Volume reduction in the caudate nucleus following stereotactic placement of lesions in the anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study


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Object. The goal of this study was to test hypotheses regarding changes in volume in subcortical structures following anterior cingulotomy.

Methods. Morphometric magnetic resonance (MR) imaging methods were used to assess volume reductions in subcortical regions following anterior cingulate lesioning in nine patients. Magnetic resonance imaging data obtained before and 9 ± 6 months following anterior cingulotomy were subjected to segmentation and subcortical parcellation.

Significant volume reductions were predicted and found bilaterally within the caudate nucleus, but not in the amygdala, thalamus, lenticular nuclei, or hippocampus. Subcortical parcellation revealed that the volume reduction in the caudate nucleus was principally referable to the body, rather than the head. Furthermore, the magnitude of volume reduction in the caudate body was significantly correlated with total lesion volume.

Conclusions. Taken together, these findings implicate significant connectivity between a region of anterior cingulate cortex (ACC) lesioned during cingulotomy and the caudate body. This unique data set complements published findings in nonhuman primates, and advances our knowledge regarding patterns of cortical–subcortical connectivity involving the ACC in humans. Moreover, these findings indicate changes distant from the site of anterior cingulotomy lesions that may play a role in the clinical response to this neurosurgical procedure.

Key Words • cingulotomy • segmentation • parcellation • caudate nucleus • amygdala • thalamus

The ACC is a constituent of the paralimbic belt and is divisible into multiple subterritories based on distinct patterns of connectivity with other brain regions as well as on distinct functions. Much of what is known about human anterior cingulate anatomy and function has been gleaned from neuroimaging, intraoperative, and postmortem studies, or extrapolated from experiments in animals. In particular, human models of connectivity between the ACC and subcortical regions have largely been formulated on the basis of data obtained in nonhuman primates. For instance, studies of lesions in the ACC in nonhuman primates have led investigators to infer dense projections from the ACC to the caudate nucleus and nucleus accumbens septi, as well as reciprocal connections with the amygdala and thalamus (specifically the anterior and dorsomedial nuclei). Such findings are also consistent with results from animal studies in which electrophysiological and tract tracing methods have been used.

Although the cytoarchitectonics of the ACC have been well studied in human postmortem specimens, studies of human lesions are problematic because naturally occurring lesions are far less reproducible and less well circumscribed than is optimal for determining connectivity. However, clinical data obtained in psychiatric patients who have undergone bilateral stereotactic anterior cingulotomy (as a therapeutic intervention) provide a unique opportunity to investigate the distribution of projections from the lesioned territory of the ACC.

In the current study, we used morphometric MR imaging methods to measure regional brain volumes before and after anterior cingulotomy in humans, as a means for...
testing specific hypotheses regarding cortical–subcortical connectivity. Consistent with the basis for conventional lesion experiments, our premise was that lesions placed within the ACC would be associated with detectable volume reductions within subcortical regions that have dense communication with the area directly damaged by the lesion. This represents a special class of information about the human ACC that has been obtained ethically, while being of a higher experimental quality than would be possible from naturally occurring lesions. Thus, such data obtained in functional neurosurgical cases promise to provide potentially important information about normal human anatomy, as well as the consequences of the surgical procedure in question.

Materials and Methods

Clinical Material

This study was conducted with the approval of the Subcommittee on Human Studies of the MGH. Clinical data, including patient demographics, diagnostic information, and MR images, were obtained retrospectively from the hospital records of nine patients (five male and four female) who had undergone bilateral stereotactic anterior cingulotomies at MGH between 1990 and 1997 for severe, treatment-refractory OCD. It is noteworthy that approximately 40% of patients who undergo anterior cingulotomy at MGH return for a second surgical procedure; consequently, a series of patients has accrued for which initial preoperative and approximately 9-month postoperative data (that is, data obtained immediately before the second operation) are available. In this cohort, the mean (±SD) age at first cingulotomy was 35 ± 16 years, and the interval between preoperative and postoperative MR imaging was 9 ± 6 months (range 4–23 months). All patients suffered from comorbid MDD, were receiving a variety of psychotropic medications, and were otherwise without major neurological disorders. In particular, all patients were free of histories of significant head trauma, stroke, or other known organic brain lesions. It is critical to appreciate that this select cohort, who returned for a second operation, is skewed with respect to outcome after the first cingulotomy. Specifically, whereas approximately 30% of patients who undergo cingulotomy for OCD ultimately meet the clinical criteria of responding to treatment (for example, a 35% reduction in Yale–Brown Obsessive Compulsive Scale scores), none of the patients in our cohort met such criteria at the time of their return for a second operation. Therefore, analyses pertaining to predictors of treatment response were not indicated.

