Tractography Study of Deep Brain Stimulation of the Anterior Cingulate Cortex in Chronic Pain: Key to Improve the Targeting

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BACKGROUND: **Deep brain stimulation (DBS) of the anterior cingulate cortex (ACC) is a new treatment for alleviating intractable neuropathic pain. However, it fails to help some patients. The large size of the ACC and the intersubject variability make it difficult to determine the optimal site to position DBS electrodes. The aim of this work was therefore to compare the ACC connectivity of patients with successful versus unsuccessful DBS outcomes to help guide future electrode placement.**

METHODS: **Diffusion magnetic resonance imaging (dMRI) and probabilistic tractography were performed preoperatively in 8 chronic pain patients (age 53.4 ± 6.1 years, 2 females) with ACC DBS, of whom 6 had successful (SO) and 2 unsuccessful outcomes (UOs) during a period of trialing.**

RESULTS: **The number of patients was too small to demonstrate any statistically significant differences. Nevertheless, we observed differences between patients with successful and unsuccessful outcomes in the fiber tract projections emanating from the volume of activated tissue around the electrodes. A strong connectivity to the precuneus area seems to predict unsuccessful outcomes in our patients (UO: 160n/SO: 27n), with (*n*), the number of streamlines per nonzero voxel. On the other hand, connectivity to the thalamus and brainstem through the medial forebrain bundle (MFB) was only observed in SO patients.**

CONCLUSIONS: **These findings could help improve presurgical planning by optimizing electrode placement, to selectively target the tracts that help to relieve patients' pain and to avoid those leading to unwanted effects.**

Key words
- Anterior cingulate cortex
- Deep brain stimulation
- Precuneus
- Targeting
- Tractography

Abbreviations and Acronyms
ACC: Anterior cingulate cortex
ATR: Anterior thalamic radiation
BET: Brain extraction tool
BPI: Brachial plexus injury
CT: Computed tomography
DBS: Deep brain stimulation
dMRI: Diffusion magnetic resonance imaging
DTI: Diffusion tensor imaging
EQ-5D: EuroQol questionnaire
FBSS: Failed back surgery syndrome
FLIRT: FMRIB linear image registration tools
FSL: FMRIB Software Library
MFB: Medial forebrain bundle
MNI: Montreal Neurological Institute
MPQ: McGill Pain Questionnaire
MRI: Magnetic resonance imaging
PAG: Periaqueductal gray area
PCC: Posterior cingulate cortex
PVG: Periventricular gray area
ROI: Region of interest
SF-36: Short-Form36 questionnaire
SMF: Superior middle frontal gyrus
SO: Successful outcomes
STN: Subthalamic nucleus
UO: Unsuccessful outcomes
VAS: Visual Analog Scale
VAT: Volume of activated tissue
vmPFC: Ventromedial prefrontal cortex

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INTRODUCTION

Deep brain stimulation (DBS) for severe pharmacoresistant pain was first introduced more than 60 years ago.[1] Different brain structures have been targeted, including the periaqueductal gray area (PAG)[2] and the ventral posterior medial and lateral nuclei of the sensory thalamus.[3] As described in a recent case series,[4] DBS of these areas can alleviate pain of various etiologies. Even though DBS is widely used, most commonly in the subthalamic nucleus (STN) for Parkinson disease, its mechanism of action remains incompletely understood.[5-7] DBS probably modulates a large network of interconnected brain regions.[8,9] We hypothesized that the optimum target in the anterior cingulate cortex (ACC) to relieve pain might be determined by the connectivity of the stimulated site rather than simply its location.[10]

Pain is a multifaceted sensation with 3 main dimensions: sensory (pain intensity), affective (pain unpleasantness), and cognitive.[11] We recently demonstrated that some patients who are unsuitable for DBS of sensory thalamus and PVG/PAG (e.g., because their pain is too widespread) may benefit from targeting a specific part of the ACC,[12,13] an area of the brain that is particularly involved in the affective dimension of pain.[14,15] Unlike targets in the basal ganglia, the volume of activated tissue (VAT) surrounding the active contacts in the ACC predominantly contains white matter.

