MRI morphological and volumetric study of the cingulate gyrus and its relevance in partial epileptic patients

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Received December 9, 2002; Accepted April 25, 2003

ABSTRACT − The cingulate gyrus (CG) is often involved during partial epileptic seizures. The purpose of the study was to analyse the CG morphology and to measure the CG volume in epileptic patients, in order to detect subtle MRI abnormalities such as atrophy, which could be indicative of its implication in the epileptogenic area. The population consisted of 20 epileptic patients (31.2 ± 9.4 years) and 20 normal volunteers (31.8 ± 7.7 years). The epileptic patients underwent intracerebral recordings, and were sub-divided into five patients presenting with seizures involving the CG (CG 1), seven patients in whom the CG was only secondarily involved (CG 2) and eight patients in whom the CG was not involved at all (CG 3). All subjects were investigated by MRI (1.5 tesla Gyroscan Philips): axial T1w 3D Gradient Echo acquisitions, thickness 1.5 mm, reconstructions in all planes. At first, we described the sulcal limits of the CG, trying to define a “normalised CG”. In a second step, we segmented the CG intrasulcal grey matter using the “Surgiscope Scopeplan” (Elekta). We compared (Mann and Whitney U test [α=0.05]), the CG volumes of CG 1 to CG 2 + 3, and the volume of CG 1 and of CG 1 + 2 + 3 to that of normal volunteers. There was no significant difference between CG 1 and CG 2 + 3 (P = 0.89), between CG 1 and normal volunteers (P = 0.75) or between CG 1 + 2 + 3 and normal volunteers (P = 0.83). The volumetric analysis showed no atrophy of the CG in epileptic patients and did not distinguish the group in whom seizures involved the CG, from the other groups.

KEY WORDS: MR, central nervous system, epilepsy, cingulate gyrus

For more than a decade, MRI has proved to be an essential examination in presurgical management of patients with medically intractable partial seizures [1]. In almost 90% of the cases, it shows space-occupying lesions or morphological abnormalities, which can help to delineate the epileptogenic area [2]. In temporal lobe epilepsy, the most frequent form of drug resistant epilepsies (78% in the surgical series) [3], hippocampal sclerosis is present in 70% of the cases [3, 4], and seems to be a reliable marker of
the side, and even of the site of the epileptic discharges [1].

Since the cingulate gyrus is connected to several limbic structures through the Papez pathways [5-7], and since it can be involved in the propagation, or in the genesis of partial epileptic seizures [8, 9], it could be interesting to look for subtle MRI abnormalities in the cingulate gyrus, such as atrophy, which could be indicative of its implication in the epileptogenic area.

However, the cingulate gyrus is a complex anatomical structure, limited by several sulci or sulcus portions, with marked morphological variability, as shown by Ono et al. [10], explaining the difficulties in its delineation (figure 1).

The aims of this work were:

First to describe the sulcal limits of the cingulate gyrus, trying to define a “normalised cingulate gyrus”.

Secondly, by using these limits, to look for cingulate gyrus atrophy, using volumetric MRI analysis, in patients with involvement of the cingulate gyrus in the epileptogenic area, as shown by stereotactic intracerebral EEG (SEEG).

**Patients and methods**

**Patients**

MRI examinations were performed for 20 patients (9 females and 11 males, age: 31.2 ± 9.39 years), suffering from partial drug-resistant epilepsy, and for 20 healthy volunteers (10 females and 10 males, age: 31.8 ± 7.7 years).

In the epileptic group, two were left-handed and 18 were right-handed, and in the volunteer group, 10 were left-handed and 10 were right-handed, as assessed by the Edinburgh inventory. In the epileptic group, the Wada-test confirmed a left hemispheric dominance for language in the 18 right-handed patients, and a right hemispheric dominance in the two left-handed patients.

Epileptic patients were included based upon the following criteria:

- adults more than 18 years old;
- negative history of psychiatric disorders;
- no obvious cerebral morphological lesion in the cingulate gyrus or in the neighboring structures on MRI;
- cingulate gyrus recording with at least one intracingulate electrode, during the intracerebral electrode recording procedure;
- planned and accepted surgical treatment of their epilepsy.