Neurosurgical Lesions

The procedure for bilateral stereotactic anterior cingulotomy has been described in detail previously. Briefly, a pair of burr holes (1.2 cm in diameter) are made bilaterally 9.5 cm posterior to the nasion and 1.5 cm lateral to the midline. Electrically insulated thermistor electrodes are positioned stereotactically by using MR imaging guidance. The initial targets are located 0.7 cm lateral to the midline, 2 cm posterior to the most anterior aspect of each frontal horn, and 1 mm above the roof of the ventricles. Lesions are created by heating the uninsulated tip of the electrode (1 cm in length) to 80 to 85°C for 100 seconds by using radiofrequency current. The electrode is then moved 1 cm and another lesion is made immediately dorsal to the first. Following this, the procedure is repeated on the contralateral side. Thus, this operation is intended to produce lesions of approximately 1 × 1 × 2 cm within the ACC of each hemisphere (that is, a total lesion volume of approximately 4 cm³; Figs. 1 and 2).

Morphometric MR Imaging Acquisition. The clinical MR imaging data that were subjected to morphometric analysis had been obtained between 1990 and 1997 by using a 1.5-tesla MR magnet (General Electric Medical Systems, Milwaukee, WI). The acquisition protocol entailed obtaining routine sagittal scout images, followed by a three-dimensional T₁-weighted spoiled gradient-echo sequence (TR 50 msec, TE 9 msec, flip angle 50°, field of view 24 cm, matrix 256 × 256, average 1) to obtain contiguous 3-mm-thick coronal slices covering the entire brain.

Morphometry. The MR imaging data were harvested from patient hospital records retrospectively and assigned random identification numbers so that the investigators performing the segmentations were blind to any correspondence between images and patients. The investigators performing the segmentations and parcellations were also blind to the a priori hypotheses of the study.

Following image acquisition, the images underwent positional normalization, general anatomical segmentation, cortical parcellation, and subcortical gray matter parcellation. These procedures are summarized briefly here. Positional normalization entails the reformatting of the original coronal volumetric image dataset, so that the interhemispheric fissure is within the sagittal plane and the anterior commissure–posterior commissure line is perpendicular to the coronal plane. General anatomical segmentation involves identifying the boundaries of the principal gray and white matter structures of the cerebral cortex based on the natural gray or white matter boundaries, as distinguished by differential signal intensities in the T₁-weighted images. These demarcations are made in a semiautomated fashion guided by landmark conventions and signal-intensity histograms. Subdivision of the cortical ribbon into gyrus-based subdivisions (cortical parcellation) follows the scheme originally developed by Caviness and associates. This procedure results in the identification of 48 parcellation units per hemisphere, and involves: 1) identification of a set of 42 anatomical landmarks, which delimit the anterior and posterior boundaries; and 2) identification of the idealized courses of 31 prominent fissures, which provides the medial–lateral boundaries of the cortical regions. The subcortical gray matter structures are also subdivided based on topographic criteria. Specifically, the genu of the internal capsule subdivides the caudate nucleus, putamen, and pallidum into anterior and posterior subdivisions. For the caudate nucleus, the anterior and posterior subdivisions correspond predominantly to the head and body of the caudate nucleus, respectively.
For the purposes of this study, segmentation of the lesion was based on anomalous T1-weighted signal characteristics. The signal anomalies consisted of both hyperintense and hypointense regions (Figs. 1 and 2).

Hypotheses and Statistical Analysis

We hypothesized that comparisons between the preoperative and postoperative MR imaging data would show volume reductions in specific subcortical regions that normally share dense connections with the territory within the ACC that is lesioned during cingulotomy. Given the reported efficacy of this procedure as a treatment for OCD and MDD, we also considered the purported role of subcortical regions in contemporary neurobiological models of these diseases. A priori, we sought to test for volume reductions in the caudate nucleus, amygdala, and thalamus. In addition to anatomical data indicating substantial projections from the ACC to all of these nuclei, each of them has been implicated in the pathophysiology of both OCD and MDD.9,10,12,26,33 Statistical analyses were performed hierarchically by using a significance threshold of 0.05 (uncorrected for multiple comparisons). Because our hypotheses were unidirectional, we used one-tailed tests.

First, using paired t-tests, we performed six comparisons, one for each structure on the right side and each structure on the left side. Given that the lesions were made bilaterally, we reasoned that bilateral findings of significant volume reductions within a given region of interest would represent a kind of internal replication. Further, we tested for comparable volume reductions in several other segmented control regions (the putamen, hippocampus, and globus pallidus) to assess the specificity of any significant reductions predicted a priori. Also, we checked for significant differences in total cerebral volume as well as the total volume of the lateral ventricles.

