Distinct white matter alterations following severe stroke
Longitudinal DTI study in neglect

ABSTRACT

Objective: To distinguish white matter remodeling directly induced by stroke lesion from that evoked by remote network dysfunction, using spatial neglect as a model.

Methods: We examined 24 visual neglect/extinction patients and 17 control patients combining comprehensive analyses of diffusion tensor metrics and global fiber tracking with neuropsychological testing in the acute (6.3 ± 0.5 days poststroke) and chronic (134 ± 7 days poststroke) stroke phases.

Results: Compared to stroke controls, patients with spatial neglect/extinction displayed longitudinal white matter alterations with 2 defining signatures: (1) perilesional degenerative changes characterized by congruently reduced fractional anisotropy and increased radial diffusivity (RD), axial diffusivity, and mean diffusivity, all suggestive of direct axonal damage by lesion and therefore nonspecific for impaired attention network and (2) transneuronal changes characterized by an increased RD in contralesional frontoparietal and bilateral occipital connections, suggestive of primary periaxonal involvement; these changes were distinctly related to the degree of unrecovered neglect symptoms in chronic stroke, hence emerging as network-specific alterations.

Conclusions: The present data show how stroke entails global alterations of lesion-spared network architecture over time. Sufficiently large lesions of widely interconnected association cortex induce distinct, large-scale structural reorganization in domain-specific network connections. Besides their relevance to unrecovered domain-specific symptoms, these effects might also explain mechanisms of domain-general deficits in stroke patients, pointing to potential targets for therapeutic intervention.

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GLOSSARY

AD = axial diffusivity; DARTEL = diffeomorphic anatomical registration using exponentiated lie algebra; DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; FA = fractional anisotropy; FWE = family-wise error correction; HARDI = high angular resolution diffusion imaging; MD = mean diffusivity; MNI = Montreal Neurological Institute; NIHSS = NIH Stroke Scale; PCA = principal component analysis; RD = radial diffusivity; VBM = voxel-based morphometry.

Besides focal damage, major stroke induces network-specific remote dysfunction associated with changes in network functional connectivity. Whether these large-scale functional alterations are accompanied by structural changes to remote white matter tracts remains uninvestigated. Representing different types of maladaptive responses to stroke, structural network alterations can (1) be directly induced by the lesion in terms of anterograde and retrograde axonal degeneration, or (2) represent remote remodeling of fibers not directly connected to the lesion, i.e., transneuronal degeneration.

Dysfunction of remote attention centers is an underlying characteristic of spatial neglect associated with poor execution in nonspatial cognitive domains and worse stroke outcome. Hence, neglect serves as a model for severe stroke damage and remote network dysfunction. Cross-sectional studies in neglect showed reduction of fractional anisotropy (FA) in the inter-hemispheric and perilesional fiber tracts that most likely represents anterograde and retrograde...
degeneration of fibers directly disrupted by lesion, similar to Wallerian degeneration.\textsuperscript{10,11} Our previous study in acute stroke demonstrated FA reduction in the contralesional domain-specific connections in neglect patients.\textsuperscript{12} This is suggestive of early transneuronal degeneration, which, however, can only be validated longitudinally.\textsuperscript{3}

To this end, we performed a comprehensive longitudinal diffusion tensor imaging (DTI) and fiber tracking analysis in the undamaged white matter of stroke patients with visuospatial attention deficit. Based on previous functional MRI\textsuperscript{5,5,13} and cross-sectional DTI studies,\textsuperscript{8,9,12} we hypothesized distinct stroke-induced alterations of remote white matter: direct axonal disruption by lesion and transneuronal changes within the attention network.

**METHODS** Participants. We obtained longitudinal DTI data in 41 patients based on eligibility criteria as summarized in the e-Methods at Neurology.org.\textsuperscript{12} All patients underwent a standard treatment and rehabilitation program according to the Guidelines of the German Society of Neurology. In addition, we recruited 20 age-matched healthy right-handed controls (10 male), 67 ± 1 years old (mean ± SEM).

