A Two-Year Longitudinal Study of Post-Stroke Mood Disorders: Dynamic Changes in Associated Variables Over the First Six Months of Follow-Up

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SUMMARY We are prospectively studying a group of 103 stroke patients over the first 2 years after infarction to determine the variables which are associated with the development of depression. At both 3 and 6 months post-stroke, patients with left hemisphere infarcts showed a strong relationship between severity of depression and distance of the lesion on CT scan from the frontal pole. The strength of this association was unchanged from the immediate post-infarction period. In contrast, the correlation between degree of functional physical impairment and severity of depression steadily increased over the 6 month follow-up. The correlation between severity of depression and Mini-Mental score or between depression and social functioning score dropped between in-hospital and 3 months but then increased significantly between 3 and 6 months post-stroke. Age did not correlate with depression beyond the acute post-stroke period. Whether the increasing strength of the relationships between impairment and depression over the first 6 months post-stroke indicates that continued depression led to delayed recovery or whether continued severe impairments led to depression is not known, however, this issue will be addressed in further data evaluation from this prospective study.

DURING THE PAST SEVERAL YEARS we have been investigating mood disorders in stroke patients.1-9 We have reported that intrahemispheric as well as interhemispheric lesion location was important and that patients with left anterior strokes were significantly more depressed than patients with lesions of any other location.5,7 The importance of left anterior lesion location for depression held up even when we examined patients who had bilateral strokes3 and we have shown in several studies that the closer the lesion was to the frontal pole on CT scan, the more severe the depression.1,3,5

In addition to these studies of lesion location, we have been conducting a prospective study of stroke patients who were entered in the NINCDS Stroke Data Bank10 and have been following them over a two year post-stroke period. We have found that during the acute stroke period several variables were correlated with severity of depression, including anterior left hemisphere lesion location, the severity of impairment in activities of daily living, degree of cognitive impairment, the quality of available social supports and the patient’s age.6

We have recently begun to analyze the follow-up data from this group of patients. During the six month follow-up, the prevalence of clinically significant depressions defined as meeting DSM III symptom crite-
ria for a diagnosis of major or minor depression, increased from 44% to 60%. Additionally, 21 of the 22 patients (95%) who were found to be depressed at the initial evaluation remained depressed at six month follow-up, while 29% of the patients who were not depressed at the time of the initial interview became depressed during the first six months.9

Since patients did not appear to be getting better during the first 6 months and additional patients developed depressions during this time, we examined the factors associated with depression over the first 6 months post-stroke to see if there was a change during this time that might explain the increasing prevalence of depression and whether factors such as lesion location, found to be important during this first evaluation, continued to have the same strong association with depression at follow-up.

3. Physical and Intellectual Impairment and Social Functioning

Quantitative evaluations of physical, cognitive and social functioning were made in conjunction with the psychiatric assessment. The Mini-Mental State Exam,14 the Johns Hopkins Functioning Inventory (JHFI)1,2 and the Social Functioning Exam (SFE)3,4 have all been described in previous publication.1,2,5

4. CT Scan Analysis

All CT scans were analyzed by the attending neuroradiologist (KR) who was blind to the psychiatric assessment. Lesion size, calculated by a computer program using an electronic cursor, was determined for each slice where it was visible and the total lesion volume was divided by the overall brain volume as described in previous publication.5,8 The distance of the lesion from the frontal pole was determined by measuring the distance of the anterior border of the lesion from the frontal pole and dividing by the overall A-P distance in that brain slice. This measurement was done in all slices where the lesion was visible and a mean distance was calculated.

5. Statistical Analysis

Means and standard deviations were computed for all quantitative measures. Intergroup comparisons were done using analysis of variance and appropriate post hoc tests. Comparisons of scores in-hospital with those at follow-up for the same patients were done using paired t-tests and Pearson correlation coefficients. The relationships between different measures done during the same examination were calculated using Pearson correlation coefficients. Chi-square statistics were used to compare non-parametric between-group measures.

