A Magnetic Resonance Imaging Study of Regional Cortical Volumes Following Stereotactic Anterior Cingulotomy
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ABSTRACT

The purpose of this study was to test the hypothesis that orbitofrontal cortical volume would be reduced following anterior cingulotomy for obsessive-compulsive disorder (OCD). Whole brain cortical parcellation was performed on magnetic resonance imaging (MRI) data from nine patients, before and 9 (±6) months following anterior cingulotomy. No significant volumetric reductions were found in the orbitofrontal cortex. Exploratory findings of reduced volume in ventral temporofusiform and posterior cingulate regions were consistent with chance differences, in the face of multiple comparisons. Therefore, though the circumscribed lesions of anterior cingulotomy have recently been associated with corresponding volumetric reductions in the caudate nucleus, no comparable volumetric reductions are evident in cortical territories. Taken together, these results are most consistent with a model of cingulo-striatal perturbation as a putative mechanism for the efficacy of this procedure. While limitations in sensitivity may have also contributed to these negative findings, the methods employed have previously proven sufficient to detect cortical volumetric abnormalities in OCD. The current results may reflect a relatively diffuse pattern of cortico-cortical connections involving the neurons at the site of cingulotomy lesions. Future functional neuroimaging studies are warranted to assess possible cortical or subcortical metabolic changes associated with anterior cingulotomy, as well as predictors of treatment response.

Introduction

Bilateral stereotactic anterior cingulotomy is a procedure that is currently performed in cases of severe and otherwise treatment-refractory obsessive-compulsive disorder (OCD) or major depressive disorder.1 Though research in this area has suggested modest efficacy and relative safety,2-6 little is known about the mechanism by which this or other neurosurgical procedures for psychiatric indications have their beneficial or adverse effects. In particular, there is a relative dearth of literature pertaining to the structural and functional neuroanatomical consequences of contemporary neurosurgical treatments for psychiatric diseases.

Recently, we assessed subcortical changes in brain volume associated with anterior cingulotomy, by conducting a morphometric magnetic resonance imaging (MRI) examination of pre-operative and post-operative data from nine patients who had undergone neurosurgical treatment for OCD at Massachusetts General Hospital (MGH).7 Consistent with a prior hypotheses, we found bilateral reduction in caudate volume post-operatively, the magnitude of which was correlated with cingulotomy lesion volume. In the current study, we sought to extend those findings by performing an analogous assessment of change in regional cortical volumes using cortical parcellation methods8,9 applied to the same MRI data sets.
We reasoned that regions that share dense connections with the site of the anterior cingulotomy would be most likely to exhibit reductions in volume post-operatively.\(^7,10\) Among cortical regions, the orbitofrontal cortex is purported to share such dense connections with the anterior cingulate.\(^11-14\) Moreover, the orbitofrontal cortex is principally implicated in the pathophysiology of OCD,\(^15,16\) and successful treatment of OCD is associated with metabolic reductions within the orbitofrontal cortex.\(^17,18\) Therefore, we predicted that, in comparison with pre-operative MRI, post-operative MRI would show significant volume reductions within the orbitofrontal cortex.

**Materials and Methods**

**Clinical Material**

This study was conducted with the approval of the Subcommittee on Human Studies of MGH. Clinical data including demographics, diagnostic information, and brain MRI were obtained retrospectively from the hospital records of nine patients (five male, four female) who received bilateral stereotactic anterior cingulotomies at MGH between 1990 and 1997 for the indication of severe, treatment-refractory OCD. Of note, approximately 40% of patients who receive anterior cingulotomy at MGH return for a second surgical procedure\(^2,3\); consequently, a series of patients has accrued for which initial pre-operative and ~9-month post-operative data (ie, obtained immediately prior to the second operation) are available. For this cohort, mean (±SD) age at first cingulotomy was 35 (±16) years, and time between pre-operative and post-operative MRI was 9 (±6; range 4—23) months. All patients had comorbid major depression, were on a variety of psychotropic medications, and were otherwise without major neurological disorders. In particular, all of these 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 first cingulotomy. Specifically, whereas ~30% of patients who undergo cingulotomy for OCD ultimately meet clinical criteria as "responders" (eg, a 35% reduction in Yale-Brown Obsessive-Compulsive Scale scores\(^2,19\)), none of the patients in this cohort met such criteria at the time of their return for a second operation.

