conclusions

Our findings underline the importance of assessing patients early and of considering individual differences, as patterns of cortical reorganization differ substantially depending on the precise location of damage and occur very soon after stroke. A better understanding of the macrostructural brain changes following stroke and their relationship with recovery may inform individualized treatment strategies.

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Glossary

ANOVA = analysis of variance; **CI** = confidence interval; **FOV** = field of view; **N-SMD** = non–striatal motor network–dominant; **NLP** = network lesion percentage; **SMD** = striatal motor network–dominant; **TE** = echo time; **TR** = repetition time.

Immediately following stroke, the vast majority of people present with at least some motor impairment,[1] regardless of the lesion site. However, the mechanisms underlying motor function recovery following stroke remain unclear. Cortical reorganization, including macroscopic changes in cortical thickness, occurs after stroke and involves areas widely distributed across the brain.[2–10] Studies have found decreased cortical thickness, indicative of secondary neurodegeneration poststroke,[11–14] as well as increased cortical thickness.[2,7,15] Cortical reorganization likely depends on a number of factors, including the site of the stroke-induced lesion. Nevertheless, the majority of stroke studies group together patients with highly variable lesion sites. This introduces heterogeneity and blurs individual differences in structural neuroplasticity and functional motor recovery. More importantly, it remains to be elucidated how this global structural reorganization evolves over time, as most imaging studies assess patients several months after stroke at limited time points.

We assessed 33 patients with stroke over 6 months, within 7 days poststroke and again at 14, 30, 90, and 180 days after the event. This constitutes an unprecedented longitudinal dataset with extensive structural and resting-state fMRI data spanning the acute, subacute, and chronic stages of stroke. We specifically recruited patients with basal ganglia stroke to homogenize the sample, and divided patients according to whether or not their lesions predominantly affected the functional motor region of the striatum, defined using resting-state fMRI.[16] We hypothesized that these groups of patients would present different patterns of motor recovery and structural neuroplasticity over time.

Methods

Participants

Thirty-five patients with first-episode basal ganglia stroke and 23 age-matched healthy control participants (mean age, 51.8 ± 6.99; 9 women) were recruited from 2008 to 2012. Eligibility criteria for patients were (1) full admission history (within 7 days after symptom onset) and clinical diagnosis of ischemic stroke, (2) unilateral infarction involving basal ganglia, (3) absence of other brain lesions or prior infarcts, (4) absence of MRI contraindications, (5) clear time of symptom onset, and (6) absence of deafness, blindness, aphasia, or visual field deficits. Eligibility criteria for healthy control participants included a lack of history of neurologic or psychiatric disease. Two patients were excluded based on motion artifacts, resulting in a sample of 33 patients (mean age, 49.24 ± 10.88 years; 7 women). Of these, 24 had a lesion in the left hemisphere and 9 in the right hemisphere. Demographics and clinical characteristics are described in table 1.

All patients received rehabilitation services according to the Guidelines for Chinese Stroke Rehabilitation. Patients were treated by neurologists at the emergency department during the acute phase until they were stabilized (i.e., with stable vital signs and without neural symptoms progressing within 48 hours). Acute inpatient rehabilitation services were delivered by a multidisciplinary team including neurologists, rehabilitation physicians, physiotherapists, and nurses for 7–14 days. Postdischarge rehabilitation was provided by community medical centers. Each patient's rehabilitation plan was personalized according to symptoms, guided by researchers and professional rehabilitation physicians in our team. These rehabilitation treatments are consistent with the American Heart Association/American Stroke Association guidelines for adult stroke rehabilitation.[17]

Standard protocol, approvals, and patient consents

The study was approved by the ethics committee of Xuanwu Hospital and written informed consent was obtained from all participants.

Neurologic assessment

Patients' motor function, balance, sensation, and joint function of the upper limbs were evaluated using the original Fugl-Meyer scale,[18,19] performed independently by 2 neurologists before and after each MRI scan (see table 2 for details). The Fugl-Meyer scale includes 33 upper extremity subitems and the motor score ranges from 0 (hemiplegia) to 66 points (normal motor performance). We did not measure lower extremity function. Scores from 2 evaluators were averaged and normalized to a full score of 100.

MRI methods

Participants underwent five 3T MRI scans at 1~7, 14, 30, 90, and 180 days poststroke/enrollment (see table 2 for details). Scans were acquired on a 3T MRI scanner (TimTrio; Siemens AG, Erlangen, Germany) using a 12-channel coil. Structural images were acquired using a sagittal magnetization-prepared rapid gradient echo 3D T1-weighted sequence (repetition time [TR] = 1,600 ms; echo time [TE] = 2.15 ms; flip angle = 9°; 1.0 mm isotropic voxels; field of view [FOV] = 256 × 256). To localize lesions, T2-weighted imaging (TR = 3,830 ms; TE = 98 ms; flip angle = 180°; 1.2 × 0.7 × 5.0 mm; FOV = 230 × 218.5 mm) and fluid-attenuated inversion recovery images (TR = 8,500 ms; TE = 87 ms; flip angle = 150°; 0.9 × 0.9 × 5.0 mm; FOV = 230 × 201.3 mm) were acquired from

Table 1 Patient characteristics and clinical scores

Patient number	Group	Sex	Lesion side	Lesion volume, mm^3	Network lesion percentage		Fugl-Meyer score				
					Striatal motor network	Striatal nonmotor network	Day 7	Day 14	Day 30	Day 90	Day 180
1	SMD	M	L	552	10.80	0.28	100	100	100	100	100
2	SMD	M	L	696	1.30	0.00	76.52	84.85	87.12	99.24	100
3	SMD	M	L	1,032	3.17	0.30	95.45	100	100	100	100
4	SMD	M	L	776	1.12	0.05	53.04	61.37	76.52	100	100
5	SMD	M	L	4,864	33.33	3.00	18.18	17.43	40.15	65.15	70.46
6	SMD	M	R	7,264	41.34	6.17	84.09	96.97	99.24	100	100
7	SMD	M	L	6,864	40.22	4.90	66.67	99.25	98.48	98.48	100
8	SMD	M	L	824	3.35	0.33	58.4	89.4	93.9	98.5	99.3
9	SMD	M	R	1,864	7.82	1.60	68.2	83.3	93.9	95.5	95.5
10	SMD	F	L	312	0.93	0.23	100	100	100	95.5	100
11	SMD	F	L	2,952	27.75	4.72	100	100	100	87.9	98.5
12	SMD	F	L	992	0.56	0.18	72.73	83.33	96.97	98.48	100
13	SMD	M	L	4,816	35.01	4.88	92.42	95.45	100	100	100
14	SMD	M	L	4,744	33.52	1.93	52.27	63.64	71.21	83.33	93.94
15	N-SMD	M	R	1,016	0.00	0.51	92.4	87.9	96.25	100	100
16	N-SMD	M	R	1,576	0.00	0.00	48.5	71.2	84.1	92.4	98.49
17	N-SMD	M	L	2,216	0.00	0.91	95.45	99.24	100	100	100
18	N-SMD	M	L	912	0.00	1.14	100	100	100	100	100
19	N-SMD	M	L	152	0.00	0.00	98.5	100	100	100	100
20	N-SMD	M	R	8,504	1.49	11.63	38.64	86.37	90.91	100	100
21	N-SMD	M	L	328	0.00	0.00	100	100	100	100	100
22	N-SMD	M	L	64	0.00	0.00	96.97	95.45	100	100	100
23	N-SMD	M	L	1,288	0.00	0.23	98.48	100	100	100	100
24	N-SMD	F	L	3,392	0.00	0.00	96.97	100	95.45	100	100
25	N-SMD	M	L	2,632	0.00	0.36	84.85	84.85	95.45	96.97	98.48
26	N-SMD	F	L	4,736	0.00	0.00	90.9	97	98.5	100	100
27	N-SMD	M	L	1,560	0.37	0.28	90.9	98.5	100	100	100
28	N-SMD	M	L	10,728	4.28	23.72	100	100	100	100	100
29	N-SMD	M	R	1,216	0.00	0.00	100	98.48	98.48	98.48	100