Results

Patients seen in the follow-up study were predominantly lower socio-economic class, black patients most of whom were married and many of whom had had a previous life-threatening medical illness (table 1).

In previous publication we have reported that there was no significant difference between the background characteristics or severity of depression in the follow-up group as compared with the non-follow-up group.5

<table>
<thead>
<tr>
<th>TABLE 1 Description of Follow-up Patients</th>
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</thead>
<tbody>
<tr>
<td>All patients (n = 61)</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
</tr>
<tr>
<td>Race (% black)</td>
</tr>
<tr>
<td>Sex (% male)</td>
</tr>
<tr>
<td>Marital status (% married)</td>
</tr>
<tr>
<td>(% widowed)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>Class I–III</td>
</tr>
<tr>
<td>Class IV–V</td>
</tr>
<tr>
<td>Living situation (% living alone)</td>
</tr>
<tr>
<td>History of prior stroke(s)</td>
</tr>
</tbody>
</table>
The neurological diagnosis and findings from the follow-up group of 61 patients are shown in table 2.

In-Hospital Evaluation

Of the 61 patients seen at follow-up, 23 had a positive CT scan showing a left hemisphere lesion; of these, 17 had a single left hemisphere lesion, and 6 had either bilateral infarcts or more than one infarct of the left hemisphere. There were 17 patients who had CT scan evidence of right hemisphere infarction; 10 had a single right hemisphere lesion, 6 had bilateral lesions or multiple right hemisphere lesions. For the patients with single left hemisphere lesions the correlation coefficient between the distance of the lesion from the frontal pole and the severity of depression is shown in figure 1. The negative correlation indicates that the closer the lesion was to the left frontal pole the more severe the depression. This finding is a confirmation of previous findings in other groups of stroke patients.1,3,8 We also confirmed our previous findings that patients with left frontal brain injury were significantly more depressed than patients with lesions of any other location (table 3). The distance of the lesion from the left frontal pole did not correlate significantly with Mini-Mental, SFE or JHFI score (table 4). The lesion volume also did not correlate significantly with the Mini-Mental score and the activities of daily living (JHFI score) as measured by the JHFI score, the Social Functioning Exam score and the patient's age are shown in figures 2 and 3. During the acute hospitalization, the most severe impairments in functional physical activity or cognition were associated with the greatest severity of depression. In addition, patients with the poorest quality of social supports and younger patients tended to be more depressed than those with better social supports or older age. However, the strength of these associations with depression were less strong than the relationship to lesion location and were in good agreement with our previously reported findings.6

Three Month Follow-up

There were 9 patients with single left hemisphere lesions demonstrable on CT scan who were seen at 3 months post stroke. The distance of the lesion from the frontal pole continued to be significantly associated with severity of depression (fig. 1). The volume of lesion continued to be significantly associated with Mini-Mental but not with severity of depression (table 5). The lesion volume also continued to be significantly related to activities of daily living (JHFI score) as was the lesion location (table 5). Because there were not enough patients with right hemisphere lesions who were seen at 3 months follow-up, this data will be presented under the 6 month follow-up data.

The strength of the association between functional physical impairment as measured by the JHFI score and the severity of depression increased at 3 months post-stroke (fig. 2). However, the relationship between severity of depression and Mini-Mental score declined during this same period (fig. 2). The relationship between severity of depression and social functioning score and age both declined from significant levels of correlation during the acute post-stroke period to non-significant levels of correlation at 3 months follow-up (fig. 3).