They were divided into three groups according to the involvement of the cingulate gyrus in the genesis of seizures, as defined by intracerebral recordings:

- CG 1 comprised five patients whose seizures clearly involved the cingulate gyrus, and which was therefore considered as part of the epileptogenic zone, thus justifying its resection (none of the resected specimens showed any ‘specific’ histological changes inside the CG);
- CG 2 comprised seven patients in whom the cingulate gyrus was only part of the discharges spread (no surgical resection);
- CG 3 comprised eight patients whose cingulate gyrus was not involved at all.

Informed consent was obtained from the volunteers, who were included in the study on the following criteria:

- adults more than 18 years old;
- negative history of neurologic and/or psychiatric disorders;
- no evident abnormality in the cingulate gyrus or surrounding structures on the MRI.

**Neuroimaging**

All MR studies were performed at 1.5 T on a Gyroscan unit (Philips Medical Systems): axial T1w 3D Gradient Echo acquisitions, thickness: 1.5 mm, reformatting in all planes. The sulci (anterior paraolfactory sulcus, cingulate sulcus, and subparietal sulcus) were described on these MRI and the intrasulcal gray matter was segmented in a semi-automatic manner using the “Surgiscope Scopeplan” software by Elekta on a Hewlett-Packard workstation.

The limits were drawn manually in the frontal plane, cuts were apart and instant checking was available in the other planes simultaneously visualized. These measurements were performed on both cerebral hemispheres of the epileptic patients and normal volunteers.
The Scopeplan software starting from the presented limits, calculated the volume (cc) of the cingulate gyrus.

Morphological study

The anterior limit of the cingulate gyrus is formed by the anterior paraolfactory sulcus and the lamina terminalis, the superior limit by the cingulate sulcus, then the subparietal sulcus and more posteriorly by the anterior part of the antecalcarine sulcus, the inferior margin by the callosal sulcus, and the posterior border by the isthmus of the cingulate gyrus (figure 1). We studied the major sulci that showed, in agreement with Ono’s description [10], important morphological variations, namely the cingulate sulcus, the subparietal sulcus and the anterior paraolfactory sulcus.

For the cingulate sulcus the following features were noted:
– the position of its anterior end, according to Ono’s classification [10] (figure 2);
– its connection with the superior rostral sulcus;
– the presence of interruptions, defined as a rupture of the continuity of the sulcus, visible on all MRI planes (figure 3);
– double parallel patterns, defined as a division of the cingulate sulcus in 2 parallel subsulci, not connected with each other (figure 3);
– The presence of an intracingulate sulcus, defined as a sulcus starting at the anterior part of the corpus callosum and joining the middle part of the cingulate sulcus (figure 3).

For the subparietal sulcus (figure 4): according to Ono’s classification [10], it was postulated that the subparietal sulcus has, most of the time, an H-pattern, defined by a horizontal sulcus prolonging posteriorly the cingulate sulcus, and two upwardly-oriented side-branches, and two downwardly-oriented side-branches. The following features were noted:
– the number of side branches;
– the connection with the posterior end of the cingulate sulcus and the route of connection;
– double parallel patterns;
– atypical patterns.

For the anterior paraolfactory sulcus, the following features were studied:
– whether or not it was distinguishable;
– the connection of the anterior paraolfactory sulcus with the cingulate sulcus.

These analyses were performed blind on both cerebral hemispheres of each patient, by two independent observers (SK, MB).

Statistical analysis was performed using the Chi square test or Fisher exact test, a P value of 0.05 was regarded as significant.

Figure 2. Position of the anterior end of the cingulate sulcus (Ono): a: sub-callosal; b: supra-orbitary; c: prefrontal.

Figure 3. Examples of anatomical variations of the cingulate sulcus: a: single cingulate sulcus; b: double parallel pattern; c: single cingulate sulcus with one interruption; d: double parallel pattern with one interruption of the external sulcus; e: intracingulate sulcus.