Standard protocol approvals, registrations, and patient consents. The Ethics Committee of the University Medical Centre Freiburg approved the study. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Clinical and behavioral testing. Both neuropsychological and MRI examinations were performed in the acute (3–9 days post-stroke) and the chronic (3–5 months poststroke) stroke phase. At the time of the MRI scanning, all patients underwent neuropsychological neglect testing as previously described\textsuperscript{15} and were tested for visual extinction\textsuperscript{14} (e-Methods). Based on the neuropsychological testing in the acute stroke phase, patients were divided into 2 groups: (1) with visuospatial attention deficit (visual neglect or visual extinction), i.e., neglect/extinction group; (2) without visuospatial attention deficit (neither neglect nor extinction), i.e., stroke controls. Demographic and clinical parameters were compared using a 2-sample t test; neglect testing data were non-normally distributed and analyzed nonparametrically.

To reduce the discretization bias introduced by patient dichotomization into 2 groups, we performed several correlation analyses with the individual performance score reflecting neglect severity calculated as mean of neglect tests’ scores\textsuperscript{15} (e-Methods). Whereas overall neglect severity score in the acute stroke phase correlated strongly with deficient performance in each subset ($r > 0.358, p < 0.023$), this was not the case in the chronic phase.\textsuperscript{3} Therefore, principal component analysis (PCA) was applied to the neuropsychological data of the follow-up examination to identify factors characterizing unrecovered neglect profiles\textsuperscript{16} (oblimin rotation, Kaiser-Meyer-Olkin = 0.514; Bartlett test $p < 0.001$, determinant 0.022), which were used for further correlational analysis.

Image preprocessing and data analysis. All images were acquired and preprocessed as previously described\textsuperscript{15} (e-Methods). Lesion delineation was performed semiautomatically on individual diffusion-weighted imaging (DWI) and then spatially normalized to Montreal Neurological Institute (MNI) space. Lesion anatomy between groups was compared by a statistical voxel-wise lesion-symptom mapping analysis (Liebermeister test),\textsuperscript{19} including controlling for lesion volume (logistic regression with lesion volume as covariate) using MRicron software.

Preprocessing of imaging data. For acute and follow-up examinations, each participant’s DTI metrics were calculated including FA, radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD) maps, derived from the high angular resolution diffusion imaging (HARDI) data using the DTI toolbox implemented in SPM8. All individual DTI and T1 images were nonlinear normalized using a fast diffeomorphic registration algorithm (diffeomorphic anatomical registration using exponentiated lie algebra [DARTEL]) by nonlinear transformation to the customized T1 template, followed by a linear normalization to standard MNI space and 10-mm full width at half maximum Gaussian smoothing.\textsuperscript{12} To ensure that the results did not arise from misregistration or inappropriate warping, the analysis was repeated with affine linear normalization. To control for volume changes in white and gray matter segments, they were analyzed by voxel-based morphometry (VBM) (e-Methods).

Statistical analysis of imaging data. The imaging data were analyzed using whole-brain voxel-wise statistics. Cross-sectionally, patient groups were compared using 2-sample t test; for the within-group longitudinal analysis, a paired t test was applied. For direct contrast of longitudinal changes between patient groups (interaction effect time × group), we first calculated individual voxel-wise longitudinal changes for each DTI metric by simple subtraction (acute DTI map – chronic DTI map). We then contrasted the calculated DTI maps capturing the longitudinal changes between patient groups using a 2-sample t test. This was repeated with adjustment for lesions size and NIH Stroke Scale (NIHSS) at admission to control for the variance introduced by these factors. To clarify the relationship between DTI changes and neglect outcome, whole-brain regression analysis on longitudinal DTI maps was applied within the neglect/extinction group using 3 PCA factors of persistent neglect as regressors. Explorative Spearman correlation analysis was performed between clinical characteristics and magnitude of longitudinal DTI changes extracted from peaks of significant clusters. Both groups of patients were contrasted with age-matched healthy controls by a 2-sample t test to additionally delineate changes related to stroke in general and to neglect. Voxels with >20% probability of containing white matter were included in the whole-brain statistical analysis; we excluded from the analysis all voxels damaged at least in one patient to avoid false-positive results and distortion due to lesion. We applied whole-brain family-wise error correction (FWE) for multiple comparisons at $p < 0.05$, cluster extend threshold >5 voxels. For illustration purposes, the changes at $p < 0.001$ (uncorrected) are also reported.