In order to determine whether these trends of change

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**Table 2** Neurological Diagnosis and Findings in 61 Follow-up Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Left hemisphere (n = 28)</th>
<th>Right hemisphere (n = 14)</th>
<th>Bilateral (n = 3)</th>
<th>Brain stem (n = 14)</th>
<th>Subarachnoid (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic</td>
<td>23</td>
<td>13</td>
<td>3</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Examination findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis/monoparesis (moderate-severe)</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Touch-pain deficit (moderate-severe)</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Visual neglect</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aphasia</td>
<td>Broca's</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wernicke's</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td></td>
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</tbody>
</table>

Neurological diagnosis was made by CT scan analysis and/or clinical symptoms.
POST-STROKE MOOD DISORDERS/Robinson et al

DISTANCE FROM LEFT FRONTAL POLE and DEPRESSION SCORE

OJ  -100

-80  -60  -40  0  +40  +60  +80

2WKS  3MO  6MO

P <.001

P <.01

P <.001

FIGURE 1. The top graph shows the mean correlation coefficient between the distance of the lesion from the left frontal pole at the time of hospital evaluation and the depression severity from the three depression scales obtained in-hospital (N = 17) and from the same patients at 3 months (N = 9) and from patients with anterior lesions at 6 months (N = 9). All patients had CT scan evidence of a single left hemisphere lesion. There is no significant change in this relationship over the 6 month follow-up and all correlations are statistically significant. The bottom graph shows the correlation coefficient between the distance of the lesion from the right frontal pole at the time of hospital evaluation and the depression severity from the Hamilton depression scale obtained in-hospital (N = 10) and from the same patients at either 3 or 6 months follow-up. All patients had CT scan evidence of a single right hemisphere lesion. The correlation switched from positive to negative during this time. That is, greater depression was associated with posterior lesions in-hospital while greater depression was associated with anterior lesions at 6 months follow-up.

in the correlation between depression and other variables reflected slight differences in the composition of the follow-up groups seen at each interval, we looked at the relationship between depression and the other variables in the 29 patients who were seen both at 3 and 6 month follow-up. These patients confirmed the findings in the overall group. Specifically, the correlation coefficient between the Mini-Mental score and each of the depression scales had dropped from a mean value of -0.34 during the acute hospitalization to -0.18 at 3 months post-stroke. (Compare with values shown in fig. 2.) The mean correlation coefficient between JHFI score and the three depression measures was 0.38 during the acute stroke period and was 0.39 at 3 months post-stroke. The mean correlation coefficient for the three depression scales with social functioning had dropped from 0.27 during the acute post-stroke period to 0.31 at 3 months follow-up. (Compare with values shown in Figure 3.) Similarly, the correlation coefficient with age had dropped from 0.11 to 0.02 during the first 3 months of follow-up. Thus, our findings in the 29 patients seen at both 3 and 6 months was in close

DISTANCE FROM RIGHT FRONTAL POLE and DEPRESSION SCORE

MINI-MENTAL SCORE and DEPRESSION SCORE

JHFI SCORE and DEPRESSION SCORE

TIME POST-STROKE

TIME POST-STROKE

PEAPSON CORRELATION COEFFICIENT

PEAPSON CORRELATION COEFFICIENT

FIGURE 2. The top graph shows the mean correlation coefficient between Mini-Mental score and the three depression scales obtained in-hospital (N = 61) and from the same patients at 3 months follow-up (N = 40) and 6 months follow-up (N = 50). Between 3 and 6 months follow-up there was a change from a non-significant correlation to a highly significant correlation. This finding of a change from non-significant to significant correlation was also obtained when only the data from the 29 patients seen at both 3 and 6 months was analyzed. The lower graph shows the mean correlation coefficient between activities of daily living as measured by JHFI score and the three depression scales obtained in-hospital (N = 61) and from the same patients at 3 months (N = 40) and 6 months (N = 50) follow-up. Over the 6 months of follow-up there was a steadily increasing strength of association between JHFI score and severity of depression. The finding of an increasing strength of association between depression and function physical impairment was also obtained when only the data from the 29 patients seen at both 3 and 6 months was analyzed.
agreement with the findings in the overall group of 40 seen at this interval.