Continued

Table 1 Patient characteristics and clinical scores *(continued)*

Patient number	Group	Sex	Lesion side	Lesion volume, mm^3	Network lesion percentage		Fugl-Meyer score				
					Striatal motor network	Striatal nonmotor network	Day 7	Day 14	Day 30	Day 90	Day 180
30	N-SMD	F	R	464	0.00	0.20	87.88	96.97	100	100	100
31	N-SMD	M	R	1,032	0.00	0.18	84.09	98.48	100	100	100
32	N-SMD	M	R	1,776	0.00	1.30	98.48	100	100	100	100
33	N-SMD	F	L	672	0.00	0.13	93.94	100	100	100	100

Abbreviations: N-SMD = non–striatal motor network–dominant; SMD = striatal motor network–dominant.

patients. Structural MRI data were preprocessed using FreeSurfer (surfer.nmr.mgh.harvard.edu),[20] which included steps such as motion correction, intensity normalization, nonlinear registration, white and gray matter segmentation, and surface mesh representation of the cortex. The data were registered to the FreeSurfer nonlinear volumetric template.[21,22] We conducted quality control and verified that registration and segmentation were not affected by the lesions and were accurate in all participants. Cortical thickness data were registered to a symmetric surface template allowing for flipping the lesion to the other hemisphere.[23] In patients with a right-sided lesion, the lesion and cortical thickness data were flipped so that the left hemisphere was always the lesioned hemisphere, which is a common practice in the stroke research literature.[24–26] The data were smoothed with a full-width half maximum Gaussian kernel of 10 mm and downsampled to 10,242 vertices in each hemisphere. We calculated cortical thickness at each vertex by computing the distance across the cortical mantle for each individual.

Group classification

We categorized patients into 2 groups based on whether their lesions predominantly overlapped with the motor network region of the striatum defined by resting-state fMRI.[16] The functional subdivision of the striatum was performed according to its connectivity with 7 cortical functional networks, as described previously[16]; note that the tail of the caudate is not included in the current striatum mask. We quantified the extent to which the lesions overlapped with (1) the sensorimotor regions of the striatum and (2) the non-sensorimotor regions of the striatum (visual, dorsal attention, ventral attention, limbic, frontoparietal control, and default

Table 2 Timing details at the 5 time points and neurologists' Fugl-Meyer assessments

	Day 1–7	Day 14	Day 30	Day 90	Day 180
Time point details					
Mean number of days following stroke	4.70	14.33	32.36	92.52	184.61
Standard error	0.32	0.37	0.65	0.70	0.89
Minimum value	1	10	27	87	176
Maximum value	8	20	44	105	199
Neurologist evaluations					
SMD group					
Neurologist 1	74.14	83.77	89.71	94.38	96.98
Neurologist 2	72.15	82.86	89.93	94.49	96.97
N-SMD group					
Neurologist 1	89.31	95.14	97.93	99.36	99.84
Neurologist 2	91.01	97.22	97.77	99.36	99.84

Abbreviations: N-SMD = non–striatal motor network–dominant; SMD = striatal motor network–dominant.

networks) by calculating the network lesion percentage (NLP) for both of these sets of regions. The NLP was defined as the number of voxels within the lesion belonging to a given network divided by the total number of striatal voxels in that network. Within each patient, we compared the NLP in the striatal motor and nonmotor networks. We classified patients with lesions predominantly overlapping with the motor network region as the striatal motor network–dominant (SMD) group, and classified the remaining patients as the non–striatal motor network–dominant (N-SMD) group. Because the combination of the nonmotor networks is much larger than the motor network, we ensured that patients who have almost exactly the same NLPs in the motor and nonmotor networks are not categorized into the SMD group, so as to maximize homogeneity in the SMD group. Patients were classified into the SMD group only if their striatal motor network NLP was greater than the striatal nonmotor network NLP by at least 0.1%, otherwise they were classified into the N-SMD group. For example, patient 27's striatal motor network NLP was no greater than the nonmotor NLP according to this criterion (difference <0.1%), and was categorized into the N-SMD group (table 1). According to this criterion, 14 patients were classified into the SMD group and 19 were assigned to the N-SMD group (figure 1A). In figure 1B, we show the lesion overlap for all patients (SMD and N-SMD combined), as well as for each group of patients separately. Note that some patients in the N-SMD group had damage to the globus pallidus, and some lesions slightly encroached on the thalamus.

Data analysis

SPSS Statistics 20 (IBM, Armonk, NY) was used to analyze data. We identified cortical thickness changes apparent at the 6-month mark (at the whole-group level and at the level of each patient group by generating masks for each group) and investigated the evolution of these changes over time. An alternative approach would be comparing cortical thickness between the first 2 time points and exploring these changes over 6 months; however, this approach may miss important changes that occur later. The following steps were performed: (1) cortical thickness at each vertex was compared between the first session (baseline, 1–7 days poststroke) and the fifth session (180 days poststroke) using paired t tests; (2) clusterwise correction for multiple comparisons was performed at significance threshold = $p < 0.001$ and cluster size threshold = 200 mm^2; (3) regions that exhibited significant cortical thickness changes were extracted as masks; (4) cortical thickness within the masks was averaged for each participant and time point; (5) the percent change in cortical thickness was calculated as follows: $(\text{thickness}_{\text{time point}} - \text{thickness}_{\text{baseline}})/\text{thickness}_{\text{baseline}} \times 100$. The significant changes we observed range between ~2% and 6%, representing differences of ~0.05–0.15 mm given that average cortical thickness is ~2.5 mm.