**Neurosurgical Lesions**

The procedure for bilateral stereotactic anterior cingulotomy has been described in detail previously.\(^1,20\) 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 with MRI 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 (1 cm in length) to 80—85°C for 100 seconds by radiofrequency current. The electrode is then withdrawn 1 cm and another lesion is made immediately dorsal to the first. The procedure is then repeated on the contralateral side. Thus, this operation is intended to produce lesions of approximately 1x1x2 cm within the anterior cingulate cortex of each hemisphere (ie, total lesion volume =~4 cc).\(^7\)

**MRI Acquisition and Morphometry**

The clinical MRI data that were subjected to morphometric analysis had been obtained between 1990 and 1997 with a 1.5 Tesla MR scanner (General Electric, Milwaukee, Wisconsin). The acquisition protocol entailed routine sagittal scout scans, 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=256x256, averages=1) to obtain contiguous coronal slices (3 mm thick) covering the entire brain.

MRI data were harvested retrospectively and assigned random identification numbers so that the investigators performing the segmentations and parcellations could remain blind to any correspondence between images and subjects. The investigators performing the segmentations and parcellations were also blind to our a priori hypotheses.

Following image acquisition, the images underwent positional normalization, general anatomic segmentation, cortical parcellation, and subcortical gray matter parcellation. These procedures are summarized briefly here. Positional normalization entails the reformating of the original coronal volumetric image dataset so that the interhemispheric fissure is within the sagittal plane and the anterior commissure-posterior commissure (AC-PC) line is perpendicular to the coronal plane.\(^21\) General anatomic segmentation involves identifying the boundaries of the principal gray and white matter structures of the cerebrum based upon the natural gray or white matter boundaries as distinguished by differential signal intensities in the T1-weighted images.\(^21\) These demarcations are made in a semi-automated fashion guided by landmark conventions and signal intensity histograms.

Subdivision of the cortical ribbon into gyral-based subdivisions (cortical parcellation)
follows the scheme originally developed by Rademacher and colleagues and subsequently refined by Caviness and colleagues (see Figure). This procedure results in the identification of 48 parcellation units (PUs) per hemisphere and involves: (1) identification of a set of 42 anatomic landmarks that delimits the anterior and posterior boundaries, and (2) identification of the idealized courses of 31 prominent fissures that provide the medial-lateral boundaries of the cortical regions.

Hypotheses and Statistical Analyses

We hypothesized that comparisons between the pre-operative and post-operative MRI data would show volumetric reductions in specific frontal cortical regions that are believed to communicate with the territory of the anterior cingulate that is lesioned during cingulotomy; specifically, the PUs corresponding with the orbitofrontal cortex (fronto-orbital cortex [FOC], frontomedial cortex [FMC], and frontal pole [FP]) were principally assessed. Paired t-tests were performed using a significance threshold of 0.05 (uncorrected for multiple comparisons). Following assessment of the three predicted PUs, pre-operative and post-operative volumes for the remaining 45 PUs were also compared, in an exploratory fashion.

For the purposes of this initial study, total (ie, right+left) volumes were used. Given that cingulotomy lesions are made bilaterally (and approximately symmetrically), bilateral cortical volume changes were predicted. This approach conferred several benefits: by using total volumes (rather than separately comparing each side), the number of multiple comparisons and the variance for each PU were minimized, while power was presumably optimized. Finally, a priori, we planned to follow up any significant differences in regional total volumes with separate comparisons of right and left components of the corresponding PU; thus, positive findings would be most compelling in cases where differences in total regional volume could be attributed to bilateral changes.

Results

The comparison of post-operative with pre-operative volumes yielded no significant difference in orbitofrontal cortex (all P>0.3). Our statistical power to detect a "large" effect size (Cohen's d convention of 0.8 SD) between pre-operative and post-operative volumes by paired t-test was 0.77 for P<0.05 and 0.88 for P<0.10; N=9 and assuming r=0.70 between pre-operative and post-operative measures.

Next, an exploratory analysis of all other PUs found only two (of 45) comparisons that achieved the statistical threshold of P<0.05, uncorrected for multiple comparisons. Specifically, statistical evidence of volume reductions were found within the posterior temporal fusiform gyrus (PU=TFp; t(8)=3.57, P=0.007) and the posterior cingulate cortex (PU=CGp; t(8)=2.50, P=0.04). As noted, this number of comparisons would be expected to yield ~2—3 findings of P<0.05 by chance alone. However, for bona-fide lesion-related volume reductions, we should expect bilateral findings in corresponding PUs. Here, when each side was assessed separately, the finding in the posterior temporal fusiform gyrus was significant only on the left (left: t(8)=3.11, P=0.01; right: t(8)=1.67, P=0.13) and the finding in the posterior cingulate cortex only approached significance on the right (right: t(8)=2.03, P=0.08; left: t(8)=1.46, P=0.18). Thus, in neither case was there strong evidence of bilateral volume reduction for these cortical regions.