Six Month Follow-up

There were 15 patients with positive CT scans showing left hemisphere injury who were seen at 6 months post-stroke. The correlation between the distance of the lesion from frontal pole, measured during the acute hospitalization, and the depression score at 6 months is shown on figure 1. There continued to be a significant association between the distance of the lesion from the frontal pole and severity of depression but only for the patients with anterior lesions (N = 9) (table 5). Lesion volume continued to be significantly correlated with both Mini-Mental and JHFI score at 6 months follow-up (table 5).

There were 10 patients with single right hemisphere lesions demonstrable on CT scan who were followed-up at either 3 or 6 months post-stroke (8 at 6 months post-stroke and 2 at 3 months post-stroke). Although we found during the acute post-stroke period that patients whose lesions were farthest from the frontal pole were the most depressed, during the 3 to 6 month follow-up period we found that the direction of this correlation had reversed. The correlations, however, reached statistical significance only for the Hamilton scale, and when we looked at the individual data, there were two patients with right frontal lesions who had developed major depression during the first 6 months post-stroke. One of these two patients had the symptom of undue cheerfulness during the acute stroke period.7

Lesion location did not correlate significantly with social functioning, Mini-Mental scores or JHFI, but lesion volume did correlate significantly with activities of daily living score (JHFI) (table 5).

By 6 months post-stroke, the strength of the relationship between functional physical impairment as measured by JHFI score and depression score was approaching the strength of the relationship between lesion location and severity of depression (fig. 1 and 2). Thus, over the first 6 months follow-up, there was a continuous increase in the strength of the association between functional physical impairment and severity of depression. Between 3 and 6 months post-stroke, there was also an increase in the strength of the association between severity of depression and Mini-Mental score and even a larger increase in the relationship between depression and social functioning score (fig. 3). Age, on the other hand, continued to show no significant relationship to depression score at 6 months post-stroke.

Data from the 29 patients who were seen at both 3 and 6 months follow-up supported the findings in the overall group. Specifically, the mean correlation coefficient between the JHFI score and the three depression scales at 6 months post-stroke for the 29 patients had increased from .39 at 3 months follow-up to .63 at 6 months post-stroke. The mean correlation coefficient between Mini-Mental score and the three depression scales at 6 months post-stroke was .73.

<table>
<thead>
<tr>
<th>Table 3: Lesion Location From CT Scan Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Hemisphere</strong></td>
</tr>
<tr>
<td><strong>Anterior (n = 7)</strong></td>
</tr>
<tr>
<td><strong>PSE</strong></td>
</tr>
<tr>
<td><strong>Hamilton</strong></td>
</tr>
<tr>
<td><strong>Zung</strong></td>
</tr>
<tr>
<td><strong>Mini-mental†</strong></td>
</tr>
<tr>
<td><strong>JHFI</strong></td>
</tr>
</tbody>
</table>

*Significantly different than left anterior p < 0.05.
†Lower score indicates greater impairment.
††Higher score indicates greater impairment.
A lesion was "anterior" if its rostral border was anterior to 40% of the A-P distance and a lesion was "posterior" if its rostral border was posterior to 40% of the A-P distance. This anterior-posterior dichotomy has been described in previous publication.5, 8

<table>
<thead>
<tr>
<th>Table 4: Correlation Coefficients for In-hospital Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left hemisphere</strong></td>
</tr>
<tr>
<td>lesion volume (n = 17)</td>
</tr>
<tr>
<td><strong>PSE</strong></td>
</tr>
<tr>
<td><strong>Hamilton</strong></td>
</tr>
<tr>
<td><strong>Zung</strong></td>
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<tr>
<td><strong>Mini-Mental</strong></td>
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<tr>
<td><strong>JHFI</strong></td>
</tr>
<tr>
<td><strong>SFE</strong></td>
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</tbody>
</table>

NS = non-significant correlation p = 0.05.
†p = 0.05.
††p = 0.01.
scales had increased from $-0.18$ (NS) at 3 months to $-0.31$ at 6 months while the mean correlation between social functioning exam score and the three depression scales had increased from $0.09$ (NS) at 3 months to $0.45$ at 6 months follow-up. Age remained non-significantly correlated with depression ($r = -0.13$) at 6 months. Thus, the group of 29 patients seen at both 3 and 6 months post-stroke confirmed that the variable with the strongest association to severity of depression, besides lesion location, was functional physical impairment and that the strength of the relationship between social functioning and severity of depression dramatically increased between 3 and 6 months post-stroke.