We conducted repeated-measures analyses of variance (ANOVAs) to investigate whether cortical thickness changed over time within each group. The within-subjects factor was time (time points: day 14, 30, 90, 180). In cases where there is a significant effect of time, we report whether the trend is linear. We conducted Sidak-corrected post hoc analyses to investigate whether cortical thickness differed from baseline at each time point. Intracranial volumes were compared across groups to determine whether to use this measure as a covariate. No between-group analyses were performed for the cortical thickness analyses because we created group-specific masks; comparing the groups using a mask that is based on one group would inherently bias the results. We calculated the Dice coefficient to compare the spatial distribution of cortical thickness changes (180 days vs baseline) between the patient groups. We investigated motor recovery over time and group differences in Fugl-Meyer scores using a repeated-measures ANOVA. Because our a priori hypothesis was that the 2 patient groups would differ on Fugl-Meyer scores, no correction for multiple comparisons was applied. For ANOVAs and t tests, we indicate the effect size using partial eta^2 (η_p^2). To determine whether to use lesion volume as a covariate, we evaluated the relationship between Fugl-Meyer scores and lesion volume using Pearson correlation, and tested whether the SMD and N-SMD groups significantly differed in lesion volume using an independent samples t test. The significance threshold was $p = 0.05$. Finally, we investigated whether cortical thickness changes were associated with improvement in Fugl-Meyer scores over 6 months or with Fugl-Meyer scores at baseline using Pearson correlations and using the whole-group mask (with ipsilesional and contralesional hemispheres combined). There were no missing data.

Data availability

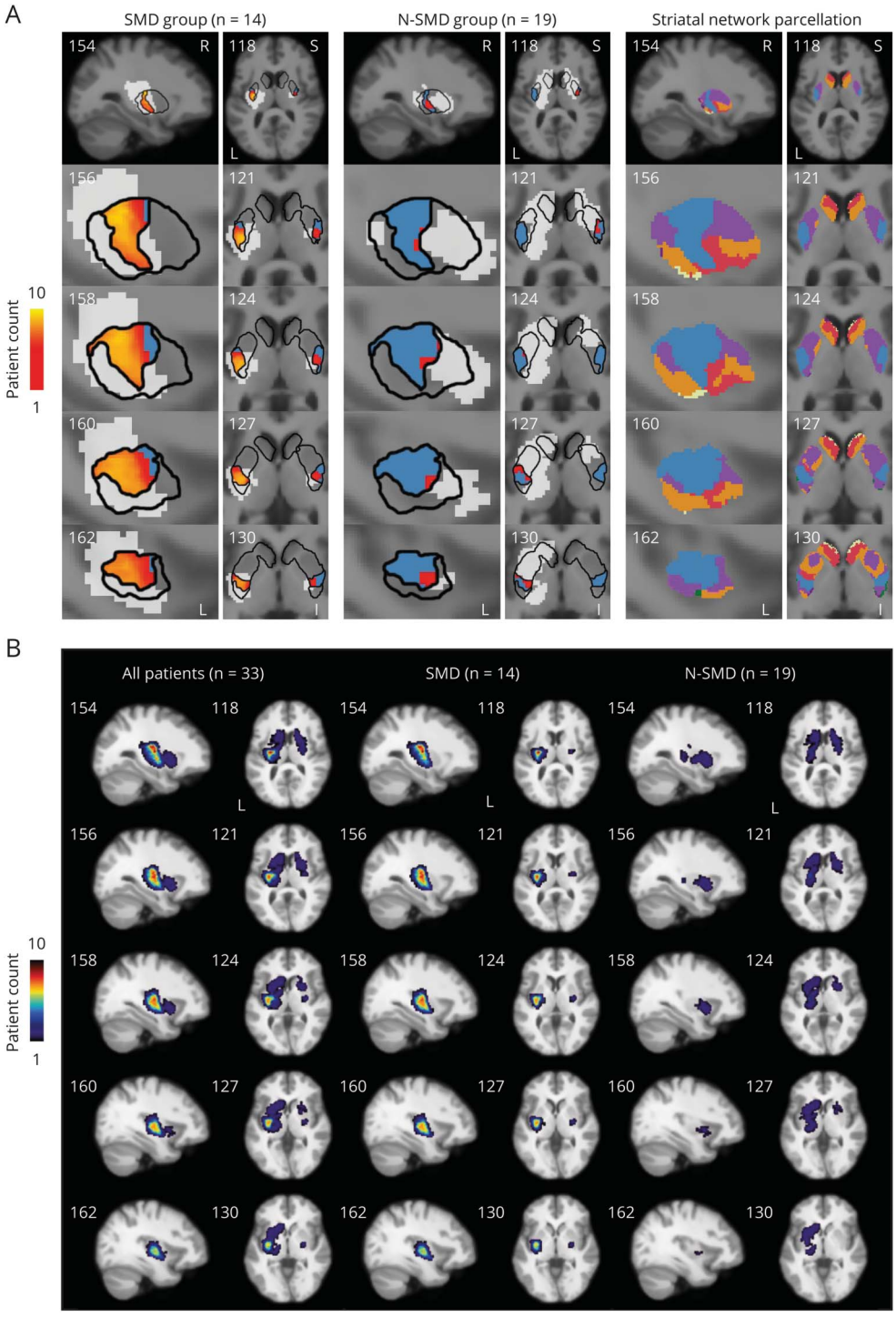
Anonymized data will be shared by request from any qualified investigator.

Results

Motor impairment severity and recovery depend on the location of lesion in the basal ganglia