Anterior Cingulate Cortex

The cingulate cortex is a structure of the limbic system, and it is divided into an anterior part (ACC) and a posterior part (posterior cingulate cortex [PCC]). The ACC consists of Broadmann's area 32, 24 and 25, and the PCC of areas 29, 30, 23, and 31. Even though they are parts of the same structure, they seem to perform different functions.[16] The ACC is a large heterogeneous area with complex connectivity patterns[17-19] lying in the anterior part of the cingulum, dorsal to the corpus callosum and ventral to the superior frontal gyrus. It seems to be involved in both emotional reactions and executive functions. Thus there is a nociceptive region in the ACC, responsible for the affective responses to noxious stimuli.[20] Patients with lesions in this area report that they can still localize their pain but are not bothered by it anymore.[21,22] In 1952, MacLean defined the ACC as "a visceral brain that interprets and gives expression to its incoming information in terms of feeling".[23] Its involvement in the affective component of pain is what suggested that it might be a potential target to relieve pain.[12,13] Several studies have also found a link between the PCC and pain. Brain imaging showed that nociceptive inputs reach the caudal part of the cingulate cortex first, before further projection to the ACC.[24-26]

The landmark used for targeting ACC DBS electrodes (the tip of the frontal horn of the lateral ventricle) is likely to be subject to significant interindividual variability. Furthermore, unlike DBS of the thalamus or periaqueductal gray area (PAG), the optimal location within the ACC cannot be defined intraoperatively using test stimulation because the analgesic effect can take a few days to develop.

This pilot study offers insights into the mechanism of action of ACC DBS and suggests how that might help determine optimal targeting in the future.

Tractography

Diffusion magnetic resonance imaging (MRI) tractography is a technique that quantifies the anisotropy of water diffusion in brain tissues.[27] Under the assumption that diffusion is less hindered along, rather than across, axon bundles, tractography algorithms use local modelling of diffusion to provide estimates of white matter bundles by following the direction of least hindrance to diffusion.[28] Even though these connection probabilities do not provide real counts of axon numbers per se, they are thought, at least, to be modulated by connection strength.[29,30] In our study, for every patient, putative connectivity was computed from the tissue around the electrodes likely to be activated by the stimulation (VAT). Because we used bipolar stimulation, unlike in most other DBS tractography studies, we used the area surrounding the whole electrode as the seed region.

We report here our diffusion MRI tractography[31] results tracing the white matter connectivity of tissue adjacent to active electrode contacts in patients undergoing DBS of the ACC. We focused our analysis on areas known to be involved in pain pathways and the precuneus, recently found to be involved in pain processing.[32]

MATERIALS AND METHODS

Patients

Eight patients (2 females) with chronic pain were included in the study (**Table 1**). Mean age of patients (±standard deviation) was 53.4 ± 6.1 years, and their mean preoperative visual analog scale (VAS) pain score was 8.4 (range, 6–10). Patients were referred by clinicians nationally to a single-center, multidisciplinary team consisting of pain specialists, neuropsychologists, and neurosurgeons. Neuropsychological evaluation excluded psychiatric disorders. Pain refractory to medication for at least 2 years, together with absence of surgical contraindications, such as coagulopathy or ventriculomegaly, permitted application for treatment funding. Informed consent was obtained from all patients proceeding to surgery, and the study was approved by the local ethics committee. Of the 8 operated patients, patient **B** and **C** did not feel any relief during the trial week. Therefore patients **B** and **C** were classified as '**Unsuccessful Outcomes**' (UOs). The 6 other patients, **A**, **D**, **E**, **F**, **G**, and **H**, were improved and classified as '**Successful Outcomes**' (SOs).

SURGICAL PROCEDURE AND EVALUATION OF ELECTRODE POSITION

The surgical technique has been described previously.[6,13] Briefly, a Cosman-Roberts-Wells (CRW) stereotactic frame was applied to the patient's head and a stereotactic CT scan was performed presurgically; this was volumetrically fused with the preoperative MRI using Renishaw Neuroinspire software (Renishaw, Gloucestershire, United Kingdom). The ACC was targeted in a coronal plane 20 mm posterior to the tip of the frontal horn of the lateral ventricle. After surgery, patients had a second stereotactic CT scan to check electrode placement. The implantable pulse generator was placed under the skin of the patient's upper chest after a 1-week trial period of stimulation on the ward. 130 Hz, 450-μsec bipolar stimulation was applied between the first (Co-) and last (C3+) contacts in all the patients. Amplitude varied