**Discussion**

This study has demonstrated that during the first 6 months after cerebral infarction there are dynamic changes in the relationships between post-stroke mood disorders and lesion size, cognitive impairment, functional physical impairment, quality of social supports and age. We have continued to confirm our earlier findings that patients with left frontal lesions are the most depressed group and that over the entire 6 month follow-up the severity of depression continued to be strongly associated with the proximity of the lesion to the frontal pole. We also found a steadily strengthening association between depression and functional physical impairment. In addition, between 3 and 6 months post-stroke there was a significant increase in the correlation between quality of social supports and severity of depression.

This follow-up study was conducted in a predominantly lower socio-economic class, black population who were physically able to return to the hospital's outpatient clinic for a follow-up evaluation. Thus, the most severely impaired patients who required continued institutional care or who had died during the first 6 months were not included in this follow-up study. Any or all of these background and impairment factors may have influenced the results of this study and these findings may not be applicable to all groups of post-stroke patients. We did, however, try to include a consecutive series of stroke patients in the original study and the only patients excluded were those with significant comprehension deficits or decreased level of consciousness. We also obtained follow-up evaluations in almost 70% of the patients who survived past the first 6 months post-stroke.

Although there may be some limitations in the applicability of these results to the general stroke population, there were some interesting results worthy of discussion. The most significant overall finding was that the relationships between post-stroke depression and social functioning or severity of impairment seemed to be changing over the course of the first 6 months. These results emphasize the dynamic nature and probable multiple etiologies of post-stroke mood disorders and indicate that studies of post-stroke mood disorders need to take careful account of the time since brain injury.

Another interesting finding from this study was that the strength of the relationship between lesion location and severity of depression in left hemisphere lesion patients did not change over the first 6 months post-stroke while in patients with right hemisphere lesions, the direction of the correlation changed. Although this finding was primarily dependent on 2 patients developing depression and is therefore quite preliminary, this may be why some previous investigators using chronic stroke patients have not shown right-left differences in severity of depression.\(^{15,18}\) These findings suggest that there may be some dynamic changes occurring in the right frontal brain region over time and are consistent with the suggestion of other investigators that this brain region may play an important role in the regulation of mood.\(^{19,20}\)
It has been known for many years that frontal lesions produce abulia, unconcern and apathy. The question might be raised whether the stroke patients in this study with frontal lesions are simply examples of this syndrome. Although there appears to be some overlap between this "frontal emotional syndrome" and the finding in anterior stroke patients particularly those with right frontal lesions, the depression in left frontal patients includes more than this "frontal syndrome" with specific symptoms of early morning awakening, appetite disturbance with weight loss, hopelessness, loss of libido and suicidal thoughts.

We also found dynamic changes in the relationship between depression and other variables (ie, impairment, social ties and age). In trying to interpret the meaning of these changes it might be hypothesized that some patients are developing depressions based on the severity of their impairment, and the patients who are already depressed are remaining depressed. These findings, however, raise the issue as to what is cause and what is effect. For instance, it might be alternatively hypothesized that the strengthening in the association between depression and functional physical impairment at 6 months post-stroke was a result of the depression limiting the amount of physical recovery.

Although we cannot resolve this cause and effect issue at the present time with this kind of cross-sectional analysis, these data are consistent with the idea that post-stroke mood disorders do not have a single etiology but rather, patients with different locations of brain injury and perhaps at different post-stroke time points, may have different etiologies for their mood disorders. In subsequent studies we are hoping to address this issue of what is cause and effect by looking at whether depression at the time of initial hospitalization predicts the severity of impairment at 6 months follow-up or whether severity of impairment predicts in-hospital depression at 6 months follow-up.