Extraction of the affected network. To dissect the longitudinally altered network, we first conducted a global fiber tracking for each subject and each examination based on native space HARDI data.\textsuperscript{12,17} The individual fiber track maps were further nonlinearly normalized into standard MNI space using the DARTEL procedure as detailed above, and then fibers traversing the affected voxels ($p < 0.05$, FWE correction) were selected. Afterwards, the density maps were calculated for each identified fiber set, for each phase of stroke and for each participant. The longitudinal reduction of fiber density was then calculated for each

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fiber set and each participant, and the mean maps for each group were calculated and reported.

RESULTS We obtained longitudinal DTI data in 24 patients with visuospatial attention deficit (neglect/extinction group) and 17 stroke patients without evidence of visuospatial attention deficit at any time (stroke control group). Neuropsychological and neuroimaging examinations were conducted in the acute (6.3 ± 0.5 days poststroke) and chronic (134 ± 7 days poststroke) phase of stroke. The demographic, clinical, and neuropsychological data are presented in table 1. Patient groups were matched by age (T39 = −0.72; p = 0.479), but the neglect/extinction group had more severe stroke with higher NIHSS score at admission (T39 = −2.73, p = 0.01) and larger lesion volumes (T39 = 4.57, p < 0.001), with more frequent damage of the supramarginal gyrus and perisylvian cortex and the adjacent white matter (Liebermeister test, p < 0.05, FWE correction, figure e-1). After controlling for lesion size, however, this group difference in lesion anatomy was no longer observed, suggesting that both large volume and critical location are prerequisites for neglect.20

Table 1  Demographic and clinical data

<table>
<thead>
<tr>
<th></th>
<th>Stroke control patients</th>
<th>Patients with visuospatial attention deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Male/female</td>
<td>9/8</td>
<td>19/5</td>
</tr>
<tr>
<td>Age, y, mean ± SEM</td>
<td>63 ± 5</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>Time from stroke to the first DTI examination, d, mean ± SEMa</td>
<td>4.8 ± 0.8</td>
<td>7.5 ± 0.5</td>
</tr>
<tr>
<td>Time from stroke to the follow-up examination, d, mean ± SEM</td>
<td>123 ± 9</td>
<td>141 ± 10</td>
</tr>
<tr>
<td>Lesion volume, cm³, mean ± SEMa</td>
<td>17.3 ± 5.2</td>
<td>63.9 ± 7.7</td>
</tr>
<tr>
<td>NIH Stroke Scale by admission, mean ± SEMa</td>
<td>4.2 ± 1.2</td>
<td>8.8 ± 0.9</td>
</tr>
<tr>
<td>Isolated extinction</td>
<td>–</td>
<td>7 from 24 patients</td>
</tr>
<tr>
<td>Chronic neglect/incomplete recoveryb</td>
<td>–</td>
<td>3 patients/5 patients</td>
</tr>
<tr>
<td>Line bisection, max 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination 1a</td>
<td>9; 7–9</td>
<td>6; 1–9</td>
</tr>
<tr>
<td>Examination 2a</td>
<td>9; −</td>
<td>9; 2–9</td>
</tr>
<tr>
<td>Coping of drawings, max 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination 1a</td>
<td>9; 7–9</td>
<td>5; 0–9</td>
</tr>
<tr>
<td>Examination 2a</td>
<td>9; −</td>
<td>9; 5–9</td>
</tr>
<tr>
<td>Line cancelation, max 18 (left/right)</td>
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<td></td>
</tr>
<tr>
<td>Examination 1</td>
<td>18; 16–18/18; 17–18</td>
<td>18; 5–18/18; 13–18</td>
</tr>
<tr>
<td>Examination 2</td>
<td>18; −/18; −</td>
<td>18; 4–18/18; 17–18</td>
</tr>
<tr>
<td>Star cancelation, max 27 (left/right)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination 1a</td>
<td>26; 23–27/26; 23–27</td>
<td>19; 0–27/22; 17–27</td>
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<tr>
<td>Examination 2</td>
<td>27; −/27; −</td>
<td>26; 11–27/26; 22–27</td>
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<tr>
<td>Letters cancellation, max 20 (left/right)</td>
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<td></td>
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<tr>
<td>Examination 1a</td>
<td>19; 18–20/19; 18–20</td>
<td>15; 0–20/18; 9–20</td>
</tr>
<tr>
<td>Examination 2</td>
<td>20; −/20; −</td>
<td>19; 4–20/18; 3–20</td>
</tr>
<tr>
<td>Reading, CoC</td>
<td></td>
<td></td>
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<tr>
<td>Examination 1a</td>
<td>0.0; −</td>
<td>0.061; 0.0–0.693</td>
</tr>
<tr>
<td>Examination 2</td>
<td>0.0; −</td>
<td>0.0; 0.0–0.389</td>
</tr>
<tr>
<td>Mean of CoCc, mean ± SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination 1a</td>
<td>0.002 ± 0.002</td>
<td>0.194 ± 0.034</td>
</tr>
<tr>
<td>Examination 2</td>
<td>0.0 ± 0</td>
<td>0.014 ± 0.001</td>
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</tbody>
</table>