Discussion

Previously, in an initial study of MRI data from this same cohort of patients, we reported the results of subcortical segmentation and parcellation. The results of that analysis revealed significant bilateral volumetric reduction of the caudate nucleus that was significantly correlated with total cingulotomy lesion volume. In the current study, we performed a complementary assessment of volumetric changes within cortical regions. Here we report that, in contrast to the subcortical findings, no significant volumetric changes were found by parcellation in the orbitofrontal cortex following cingulotomy. Exploratory findings of mean volume reduction in the posterior temporal fusiform gyrus and the posterior cingulate cortex may well be due to chance, in the face of multiple comparisons. Taken together, morphometric MRI studies of cingulotomy demonstrate gross structural modification of cingulostriatal circuitry, in the absence of detectable changes in the orbitofrontal cortex.

Post hoc findings of volume changes in other cortical regions should not be taken as compelling, pending replication. However, the observation of volume reduction in the posterior cingulate cortex is most intriguing given the recent preliminary finding that pre-operative metabolic rates within the posterior cingulate cortex correlate with subsequent treatment response in patients undergoing cingulotomy for...
OCD,23 Volumetric reductions in the posterior cingulate cortex following cingulotomy are consistent with the fact that these regions are purported to share dense connections with one another.24 Moreover, although contemporary neurocircuitry models of OCD have emphasized the role of the orbitofrontal cortex, the anterior cingulate cortex, and the caudate nucleus,15,16 several functional imaging studies have also pointed to a role for the posterior cingulate cortex in OCD.25,26 Consequently, these unanticipated yet convergent results merit further investigation.

Several factors limit the interpretations of the current study: (1) it is possible that insufficient sensitivity to detect volumetric differences by these techniques obscured substantial changes in cortical anatomy following cingulotomy. Volumetric changes would likely not be apparent except in regions that share direct and dense connections with the site of the lesion. Thus, the absence of significant findings in the orbitofrontal cortex may reflect that it has a relatively diffuse pattern of connections, as is characteristic of higher-order associative regions. In addition, it is possible that regional effects were more circumscribed than those encompassed by a single parcellation unit. In this regard, however, it is important to note that similar methods were of sufficient sensitivity to detect cortical volumetric abnormalities in OCD,27 even in the context of between-group comparisons that necessarily confer lesser statistical power. Furthermore, in the current data set, none of the orbitofrontal PUs exhibited changes that even approached statistical significance (all P>0.3), indicating exceedingly small effect sizes. (2) Nonetheless, it is possible that the neuroanatomical effects observed in this cohort, who all returned for a second operation following insufficient response to an initial cingulotomy, are not generalized to patients who derived benefit from the operation. For instance, it is conceivable that a cohort of patients whose OCD improved following cingulotomy would exhibit reduced orbitofrontal cortical volumes.

(3) Finally, it is likely that significant changes in brain function may have occurred following cingulotomy in regions where gross changes in brain volume are not evident by morphometric MRI techniques. For these reasons, it will be important to extend these initial findings with further studies of consecutive cases and analysis of functional as well as structural neuroimaging data.

In conclusion, the current study found no significant frontal cortical volumetric reductions following cingulotomy, beyond the site of the lesions. In contrast, our prior study of subcortical structures showed bilateral and specific volumetric reductions of the caudate nucleus following cingulotomy. Taken together, these findings are consistent with disruption of cingulo-striatal circuitry as one possible mechanism for the purported efficacy of anterior cingulotomy. Technical limitations of the current study prevent a high degree of confidence that cortico-cortical perturbations are not also a major consequence of this procedure. Future studies using functional imaging methods will be crucial for definitively delineating the functional consequences of anterior cingulotomy. In addition, we propose that the analysis of pre-operative functional imaging data together with clinical outcome measures may provide neuroimaging predictors of treatment response to guide future patient selection for this extraordinary clinical intervention.23 Likewise, analogous studies of other neurosurgical procedures for psychiatric illness are also warranted.28 Finally, the development of alternative, non-ablative somatic treatments, such as deep brain stimulation29,30 or transcranial magnetic stimulation,31 for refractory psychiatric diseases may be facilitated by improved understanding of contemporary neurosurgical interventions and their consequences.

References


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