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19. Ross ED, Rush AJ. Diagnosis and neuroanatomical correlates of...
The Value of Histopathological Examination of Surgically Removed Blood Clot in Determining the Etiology of Spontaneous Intracerebral Hemorrhage†

DAVID R. HINTON, M.D., EUGEN DOLAN, M.D., M.SC., ANDERS A. F. SIMA, M.D., PH.D.*

SUMMARY The surgical specimens from all evacuated spontaneous intracerebral and intracerebellar hemorrhages at the Toronto General Hospital from 1976 to 1981 were reviewed. Cases resulting from trauma or from pre-operatively diagnosed aneurysms or arteriovenous malformations were excluded, leaving 84 cases in which the etiology was unknown. Seventy-five of the cases were intracerebral hemorrhages, while 6 were intracerebellar and 3 were intraventricular. Brain tissue was received with the blood clot in 54 cases (64%). From this tissue, an anatomic diagnosis was made in 37 cases; and in 14, the specific etiology of the hemorrhage could be determined. The specific etiologic diagnoses were tumor (7), amyloid angiopathy (6) and abscess (1). In 4 other cases, vasculopathy associated with hypertension was suggested as a possible etiologic diagnosis.

The high incidence of a specific etiologic diagnosis made from specimens in which tissue was included (25%) suggests that biopsy of adjacent brain tissue or preservation of tissue fragments identified at the time of surgery is of diagnostic value.

HISTOLOGIC EXAMINATION of surgically removed blood clot from patients with intracerebral hemorrhage of uncertain etiology is not always performed and has been the subject of only a few reports. In a series of 112 operated cases, reported by Jel linger,1 61 angiomas, 12 tumors and 5 angiitides were found on histologic examination. The number of these cases in which the diagnosis was not known before surgery is not commented upon. In contrast, in a series published by Luyendijk,2 examination of the clot revealed an etiologic diagnosis in eight cases in which the diagnosis was not suspected clinically or at the time of surgery. Five of these cases were tumors while three were vascular malformations. With this information, we decided to review the anatomical features of all surgical specimens from cases of spontaneous intracerebral or intracerebellar hemorrhage of unknown etiology at the Toronto General Hospital from 1976–1981 in order to determine the value of this examination.

Materials and Methods

All cases diagnosed clinically as spontaneous intracerebral or intracerebellar hemorrhage who came to surgery from 1976–1981 were reviewed. Cases resulting from trauma, aneurysm or known arteriovenous malformation or tumor were excluded. This produced 84 cases for further analysis.

In all of these cases, the blood clot was received fixed in formalin. The amount of clot received varied from 1 cc to 100 cc (mean 9.4 cc). In many cases, only a portion of the ICH was submitted. The clot was filtered through gauze or filter paper and in all cases any tissue fragments found were submitted for histologic preparation. In seven cases clinically suspicious of tumor, biopsies of adjacent brain were taken, or tissue fragments found at surgery were preserved and submitted separately. In 55 of the 84 cases, the entire clot was processed for microscopic examination while in 29, representative areas were selected. Hematoxylin and eosin (H&E) stained tissue sections from these formalin fixed paraffin embedded clots and tissue fragments were examined retrospectively. Where blood vessels were identified, a Congo Red stain was performed and the section was examined under polarized light. Other special stains were completed in individual cases. The sites of the hematomas were identified according to the surgeon’s operative report.

Results

Eighty-four cases satisfied the review selection criteria and were included in the study. The vast majority of the hemorrhages (75/84) were intracerebral; 6 were intracerebellar and 3 were intraventricular. The lesions showed no side predilection, however, 13/20 parietal lobe lesions were situated in the right hemisphere. Of
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