Abbreviations: CoC = center of cancellation (e-Methods); DTI = diffusion tensor imaging.
a Significant group difference in 2-sample t test (p < 0.05); for neglect tests, the rightward attentional bias measured in CoC score was compared between groups.
b Patients failed in only one neglect test.
c The mean of CoC represents the overall neglect severity and is calculated as averaged CoC scores of all 6 neglect tests.

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In the chronic stroke phase, patients demonstrated distinct residual spatial and visual search deficits (table 1), which has been captured by 3 factors of PCA analysis (eigenvalue >0.8; 81.94% of the total variance explained): (1) deficient performance in the star cancellation test reflected both left and left–right omissions; (2) left omissions in the letter cancellation and drawing tests; (3) line bisection and left–right omissions in the letter cancellation test; the latter partly reflected a slight attentional bias to the left, since 11 patients from the neglect/extinction group detected 1.81 ± 0.30 more letters in the left than in the right hemisphere (table e-1).

White matter changes from acute to chronic stroke.
Stroke controls underwent the first DTI earlier (T_{39} = −2.19, p = 0.034). There were no group differences in the follow-up examination timepoint (p = 0.197). This could lead to false-positive group difference in the acute stroke phase. However, neglect/extinction and stroke control groups did not differ in DTI metrics in the acute stroke phase even when the statistical threshold was lowered (whole-brain voxelwise 2-sample t test, p < 0.001, uncorrected). Groups of patients differed in gray/white matter volumes neither in the acute nor in the chronic phase of stroke (cross-sectional VBM analysis, 2-sample t test, p < 0.05, FWE correction).

From acute to chronic stroke, stroke controls showed perilesionally constrained degenerative changes represented by FA reduction and MD/AD increase (p < 0.05, FWE correction; figure e-2). The neglect/extinction group showed large-scale longitudinal changes that included (1) ipsilesional degenerative changes with concordant FA reduction and MD, RD, and AD increases, similar to stroke controls but more extensive, and (2) contralesional RD increase (p < 0.05, FWE correction, figure e-2). To ensure that these findings did not result from a biased nonlinear spatial normalization, we confirmed the results with a robust affine (simple linear) normalization procedure (figure e-3).