Figure 4. Examples of anatomical variations of the subparietal sulcus: a: H pattern, connected through the antero-inferior side-branch with the cingulate sulcus; b: subparietal sulcus with single upwardly directed side-branch, not connected with the cingulate sulcus; c: double parallel pattern; d: atypical pattern.
significant. Due to the small number of patients in sub-
groups, the different subgroups were compared as follows:
epileptic hemispheres of CG 1 (patients who presented
seizures which involved the cingulate gyrus) with those of
CG 2 + 3 (patients in whom the cingulate gyrus was only
part of the discharges spreading or was not involved at all),
CG 1 with volunteers, CG 1 + 2 + 3 with volunteers, for
the presence of the different anatomical variations.
Inter-rater reliability was evaluated by the kappa index.

Volumetric analysis

The cingulate gyrus was measured after segmentation of
the cortical grey matter, following the different sulci as
anatomical limits defined above.

These analyses (figure 5) were performed blind on both
cerebral hemispheres of each patient, by two independent
observers (SK, MB), each one unaware of the results of the
other observer.

Statistical analysis was performed using the Mann and
Whitney U-test. The average volume of the cingulate gyrus
was compared in the different subgroups (epileptic hemi-
spheres of CG 1 (patients who presented seizures which
involved the cingulate gyrus), with CG 2 + 3 (patients in whom
the cingulate gyrus was only part of the discharges spreading or was not involved at all), CG 1 with volun-
tees, CG 1 + 2 + 3 with volunteers).

Results

Morphological study

1) Inter-rater reliability

The inter-rater reliability was excellent, with a kappa index
superior to 0.9 in all cases.

2) Statistical analysis

There was no significant statistical difference between the
different subgroups, with the exception of the double
parallel pattern that showed significantly more interrup-
tions of the external portion in the volunteer group, than in
the group CG 1 + 2 + 3 ($P = 0.019$, Chi square test). Nevertheless, these results allowed us to pool the
80 hemispheres, for the description of the sulcal variabil-
ity.

3) Description of the sulcal variations (table 1-3) (figure
6 and 7)

Volumetric study

1) Inter-rater reliability

The inter-rater reliability was excellent, with an intraclass
correlation coefficient rho = 0.92 in the volunteer group
and rho = 0.93 in the epileptic group.

2) Statistical analysis

No statistically significant difference was found between
the mean volume in CG 1 (12.58 ± 2.84) and CG 2 + 3
(12.56 ± 2.57) ($P = 0.89$), between the mean volume in
CG 1 and the volunteer group (12.56 ± 2.56) ($P = 0.75$),
or between the mean volume in CG 1 + 2 + 3
(12.46 ± 1.94) and the volunteer group ($P = 0.83$).

Table 1. Cingulate sulcus: morphological description.

<table>
<thead>
<tr>
<th>Cingulate sulcus</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position anterior end: a</td>
<td>68</td>
<td>85</td>
</tr>
<tr>
<td>Position anterior end: b</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Position anterior end: c</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Double parallel pattern</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>Single sulcus pattern</td>
<td>47</td>
<td>59</td>
</tr>
<tr>
<td>No interruption (single sulcus pattern)</td>
<td>29</td>
<td>62</td>
</tr>
<tr>
<td>One interruption</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Two interruptions</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>No interruption internal sulcus (double parallel pattern)</td>
<td>31</td>
<td>94</td>
</tr>
<tr>
<td>One interruption</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>No interruption external sulcus (double parallel pattern)</td>
<td>19</td>
<td>58</td>
</tr>
<tr>
<td>One interruption</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Intracingulate sulcus</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Cingulate sulcus-superior rostral sulcus connection</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>
The volumetry of the cingulate gyrus does not distinguish the different subgroups from each other.