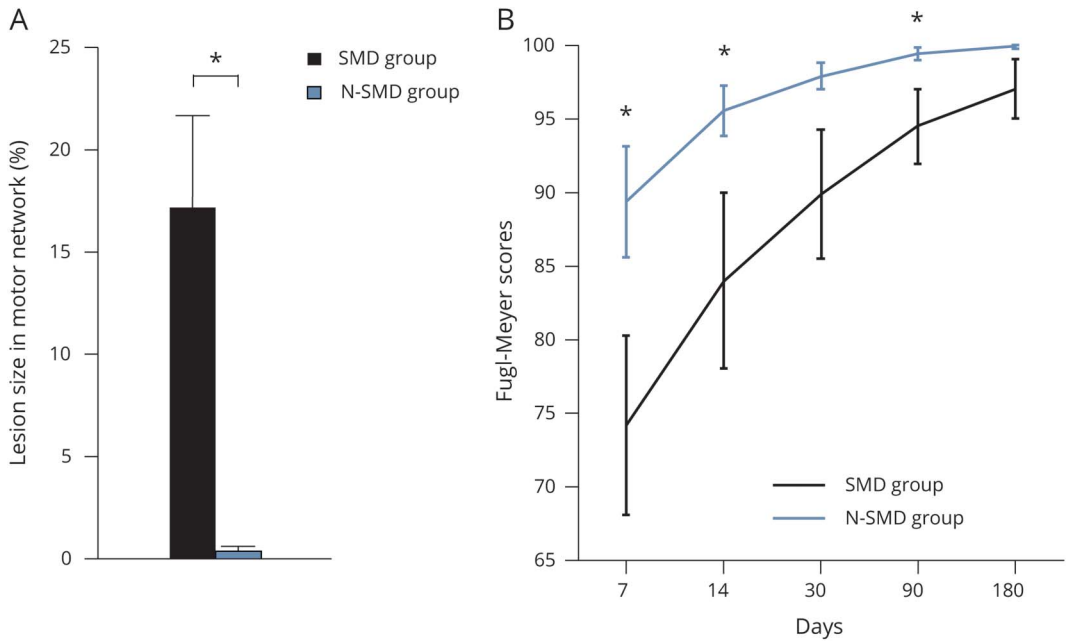
Thirty-three patients and 23 control participants were included in our analyses (see Methods and table 1 for demographic and clinical details). Concordant with the group categorization, the SMD group had a significantly greater NLP in the striatal motor network than the N-SMD group ($t_{31} = 4.40$, $p < 0.001$, $\eta_p^2 = 0.38$, mean difference = 16.84, 1-sided 95% confidence interval [CI] 10.35–23.32) (figure 2, left). We found that the SMD group exhibited significantly lower Fugl-Meyer scores compared to the N-SMD group ($F_{1,31} = 4.92$, $p = 0.03$, $\eta_p^2 = 0.14$, mean difference = −8.51, 95% CI −16.34 to −0.69) (figure 2, right). We investigated group differences at each time point and found a significant difference at baseline, i.e., within 7 days poststroke ($t_{31} = -2.15$, 1-sided $p = 0.02$, $\eta_p^2 = 0.13$, mean difference = −15.17, 1-sided 95% CI −27.15 to −3.19), a significant difference 14 days poststroke ($t_{15.11} = -1.80$, 1-sided $p = 0.046$, $\eta_p^2 = 0.12$,

Figure 1 Group categorization based on striatum network parcellation and lesion overlap



Patients with stroke were divided into a striatal motor network–dominant (SMD) group and a non–striatal motor network–dominant (N-SMD) group based on the lesion site within the striatum. (A) The striatum was parcellated into 7 functional networks according to its resting-state functional connectivity with the cortex,[16] as shown in the right-most columns. The region functionally connected to the sensorimotor cortex, deemed the motor region of the striatum, is shown in blue. Patients were split into the SMD group (left-most columns; n = 14) and the N-SMD group (center columns; n = 19) based on whether their lesions predominantly overlapped with the motor region of the striatum. Lesions are collapsed across patients. Lesion voxels that do not overlap with the motor region of the striatum are shown in light gray; the voxels that do are shown in a scale of yellow to red. The yellow to red color scale indicates the number of participants who have lesions affecting a given voxel within the motor region of the striatum. Rows depict different slices through the striatum. The numbers in the upper left corners represent the slice number; ascending numbers go from right to left and from superior to inferior. The lesions in the right hemisphere were flipped to the left hemisphere in the subsequent analysis, but are still shown in the right hemisphere here. (B) Stroke lesion overlap is shown for the whole patient group (n = 33, left columns), for the SMD group alone (middle columns), and for the N-SMD group alone (right columns). For each group, sagittal slices are shown in the left column (numbers indicate X axis coordinate) and horizontal slices in the right column (numbers indicate Z axis coordinate). The overlap is represented using a color scale showing overlap between 1 and 10 patients. I = inferior; L = left; R = right; S = superior.

Figure 2 Extent of lesion affecting the functional motor network and Fugl-Meyer scores over time



The bar graph on the left shows that there is a significant difference between the striatal motor network–dominant (SMD) and non–striatal motor network–dominant (N-SMD) groups in terms of the percentage of the functional motor network affected by lesions ($p < 0.001$). This was calculated as the ratio of the number of voxels in the lesion located in the motor network over the total number of striatal voxels in the network. The graph on the right shows the progression of Fugl-Meyer scores over time for each patient group. The SMD group exhibited significantly lower scores than N-SMD group on day 7 ($p = 0.02$), day 14 ($p = 0.046$), and day 90 ($p = 0.04$). There were no significant differences 30 days poststroke, although the means and confidence intervals are compatible with the presence of a sizable difference ($p = 0.053$), and no significant difference at the last follow-up scan at 180 days ($p = 0.10$). Error bars represent standard errors of the mean. *$p < 0.05$.