Contrast of longitudinal DTI changes between groups.
Figure 1 contrasts directly the longitudinal DTI changes (acute DTI map — chronic DTI map) between patient groups (interaction effect time × group). From the acute to chronic phase of stroke in neglect/extinction compared to stroke control group, we observed (1) ipsilesional degenerative changes with congruent FA reduction and AD, RD, and MD increases and (2) contralesional and bi-occipital RD increase, as well as MD increase in the interparietal and right occipital connections (p < 0.05, FWE correction). The magnitude of these longitudinal ipsilesional and contralesional changes correlated positively with the initial severity of neglect, lesion volume, and NIHSS at admission (table e-2). Interaction effects in other directions (e.g., FA reduction and MD, RD, and AD increase in stroke controls compared to neglect/extinction or FA increase and RD, MD, and AD reduction in neglect/extinction compared to stroke controls) were not significant.

Controlling for lesion size and initial stroke severity and clinical relevance of remote alterations. Next, we distinguished neglect-specific white matter changes from those induced by large lesion volume, as well as other stroke deficits besides neglect (e.g., paresis, sensory deficit) by repeating the previous analysis and applying whole-brain adjustment for lesion size and NIHSS on admission. When compared to stroke controls during the acute to chronic stroke phase, the neglect/extinction group showed (1) RD increase in the contralesional frontoparietal and bilateral occipital connections and posterior corpus callosum; and (2) MD increase in the left parietal and occipital regions (figure 2A). To determine whether these longitudinal RD and MD increases influenced neglect outcome, we correlated their magnitude on the whole-brain level with 3 factors capturing symptoms of unrecovered neglect, as revealed by PCA (voxel-wise linear regression analysis within the neglect/extinction group). Worse outcome on the star cancellation test (PCA factor 1) was related to a stronger MD increase in the right occipital lobe. Worse performance in drawing and more left omissions in the letter cancellation test (PCA factor 2) best correlated with the magnitude of longitudinal RD increase in the left hemisphere: left superior and inferior longitudinal fascicles and extreme capsule (p < 0.05, FWE correction, figure 2B). Representing a compensatory left-sided scanning strategy by persisting visual search deficit, detection of more left than right letters in the letter cancellation test correlated with the tendency for a less severe RD increase in the left frontal lobe (negative correlation of PCA factor 3 with contralesional RD increase, p < 0.001 uncorrected).

We did not find any correlation between longitudinal DTI changes and chronic NIHSS score (p < 0.05, FWE correction).

To additionally delineate white matter changes common to stroke in general vs those specific to neglect, we compared both groups of patients with age-matched healthy controls (no difference in age, analysis of variance, F_{2,60} = 0.627, p = 0.538). The results confirmed the previous findings on perilesionally confined changes of DTI metrics in stroke controls, and widespread remote changes in the neglect/extinction group (figure e-4).

Extraction of affected network. Figure 3A visualizes the affected networks identified by fiber tracking. Here, we extracted fibers traversing the voxels with longitudinally altered RD and MD values.
The neglect/extinction group differed from stroke controls (interaction effect time × group) by longitudinal large-scale fractional anisotropy (FA) reduction and mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) increases (voxels damaged in at least 1 patient were excluded from the analysis). Interaction effects in other directions were not significant. The pronouncement of these remote white matter alterations both in the ipsilesional and contralesional cluster peaks was defined by initial neglect severity, lesion size, and NIH Stroke Scale (NIHSS) at admission (table e-2, Spearman correlation; voxels in yellow show $p < 0.05$, family-wise error [FWE] corrected; black markers: neglect/extinction group; blue markers: stroke control group).
Figure e-5 shows the averaged maps of extracted networks and the mean longitudinal reduction in fiber density for each fiber set and group. This descriptive analysis located the longitudinal reduction in fiber density in the neglect/extinction group mainly to the cores of the affected fiber tracks; similar longitudinal alterations were observed to a more limited extent in stroke controls. This analysis emphasized that not all fibers showed reduction in density, indicating that white matter remodeling occurs besides degeneration in the networks analyzed. This was directly visualized in a single participant with neglect (figure 3B).