**Discussion**

**Description of the sulcal variability**

In the double-parallel pattern of the cingulate sulcus, there were significantly more interruptions of the external portion in the volunteer group, than in the group CG 1 + 2 + 3 ($P = 0.019$, Chi square test), but there is no pathophysi-

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**Table 2. Subparietal sulcus: morphological description.**

<table>
<thead>
<tr>
<th>Subparietal sulcus</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingulate sulcus-subparietal sulcus connection</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>Route of connection antero-inferior sidebranch</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>Ant &gt;-MR</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Horizontal branch of the H-MR</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Double parallel pattern</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Single sulcus</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>Atypical</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Upwardly oriented sidebranches 1</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Two</td>
<td>57</td>
<td>71</td>
</tr>
<tr>
<td>Three</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Atypical</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Downwardly oriented sidebranches 1</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Two</td>
<td>62</td>
<td>77</td>
</tr>
<tr>
<td>Three</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Atypical</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>H pattern</td>
<td>46</td>
<td>57</td>
</tr>
</tbody>
</table>

**Table 3. Anterior paraolfactory sulcus: morphological description.**

<table>
<thead>
<tr>
<th>Anterior paraolfactory sulcus</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior paraolfactory sulcus distinguishable</td>
<td>56</td>
<td>70</td>
</tr>
<tr>
<td>Anterior paraolfactory sulcus not distinguishable</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Connection anterior paraolfactory sulcus-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cingulate sulcus</td>
<td>34</td>
<td>61</td>
</tr>
</tbody>
</table>

The volumetry of the cingulate gyrus does not distinguish the different subgroups from each other.
The cingulate gyrus is a complex anatomical structure. It presents great sulcal variability, and in some portions no sulcal limit is found, for example at the isthmus of the cingulate gyrus, or in the case of an interruption in a sulcus or between two sulci. The definition of a “normalised cingulate gyrus”, based only on sulcal limits is not possible, and it is necessary to define arbitrary limits, based on previous studies [13-15].

There were difficulties also in the double parallel pattern of the cingulate sulcus in defining the cingulate gyrus limits. Whether the area 32 of Broadmann, situated between the two branches of the cingulate sulcus, belongs to the cingulate cortex remains a questionable issue. Pandya, Room and Albanese [13, 16, 17] consider, on studies based on the area 32 connections, that it does not belong to the anterior cingulate gyrus cortex, but to the prefrontal cortex. Talairach and Vogt [15, 18, 19] consider, based on cytoarchitectonic studies, that it represents a transitional fronto-limbic cortex, though belonging to the cingulate gyrus. This study is in agreement with these last authors, and we considers the external branch of the cingulate sulcus as the superior limit of the cingulate gyrus.

Moreover, the marginal ramus and the secondary, upwardly vertical branches of the cingulate sulcus and of the subparietal sulcus were excluded from the delimitation of the cingulate gyrus. Actually, the marginal ramus penetrates the parietal lobe and does not contain cingulate cortex. The same reasons apply to the secondary branches, penetrating the parietal lobe or the frontal lobe. The last limitation to this study, was the number of patients showing implication of the cingulate gyrus in the genesis of the epileptic seizures. Only 5 patients justifying the resection of the cingulate gyrus, were included in the study, and it is statistically difficult to show small losses of volume in the cingulate gyrus.

**Volumetry of the cingulate gyrus in the epileptic patient**

There was no difference in cingulate gyrus volume between the different subgroups of patients and the healthy volunteers. The volumetry of the cingulate gyrus did not allow us to distinguish the group in whom the cingulate gyrus is involved in the genesis of the seizures, from the other groups. There was no atrophy of the cingulate gyrus in the epileptic group, unlike the hippocampal sclerosis, which is found in 72% of the epilepsies involving the temporal lobe [3].

Different hypotheses have been proposed to explain the appearance of hippocampal sclerosis, but the most frequently cited is a past history of convulsions, which could have been due to fever or to a temporal malformative lesion [3, 4, 20].

Moreover, it has been demonstrated that epileptic seizures induced by kindling, produced hippocampal lesions, and
that hippocampal neurons are particularly vulnerable to repeated seizures, compared to other neuronal populations, which, when submitted to the same treatment did not demonstrate any degeneration [20, 21]. This leads to the hypothesis that cingulate neurons are less vulnerable to repeated seizures than the hippocampic neurons. The fact that repeated seizures induce atrophy seems to be a specific property of hippocampal neurons, and of structures directly connected to the hippocampus, such as the fornix, the mamillary bodies and the entorhinal cortex [1, 22-26]. □

References