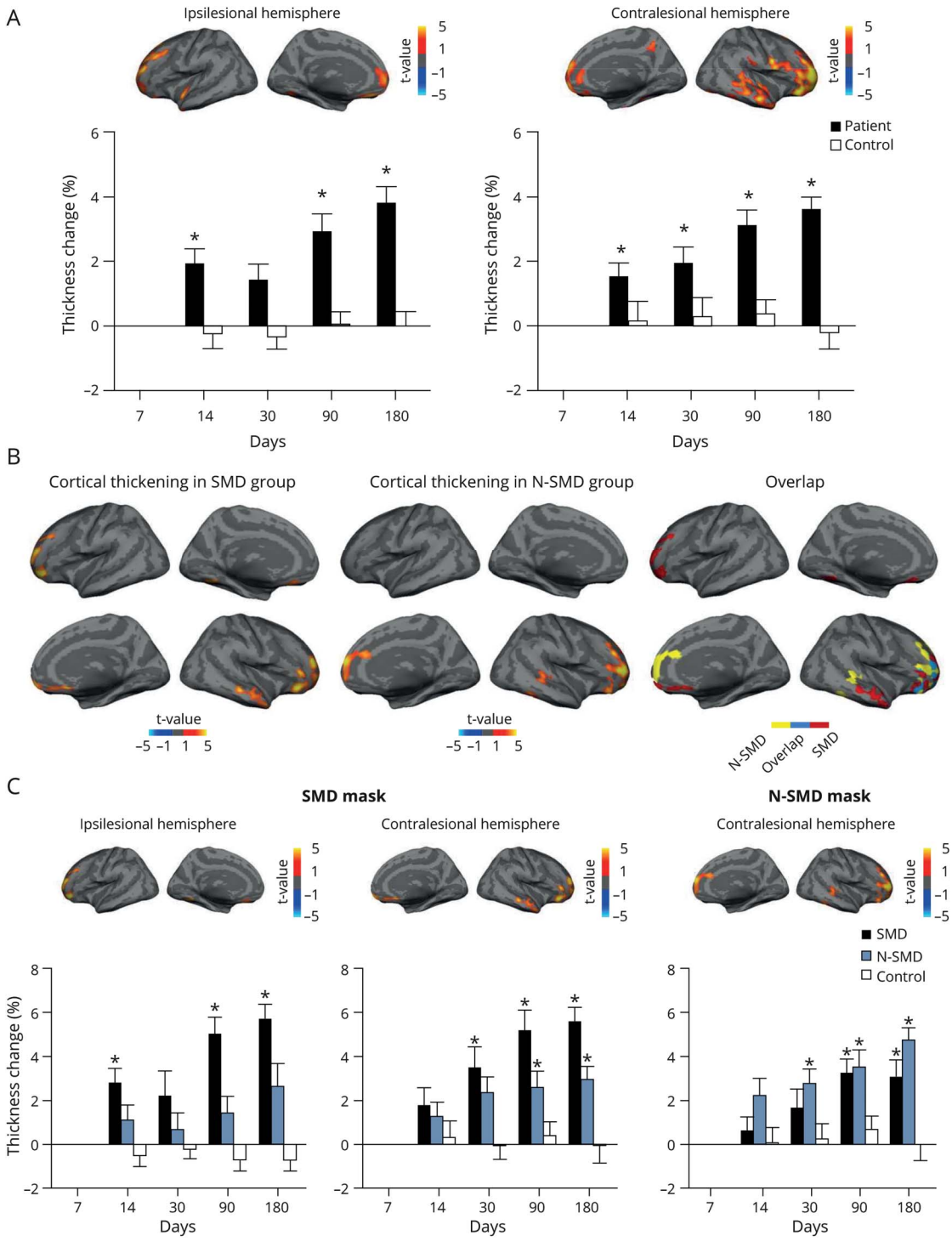
mean difference = −11.57, 1-sided 95% CI −22.82 to −0.32), no significant difference at 30 days, although the mean difference and CIs are compatible with the presence of an effect ($t_{14.14} = -1.73$, 1-sided $p = 0.053$, $\eta_p^2 = 0.11$, mean difference = −8.03, 1-sided 95% CI −16.21 to 0.15), a significant difference at 90 days ($t_{13.68} = -1.85$, 1-sided $p = 0.04$, $\eta_p^2 = 0.13$, mean difference = −4.93, 1-sided 95% CI −9.62 to −0.24), and no significant difference at 180 days ($t_{13.07} = -1.36$, $p = 0.10$, $\eta_p^2 = 0.08$, mean difference = −2.86, 1-sided 95% CI −6.59 to 0.86). Motor symptoms improved over time ($F_{1.51,46.73} = 21.65$, $p < 0.001$, $\eta_p^2 = 0.41$). The motor recovery was non-significantly steeper for the SMD group than the N-SMD group, as evidenced by an interaction that almost reached significance ($F_{1.51,46.73} = 2.98$, $p = 0.07$, $\eta_p^2 = 0.09$).

Basal ganglia stroke leads to a steady cortical thickness increase in ipsilesional and contralesional regions

Given that cortical changes stabilize over time, the study of the early stages of stroke is particularly challenging as we expect substantial individual variability in both the location and extent of neuroplastic changes. For this reason, we focused our investigation on the cortical thickness changes that were apparent at 6 months, and explored the evolution of these changes throughout the 5 time points at which patients were assessed. When comparing cortical thickness between baseline and 180 days poststroke across all participants (SMD and N-SMD combined), we found significant increases in cortical thickness in both the ipsilesional and contralesional hemispheres in the patient group ($ps < 0.001$) (figure 3A and table 3). Increased cortical thickness occurred in the ipsilesional frontal pole, superior frontal gyrus, medial prefrontal cortex (329 vertices, highest $t = 10.90$, $p < 0.001$), and orbitofrontal cortex (62 vertices, highest $t = 9.53$, $p < 0.001$), and in the contralesional precentral gyrus, frontal pole, ventrolateral prefrontal cortex, superior frontal gyrus, medial prefrontal cortex (761 vertices, highest $t = 16.43$, $p < 0.001$), precuneus (26 vertices, highest $t = 6.53$, $p < 0001$), and superior and middle temporal gyri (344 vertices, highest $t = 11.99$, $p < 0.001$), among other regions (table 3). Thus there is widespread structural plasticity in the brain following stroke. Interestingly, there were no regions showing a significant decrease in cortical thickness after correcting for multiple comparisons ($p > 0.001$).

Next we looked at the evolving structural plasticity within the set of regions identified above, by creating a group mask that encompassed these regions (table 4 for baseline values broken down by group). The patient group (SMD and N-SMD combined) showed significant increases in cortical thickness within the group mask over time, both in the ipsilesional hemisphere ($F_{4,128} = 15.95$, $p < 0.001$, $\eta_p^2 = 0.33$) and the contralesional hemisphere ($F_{4,128} = 20.18$, $p < 0.001$, $\eta_p^2 = 0.39$). Sidak post hoc tests showed that patients' cortical

Figure 3 Cortical thickness changes in patients with basal ganglia stroke during the first 6 months poststroke



(A) The cortical surface maps (top) show areas of significant cortical thickness increase at 180 days compared to baseline ($p < 0.001$). Using these regions as a mask, mean cortical thickness within the masks was estimated at the 5 time points. The bar graphs (bottom) show percent cortical thickness change in each hemisphere in the 33 patients with stroke and 23 healthy control participants, at each time point. A significant increase in cortical thickness was observed in patients with stroke at each follow-up time point (all ps < 0.05), except at 30 days ($p = 0.07$). In contrast, no significant changes were observed in healthy control participants (all ps > 0.05). Error bars represent standard errors of the mean. (B) Cortical surface maps show regions with significant changes in cortical thickness 180 days after stroke in the striatal motor network–dominant (SMD) group (left) and the non–striatal motor network–dominant (N-SMD) group (middle) ($p < 0.001$). There were no regions with significant decrease in cortical thickness in either group ($p > 0.001$). The cortical surface map on the right shows the overlap in regions of significant increase in cortical thickness (in blue, Dice overlap index = 0.16). (C) Cortical thickness changes within regions of the SMD and N-SMD masks. The SMD group exhibited significant increases in cortical thickness within the SMD mask (left and middle) over time (analysis of variance [ANOVA] $p < 0.05$). In contrast, the N-SMD group and the healthy control group did not show a significant increase within this mask over time (ANOVA $p > 0.05$). Within the N-SMD mask (right), the N-SMD group showed significant increases in cortical thickness over time (ANOVA $p < 0.05$). The SMD group exhibited significant increases over time (ANOVA $p < 0.05$) and specifically at 90 and 180 days poststroke (ps < 0.05), but not at 14 or 30 days poststroke (ps > 0.05). The healthy control group showed no significant changes in cortical thickness over time. *$p < 0.05$.