**DISCUSSION** Using longitudinal DTI and fiber tracking, we identified extensive stroke-induced white matter changes in neglect/extinction patients compared to stroke controls. These longitudinal changes showed different diffusivity signatures in the ipsilesional vs the contralesional hemisphere and were distinctly related to the severity of functional impairment.

The first signature of remote longitudinal white matter remodeling was represented by ipsilesional congruent FA decrease and MD, AD, and RD increases as correlates of degenerative white matter alteration. These changes might be explained by the anterograde or retrograde degeneration of fibers directly damaged by the lesion (figure 4). Since it correlated with lesion size and stroke severity, and not with unrecovered symptoms (figures 1 and 2),
this perilesional white matter degeneration is non-specific for neglect and its network, representing epiphenomenon of large lesions, and therefore many more disrupted axons in neglect. Its correlation to severity of initial neglect might be confounded by strong interrelation of neglect severity with lesion size.\textsuperscript{20,24} Despite being network-nonspecific, these changes are nonetheless important to consider, since they show damage to anatomical pathways linking lesioned areas to unaffected regions. This, in turn, restricts the brain’s capacity to compensate and hence compounds the severity of behavioral impairment.

Another signature of remote white matter alterations was defined primarily by an increase in contralateral RD and less by an increase in occipital MD. These changes correlated with unrecovered neglect symptoms captured by PCA factors, and were present after whole-brain correction for lesion size and stroke severity upon admission, which controlled for several nonlesional factors including hypoperfusion and the individual’s capacity to compensate (figure 2). Increased RD was observed in the contralateral tracts mirroring the fiber systems primarily affected in neglect\textsuperscript{25–27} and composing the spatial attention network in healthy participants\textsuperscript{28} (figure 3). Thus, it involved domain-specific structural networks that were preserved from the focal lesion. Hence, this DTI signature represented network-specific changes. Increased RD is a more sensitive marker for early neurodegeneration,\textsuperscript{29} and histologically correlates with the degree of myelination.\textsuperscript{30–32} The absence of corresponding changes in AD—a marker for axonal damage\textsuperscript{31,32}—implies primary involvement of the periaxonal

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**Figure 3** Longitudinal alterations to structural connectivity captured by fiber tracking

(A) The networks of fiber tracts (gray) traversing altered voxels that were derived from interaction effect time × group after adjusting for lesion size and NIH Stroke Scale. The longitudinal reduction in fiber density in neglect/extinction (red) and control stroke patients (green) are mapped (the threshold of density maps was chosen to best show the difference between acute and chronic structural connectivity). (a) Left cingulum bundle; (b) connections of occipital lobe continuing as left inferior longitudinal fascicle and (c) optic radiation; (d) left dorsal frontoparietal connections including superior longitudinal fascicle and arcuate fascicle; (e) right optic radiation/inferior longitudinal fascicle. (B) Maximum intensity projections of fiber network traversing voxels with increased radial diffusivity in a single patient, 78 years old. Besides further degeneration of fibers traversing the infarct (2), longitudinal white matter remodeling could be captured, e.g., in bilateral cingulum (1) and occipital connections including inferior longitudinal fascicle (3).
Mainly in the ipsilesional hemisphere, stroke induced degenerative changes due to the direct axonal disruption. Areas spared from the lesion domain-specific network showed large-scale transneuronal changes suggestive of periaxonal involvement. AD = axial diffusivity; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity.
signatures: (1) axonal degeneration in the ipsilesional hemisphere, including areas remote from the lesion; and (2) transneuronal alterations to the contralesional frontoparietal and bilateral occipital connections, suggestive of primary periaxial involvement (figure 4). Whereas the extent of both types of white matter remodeling is predicted by lesion size, initial NIHSS, and initial neglect severity, only the transneuronal changes are network-specific by correlating with persisting deficit.

AUTHOR CONTRIBUTIONS

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DISCLOSURE
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