Second, we planned to use subcortical parcellation methods to accomplish a more refined assessment of subterritories comprising the caudate nucleus (head and body) and the thalamus (anterior subdivision and dorsomedial subdivision), both to protect against a type II error (that is, false-negative findings) and to characterize more precisely the source(s) of volume reduction within these areas, if present. The power of this approach would be underscored, in the event that the results of this subcortical parcellation analysis yielded findings of bilateral volume reductions that were of greater statistical significance than those found when measuring the entire caudate nucleus or the entire thalamus.

Third, we planned to perform Pearson’s product-moment correlations between total lesion volumes and reduction in regional volume corresponding to those regions of interest (if any) exhibiting significant volume changes. A significant correlation of this kind would provide further evidence linking the reduction in volume to the lesions created during cingulotomy. Volume measurements are expressed as the means ± SD.

Results

Lesion Characterization

The mean total lesion volume for the cohort was 3.58 ± 1.24 cm³ (range 1.97–5.83 cm³). Figure 2 illustrates the le-
sion distribution for the group, in the form of a spatially normalized map.  

Results of Segmentation Analysis

The comparison of preoperative and postoperative volumes corresponding to the six regions of interest yielded significant differences for the right \( (t(8) = -2.27, p = 0.03) \) and left caudate nuclei \( (t(8) = -2.33, p = 0.02) \), but not for either the thalamus or amygdala (all \( p > 0.1 \); Table 1). Of note, there was no significant difference in total cerebral volume (volume within the boundaries of cerebral exterior), nor were any of the designated control regions found to exhibit significant volume reductions (all \( p > 0.1 \)). Thus, volume reduction in the caudate nucleus was bilateral and specific. A corresponding significant volume increase was found in the lateral ventricles.

Results of Subcortical Parcellation Analysis

A refined morphometric parcellation of the caudate nucleus was performed to determine whether the differences observed using segmentation could be further isolated to a particular subdivision (that is, the caudate head or caudate body; Fig. 3). Conversely, the finding of no significant difference within the thalamus was further investigated to determine whether a more refined parcellation of the anterior and dorsomedial subdivisions would reveal significant differences. Certainly, it is plausible that a more circumscribed change in volume could be obscured by an analysis of total thalamic volume. Analysis of subcortical parcellation data indicated a significant volume reduction in the caudate body bilaterally (right side: \( t(8) = -2.71, p = 0.007 \); left side: \( t(8) = -3.4, p = 0.003 \)), with no significant reduction in caudate head volume (both \( p > 0.1 \)). Subcortical parcellation of the thalamus did not reveal significant volume reductions in the anterior or dorsomedial subdivisions (all \( p > 0.1 \)).

Results of Correlation Analysis

Pearson’s product-moment correlation analysis was performed to test for an association between total lesion volume and the magnitude of reduction in caudate body volume. This analysis yielded a statistically significant correlation \( r(7) = 0.64, p = 0.03; \) Fig. 4).
Discussion

Morphometric analysis of MR imaging data obtained in patients before and after anterior cingulotomy revealed a significant volume reduction within the caudate nucleus that was present bilaterally and was specifically referrable to a reduction in the caudate body rather than in the caudate head. None of the other predicted subcortical regions exhibited significant volume reductions, nor did any of the control regions. Moreover, the magnitude of the volume reduction in the caudate body was significantly correlated with total lesion volume. Taken together, these data provide compelling evidence for dense projections from the site of the anterior cingulotomy lesions to the body of the caudate nucleus in humans.

Several investigators have previously sought to characterize in humans the connectivity between the ACC and the striatum, principally based on extrapolation from data obtained in nonhuman primates. Whereas Alexander and colleagues emphasized projections to the ventral striatum (that is, nucleus accumbens septi) and Yeterian and Van Hoesen highlighted projections to the head of the caudate nucleus, Kemp and Powell depicted termination fields extending into the caudate body. Here, it is noteworthy that these apparent discrepancies likely reflect subtle differences in the subterritories of the ACC that were targeted. Whereas Yeterian and Van Hoesen targeted BA 24, Kemp and Powell targeted a region that included BA 24 but extended posteriorly into BA 23. Thus, although the current results should not by any means be taken as evidence against connectivity between the ACC and other striatal zones, these findings are most consistent with the previous characterization given by Kemp and Powell in nonhuman primates. In humans as well, a dorsal region of the ACC, at the margin of BA 24 and 23, appears to possess dense connections with the body of the caudate nucleus.