Table 3 Regions of cortical thickness increase

Cluster	Maximum *t* value	Size, mm^2	Number of vertices	Regions
Figure 3A: Whole group, ipsilateral hemisphere				
1	10.98	3,789.25	329	Frontal pole, superior frontal gyrus, MPFC
2	9.53	662.72	62	OFC
3	9.05	175.19	19	DLPFC
4	9.04	242.94	29	Superior temporal gyrus
5	6.82	228.04	20	Lingual gyrus
6	6.61	203.44	17	Temporal pole
7	5.85	155.90	14	Occipital
8	5.32	275.89	27	OFC
Figure 3A: Whole group, contralateral hemisphere				
1	16.43	8,278.04	761	Precentral gyrus, frontal pole, superior frontal gyrus, MPFC, VLPFC
2	11.99	3,120.56	344	Superior and middle temporal gyri
3	7.44	356.90	37	OFC
4	7.13	402.43	39	DLPFC
5	7.00	195.92	21	Inferior temporal gyrus/fusiform gyrus
6	6.86	164.22	16	Inferior temporal gyrus
7	6.53	222.56	26	Precuneus
8	6.52	204.14	18	Occipital
9	6.06	214.07	21	ACC
10	5.89	151.10	23	Precentral gyrus
11	5.22	255.21	22	Inferior temporal gyrus
Figure 3C: SMD group, ipsilateral hemisphere				
1	12.33	744.80	58	VLPFC
2	10.17	1,119.25	97	Frontal pole, superior frontal gyrus
3	8.53	271.75	27	Lingual gyrus, fusiform gyrus
4	7.48	214.76	20	OFC
5	7.02	226.84	23	OFC
Figure 3C: SMD group, contralateral hemisphere				
1	9.55	2,953.97	251	Frontal pole, VLPFC
2	8.57	373.31	31	VLPFC
3	7.84	936.64	88	Middle temporal gyrus
4	7.48	275.53	27	ACC
Figure 3C: N-SMD group, contralateral hemisphere				
1	13.24	1,085.95	99	MPFC, ACC
2	11.17	1,522.07	126	Frontal pole

Continued

Table 3 Regions of cortical thickness increase *(continued)*

Cluster	Maximum *t* value	Size, mm^2	Number of vertices	Regions
3	9.62	371.39	26	VLPFC
4	7.62	327.01	32	Superior frontal gyrus
5	7.36	392.55	40	OFC
6	7.34	263.88	23	Inferior temporal gyrus
7	6.92	395.90	52	Superior temporal sulcus

Abbreviations: ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; MPFC = medial prefrontal cortex; N-SMD = non–striatal motor network–dominant; OFC = orbitofrontal cortex; SMD = striatal motor network–dominant; VLPFC = ventrolateral prefrontal cortex.

thickness significantly increased from baseline at each subsequent time point, in both hemispheres ($ps < 0.05$, largest $p = 0.01$, smallest $\eta_p^2 = 0.28$, all 95% CI excluded 0; figure 3A), except 30 days poststroke in the ipsilesional hemisphere, where there was a nonsignificant increase ($p = 0.07$, $\eta_p^2 = 0.20$, 95% CI −2.91 to 0.07). In comparison, healthy control participants demonstrated no significant cortical thickness changes over time ($F_{4,88} = 0.29$, $p = 0.89$) or at any time point (all $ps > 0.05$, largest $\eta_p^2 = 0.03$, all 95% CI crossed 0) (figure 3A).

The SMD and N-SMD groups present different patterns of cortical reorganization

We then investigated the cortical thickness changes in the SMD and N-SMD groups separately. Intracranial volume was not used as a covariate as the 3 groups (SMD, N-SMD, control) did not significantly differ in this respect ($F_{2,53} = 0.73$, $p = 0.49$, $\eta_p^2 = 0.03$). The SMD group showed increases between baseline and 180 days poststroke in the ipsilesional and contralesional hemispheres ($ps < 0.001$; table 3), with most of the changes occurring in the contralesional ventrolateral prefrontal cortex and frontal pole (251 vertices, highest $t = 9.55$, $p < 0.001$), and in the middle temporal gyrus (88 vertices, $t = 7.84$, $p < 0.001$), and ipsilesionally in the frontal pole and superior frontal gyrus (97 vertices, highest $t = 10.17$, $p < 0.001$) (figure 3B, left). The N-SMD group exhibited increases in the contralesional ($p < 0.001$) but not the ipsilesional hemisphere ($p > 0.001$) (figure 3B, middle and table 3). The contralesional changes mostly occurred in the frontal pole (126 vertices, highest $t = 11.17$, $p < 0.001$) as well as in the medial prefrontal cortex and anterior cingulate cortex (99 vertices, highest $t = 13.24$, $p < 0.001$) (figure 3B, middle). To investigate whether the SMD and N-SMD groups presented different patterns of cerebral reorganization, we compared their cortical thickness changes and found little overlap (Dice overlap index = 0.16) (figure 3B, right). These results indicate that the SMD and N-SMD groups underwent different patterns of cerebral reorganization after stroke.

Next, we investigated cortical thickness changes within the regions that showed plasticity in the SMD group at 180 days poststroke compared to baseline (SMD mask; see table 4 for baseline values). The SMD group exhibited significant changes in cortical thickness within this mask over time (ipsilesional: $F_{3,39} = 7.27$, $p < 0.001$, $\eta_p^2 = 0.36$; contralesional: $F_{3,39} = 7.34$, $p < 0.001$, $\eta_p^2 = 0.36$). Sidak post hoc tests revealed that the SMD group showed an increase in both the ipsilesional and contralesional regions as early as 14 days poststroke and at each subsequent time point, except at 30 days in the ipsilesional hemisphere and at 14 days in the contralesional hemisphere, where there were no significant increases (ipsilesional 14 days: $p = 0.009$, $\eta_p^2 = 0.58$, mean difference = −2.80, 95% CI −5.01 to −0.6; 30 days: $p = 0.53$, $\eta_p^2 = 0.23$, mean difference = −2.19, 95% CI −5.96 to 1.59; 90 days: $p < 0.001$, $\eta_p^2 = 0.76$, mean difference = −5.00, 95% CI −7.60 to −2.40; 180 days: $p < 0.001$, $\eta_p^2 = 0.85$, mean difference = −5.69, 95% CI −7.95 to −3.42;

Table 4 Baseline values of cortical thickness

	SMD	N-SMD	Control
Group mask: ipsilateral	2.38 ± 0.11	2.42 ± 0.11	2.51 ± 0.13
Group mask: contralateral	2.48 ± 0.11	2.53 ± 0.09	2.61 ± 0.14
SMD mask: ipsilateral	2.28 ± 0.11	2.34 ± 0.13	2.42 ± 0.12
SMD mask: contralateral	2.47 ± 0.12	2.55 ± 0.10	2.65 ± 0.17
N-SMD mask: contralateral	2.41 ± 0.11	2.41 ± 0.10	2.53 ± 0.16

Abbreviations: N-SMD = non–striatal motor network–dominant; SMD = striatal motor network–dominant.

contralesional 14 days: $p = 0.38$, $\eta_p^2 = 0.27$, mean difference = −1.79, 95% CI −4.51 to 0.94; 30 days: $p = 0.03$, $\eta_p^2 = 0.50$, mean difference = −3.48, 95% CI −6.70 to −0.26; 90 days: $p = 0.001$, $\eta_p^2 = 0.71$, mean difference = −5.19, 95% CI −8.30 to −2.08; 180 days: $p < 0.001$, $\eta_p^2 = 0.86$, mean difference = −5.60, 95% CI −7.71 to −3.49) (figure 3C, left). The SMD group showed an increase over time whose trend was linear, as indicated by a significant linear trend (ipsilesional: $F_{1,13} = 34.22$, $p < 0.001$, $\eta_p^2 = 0.73$; contralesional: $F_{1,13} = 15.81$, $p = 0.002$, $\eta_p^2 = 0.55$). In contrast, the N-SMD group overall exhibited nonsignificant increases within the SMD mask over time (ipsilesional: $F_{3,54} = 2.29$, $p = 0.09$, $\eta_p^2 = 0.11$; contralesional: $F_{3,54} = 2.61$, $p = 0.06$, $\eta_p^2 = 0.13$). When looking at each time point separately, the N-SMD group exhibited a significant increase only in the contralesional hemisphere 90 days ($p = 0.04$, $\eta_p^2 = 0.38$, mean difference = −2.57, 95% CI −5.00 to −0.13) and 180 days ($p = 0.001$, $\eta_p^2 = 0.58$, mean difference = −2.94, 95% CI −4.84 to −1.05) poststroke (figure 3C, left), although it is important to keep in mind that the overall effect of time was nonsignificant. The control group showed no significant changes overall (ipsilesional: $F_{3,66} = 0.31$, $p = 0.82$; contralesional: $F_{3,66} = 0.33$, $p = 0.81$) or at any time point in this mask (all ps > 0.05, largest $\eta_p^2 = 0.10$, all 95% CIs crossed 0). These results show that the SMD group underwent a specific cortical reorganization over time and that the N-SMD group did not display reorganization in the same regions, although there was some overlap.

We repeated the same analyses, this time using a mask of the regions that showed an effect in the N-SMD group at 180 days poststroke compared to baseline (N-SMD mask; see table 4 for baseline values). The mask only included contralesional regions as the N-SMD group did not exhibit any significant changes in the ipsilesional hemisphere 180 days poststroke. Within this mask, the N-SMD group exhibited a significant increase in cortical thickness over time ($F_{3,54} = 5.52$, $p = 0.002$, $\eta_p^2 = 0.24$). Sidak post hoc tests revealed that there were increases in the contralesional regions as early as 14 days poststroke, although this was nonsignificant ($p = 0.09$, $\eta_p^2 = 0.32$, mean difference = −2.27, 95% CI −4.76 to 0.22), and significant increases at all subsequent time points (30 days: $p = 0.003$, $\eta_p^2 = 0.52$, mean difference = −2.83, 95% CI −4.87 to −0.79; 90 days: $p = 0.004$, $\eta_p^2 = 0.51$, mean difference = −3.53, 95% CI −6.14 to −0.92; 180 days: $p < 0.001$, $\eta_p^2 = 0.81$, mean difference = −4.80, 95% CI −6.57 to −3.03) (figure 3C, right). The N-SMD group showed an increase over time whose trend was significantly linear ($F_{1,18} = 14.79$, $p = 0.001$, $\eta_p^2 = 0.45$). In the N-SDM mask, the SMD group also exhibited a significant increase in cortical thickness over time ($F_{3,39} = 3.70$, $p = 0.02$, $\eta_p^2 = 0.22$). Sidak post hoc tests showed that significant increases occurred starting from 90 days poststroke (90 days: $p = 0.001$, $\eta_p^2 = 0.70$, mean difference = −3.33, 95% CI −5.36 to −1.29; 180 days: $p = 0.01$, $\eta_p^2 = 0.56$, mean difference = −3.12, 95% CI −5.72 to −0.52) (figure 3C, right). Again, the control group showed no significant changes overall ($F_{3,66} = 0.59$, $p = 0.63$, $\eta_p^2 = 0.03$) or at any time point in this mask (all ps > 0.05, largest $\eta_p^2 = 0.06$, all 95% CI crossed 0; figure 3C, right).

Thus, whereas the 2 groups show substantial differences, they also show some common patterns of reorganization.

Cortical thickness increase is not associated with improvement in Fugl-Meyer scores

Cortical thickness differences between 7 and 180 days poststroke were uncorrelated with behavioral improvements in the same time period ($r = 0.12$, $p = 0.50$, 95% CI −0.23 to 0.45) or with Fugl-Meyer scores at baseline ($r = −0.16$, $p = 0.38$, 95% CI −0.48 to 0.20). The earliest cortical thickness changes (first 2 scans) similarly were not associated with long-term behavioral improvements after 180 days ($r = 0.01$, $p = 0.96$, 95% CI −0.34 to 0.35) or Fugl-Meyer scores at baseline ($r = −0.01$, $p = 0.95$, 95% CI −0.35 to 0.33). Because many patients presented high scores on the Fugl-Meyer scale following the stroke incident, we conducted a secondary analysis where we excluded from analysis the 15 patients who scored >95% on both day 7 and day 14. Again, we found no significant relationship between cortical thickness changes on day 180 and improvements on the Fugl-Meyer scale ($r = −0.24$, $p = 0.33$, 95% CI −0.64 to 0.25). These results suggest that cortical thickness changes may not have a simple, linear relationship with motor improvement. We did not use lesion volume as a covariate in this analysis as there was no significant correlation between lesion volume and Fugl-Meyer scores at baseline ($r = −0.29$; $p = 0.10$, 95% CI −0.58 to 0.06), consistent with another study,[27] and as the 2 subgroups did not significantly differ in lesion volume (SMD: 2,753.7 ± 2,472.7 mm^3, N-SMD = 2,329.7 ± 2,838.2 mm^3; $t_{31} = 0.45$, $p = 0.66$, $\eta_p^2 = 0.01$, 95% CI −1,509.06 to 2,357.12).