Of course, these results are only reflective of connections with the subterritory of the ACC that was lesioned. Given that this area approximately corresponds to the more dorsal cognitive–motor division of the ACC, it is quite plausible that other cingulate subdivisions (for example, the pregenual affective division or the ventral visceromotor division) project to other subcortical targets, including other striatal regions and/or the amygdala. The lesion method for investigating connectivity is presumed to emphasize direct projections, whereas indirect connections (that is, circuitry with multiple intervening synapses, or greater synaptic distance) are unlikely to produce detectable changes in volume. Likewise, lesion sites characterized by diffusely divergent projections, and distant territories that receive densely convergent projections from many other areas, may be less likely to exhibit substantial volume changes in such studies. These issues may be particularly germane, given the sensitivity limits of the imaging procedures used in our study. Therefore, although we can infer that substantial direct projections exist between the area of the cingulotomy lesion and the caudate body, these data should not be taken as evidence against connectivity with other subcortical regions.

There are several important additional limitations to this study. In the absence of a control group, we cannot entirely rule out the possibility that the observed volume reductions were due to passage of time, medication effects, or nonspecific aspects of surgical intervention other than the ACC lesions. However, it seems highly unlikely that such anatomically specific changes would occur over such a short time frame, and that they would correlate with lesion volume as a matter of coincidence. For instance, although antipsychotic medications have been shown to cause reversible changes in volume, they have not been shown to produce such changes selectively within the body of the caudate nucleus. In this study, few of the patients were receiving antipsychotic medications, and there was no systematic change in dose over time that could explain the observed volumetric effects. It is worth noting that the observed preoperative caudate volumes in this patient group are comparable (that is, within 0.33 SD) to previously published values, derived using the same methods at the MGH Center for Morphometric Analysis, from a cohort of psychiatrically healthy volunteers of similar age and sex composition.

We also cannot entirely rule out the possibility that the volume changes observed in the caudate nucleus were due to destruction of white matter (that is, fibers of passage originating outside the territory of the lesion) rather than the gray matter at the site of the lesion. In fact, for all nine patients, the lesioned territory included the cingulum bundle and associated white matter tracts. Although these tracts principally convey cortical–cortical and cortical–thalamic fibers, damage to cortical–stria tial projections cannot be ruled out. Similarly, for seven of the patients, the cingulotomy lesions extended beyond the margin of the corpus callosum; this part of the corpus callosum is likewise not believed to carry a substantial burden of fibers that project to the striatum. On the other hand, although the subcallosal fasciculus is purported to convey a preponderance of projections from the cortex to the striatum, only in one patient did a lesion impinge on this white matter bundle. Thus, it seems unlikely that our findings in the caudate nucleus are primarily referrable to destruction of white matter or fibers of passage at the site of the lesions.

Although we have interpreted these findings in terms of...
their implications for understanding normal human neuroanatomy, it must be recognized that these patients all suffered from psychiatric disorders that are purportedly characterized by abnormal ACC anatomy and/or function. Therefore, we cannot rule out the possibility that the apparent connectivity observed here is abnormal. Finally, the modest number of patients and the intrinsic limitations of the morphometric methods used leave open the possibility of either type I or type II errors (that is, false-positive or -negative results). Thus, as always, replication is warranted.

Beyond the apparent implications for cortical–subcortical connectivity, it would be of tremendous clinical importance to determine whether changes in volume distant from the site of cingulotomy lesions predict treatment response. Given that this cohort of patients were all nonresponders to the initial cingulotomy, no meaningful conclusions can be drawn from the current findings in this regard. However, we submit that the current findings provide a strong case to support performing analogous prospective investigations of consecutive cases, so that correlates of treatment response might be identified. Recently, structural MR imaging correlates of treatment response have been reported for capsulotomy—a different neurosurgical treatment for OCD. Such information promises a potential means to refine surgical interventions for psychiatric diseases, enhancing their efficacy and/or adverse effect profiles.

Conclusions

It can be inferred from the results of the current study that there is dense connectivity between a defined territory lesioned during cingulotomy and the body of the caudate nucleus in humans. Subsequent research in this domain will help to determine the reproducibility of these findings, and may help to refine neurological procedures performed to treat psychiatric diseases. Analogous investigations should also be conducted to examine patterns of cortical–cortical connectivity involving this region of the ACC in humans. Finally, new neuroimaging-based methods are evolving for investigating the connectivity within the human brain, and such emerging strategies will undoubtedly complement classic modes of inquiry to further advance this field.

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