Discussion

In this study, we investigated the cortical thickness changes that take place throughout 6 months in a cohort of patients with stroke specifically affecting the basal ganglia. We constrained our investigation to changes apparent at the 6-month mark in order to minimize the impact of the large individual variability that is expected in the acute and subacute stages of stroke. Doing so enabled us to detect stable and robust changes and to measure their evolution through time.

Our findings indicate that macroscopic cortical reorganization occurs early after stroke. The longitudinal aspect of our study revealed that patients exhibited increases in cortical thickness as early as 14 days following stroke. Cortical thickness continued to increase over the chronic phase and remained past the 6-month mark, when patients have recovered most of their function. At the whole-group level, patients showed widespread increases in cortical thickness within the frontal, temporal, and parietal cortices, in line with the observation that neuroplastic changes extend to brain areas beyond the lesion site,[5,6,8,9,28] and with studies showing functional and synaptic changes in the first weeks after stroke.[9,29,30] The healthy control group showed no increases in cortical

thickness, indicating that the patients' structural changes were due to poststroke cortical reorganization.

Many studies have investigated structural neuroplastic changes. Some show no change or a decrease in structural measures[2–4,7,10,15,31,32] while others show a concurrent increase in structural measures.[3,4,10,11,14,33–35] In our patients, whose lesions are limited to the basal ganglia, we only observed increases in cortical thickness, and no atrophy. Many factors can explain the discrepancies observed between studies, including patient characteristics, lesion location and extent, time of assessment, recovery process, study criteria, structural measures, and regions of interest. Our observation may suggest that cortical thickness increase is a dominating trend after basal ganglia stroke, although this is subject to future replication in independent datasets.

Another important finding is that the pattern of macroscopic cortical reorganization depends on the lesion location. The SMD group exhibited larger motor impairments than the N-SMD group up until the sixth month. The baseline difference in motor impairment underlines the importance of considering the precise location of the stroke-induced lesion when assessing symptoms and recovery.

It is important to note that the Fugl-Meyer scores did not fully and accurately reflect the state of patients' motor abilities, as some patients had perfect or near-perfect baseline scores (table 1), even though they presented with hemiparesis and subjective motor deficits. Overall, the patients' motor deficits did appear to be mild, in accordance with the structural MRI assessments showing no patient had damage to the primary motor cortex.

The pattern of cortical reorganization differs according to the specific location of the stroke lesion, indicating that lesion site has an impact on both the time course and spatial pattern of the ensuing cortical reorganization, most likely because it affects different large-scale functional cortical networks.

Whereas a decrease in structural measures is thought to reflect secondary degeneration due to direct injury or indirect injury through the damage of connecting white matter fibers,[33] an increase in structural measures might in turn be a product of motor recovery and motor compensation.[34] However, we did not find a relationship between changes in cortical thickness and either baseline motor scores or improvement in motor symptoms, similar to a previous study.[15] This is possibly due to the fact that the Fugl-Meyer scale combines various measures of limb function and therefore represents a general assessment of limb function. Honing in on the precise deficit in each patient may yield significant brain–behavior relationships. In other words, it is possible that the increases in cortical thickness we observed are related to real-life improvements in motor symptoms that are not accurately reflected by Fugl-Meyer scores. It is also possible that these neurostructural changes are related to changes in affective or cognitive functions, which are common following stroke.[36,37]

In our study, we focused on patients whose subcortical stroke affected the basal ganglia as a means to increase the homogeneity of the sample. Few studies have investigated the structural neuroplasticity of patients with similar damage.[3] One study found that, approximately 1 year after stroke, patients presented reduced gray matter in the motion-sensitive regions compared to baseline a few days after stroke.[3] They also exhibited increased gray matter in the contralateral orbitofrontal cortex and inferior and middle temporal gyri. Although we did not detect decreases in cortical thickness over the 6-month period in our cohort, the increases we have observed in distant and widespread cortical regions like the frontal and temporal cortices are concordant with the higher gray matter found in the aforementioned study.[3] The fact that we did not find ipsilesional decreases in cortical thickness, particularly around the motor cortex, may be due to our cohort having relatively mild motor impairments at baseline (average Fugl-Meyer scores at baseline = 82.88 ± 3.68; figure 2).

The N-SMD group showed less extensive changes in cortical thickness compared to the SMD group (figure 3C and table 3). It is possible that the N-SMD group presented greater heterogeneity in neurostructural changes because it was composed of patients with more varied lesion locations. Indeed, the group was made up of patients with predominant lesions to any of the 6 nonsensorimotor regions of the striatum or elsewhere in the basal ganglia, whereas the SMD group was composed of patients whose lesions predominantly overlapped with the striatal sensorimotor region only.

This study has important implications for rehabilitation treatments. The fact that patients with different stroke-induced lesions exhibit varying motor impairments and patterns of cortical reorganization suggests that they may need different rehabilitation treatments. For example, neuromodulation therapies have been successful in alleviating motor symptoms.[38–41] These therapies may differentially benefit patients based on lesion location. Although it is not possible for noninvasive brain stimulation methods to target the basal ganglia, the fact that there are structural changes occurring throughout the cortex, including in several frontal and temporal regions, indicates that these sites may be potential targets for neuromodulation. Modulating these areas, which demonstrate significant structural changes during recovery, may lead to plasticity changes in some important corticostriatal pathways and benefit motor function recovery. This hypothesis is subject to future tests in clinical trials. At 6 months, the 2 patient groups were indistinguishable in terms of their motor outcome, even though they presented different outcomes in the previous months. Thus, to best describe and characterize motor recovery in patients, and to design specific treatment plans, studies should aim to assess patients as early as possible to take advantage of the heightened brain plasticity immediately following the event. Finally, although we did not observe a linear correlation between cortical thickening and motor function improvement as assessed with the Fugl-Meyer scale, future investigations on the relation between the

longitudinal trajectory of macrostructural brain changes following stroke and functional recovery could lead to the discovery of cortical thickness–based biomarkers that could be used to track recovery progress or rehabilitation effects in clinical trials.

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Louisa Dahmani, PhD	Massachusetts General Hospital, Boston	Analyzed the data, wrote the manuscript
Hongfeng Wang, MD	Changchun University of Chinese Medicine, China	Contributed new reagents/ analytical tools
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Jie Lu, MD	Xuanwu Hospital, China	Designed the research, collected the data, analyzed the data, wrote the manuscript
Danhong Wang, MD, PhD	Massachusetts General Hospital, Boston	Designed the research, analyzed the data, wrote the manuscript

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