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Association of Clinical and Neuroanatomical Factors With Response to Ventral Tegmental Area DBS in Chronic Cluster Headache

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Abstract

Background

Deep brain stimulation (DBS) of the ventral tegmental area (VTA) is a surgical treatment option for selected patients with refractory chronic cluster headache (CCH). We aimed to identify clinical and structural neuroimaging factors associated with response to VTA DBS in CCH.

Methods

This prospective observational cohort study examines consecutive patients with refractory CCH treated with VTA DBS by a multidisciplinary team in a single tertiary neuroscience centre as part of usual care. Headache diaries and validated questionnaires were completed at baseline and regular follow up intervals. All patients underwent T1-weighted structural MRI prior to surgery. We compared clinical features using multivariable logistic regression, and neuroanatomical differences using voxel-based morphometry (VBM) between responders and non-responders.

Results

Over a ten-year period, 43 patients (mean age 53 years, SD 11.9), including 29 males, with a mean duration of CCH 12 years (SD 7.4), were treated and followed up for at least one year (mean follow-up duration 5.6 years). Overall, there was a statistically significant improvement in median attack frequency from 140 to 56 per month ($Z = -4.95$, $p < 0.001$), attack severity from 10/10 to 8/10 ($Z = -4.83$, $p < 0.001$) and duration from 110 to 60 minutes ($Z = -3.48$, $p < 0.001$). Twenty-nine (67.4%) patients experienced ≥50% improvement in attack frequency and were therefore classed as responders. There were no serious adverse events. The most common side effects were discomfort or pain around the battery site (seven patients) and transient diplopia and/or oscillopsia (six patients). There were no differences in demographics, headache characteristics, or comorbidities between responders and non-responders. VBM identified increased neural density in non-responders in several brain regions, including the orbitofrontal cortex, anterior cingulate cortex, anterior insula, and amygdala which were statistically significant ($p < 0.001$).

Discussion

VTA DBS showed no serious adverse events, and, although there was no placebo control, was effective in approximately two-thirds of patients at long-term follow up. This study did not reveal any reliable clinical predictors of response. However, non-responders had increased neural density in brain regions linked to processing of pain and autonomic function, both of which are prominent in the pathophysiology of CCH.

Key words

Cluster headache, trigeminal autonomic cephalalgias, deep brain stimulation, ventral tegmental area, voxel-based morphometry

Introduction

Cluster headache is a primary headache disorder characterised by attacks of severe unilateral headache associated with cranial autonomic symptoms.[1] Cluster headache is most commonly an episodic disorder, with attacks occurring in bouts separated by remissions of longer than three months, however approximately 15% have chronic cluster headache (CCH) with no remissions.[2] A proportion of those with CCH are refractory to the available preventive treatments, in which case it represents a major medical problem with a high degree of disability.

Ventral tegmental area deep brain stimulation (VTA DBS) has been reported in case series to be effective in 60-80% of patients with treatment refractory CCH.[3-5] Currently it is unknown why some patients respond to VTA DBS while others do not. Potential reasons include clinical characteristics, comorbidities, differences in headache pathophysiology, neuroanatomical differences, or in lead location of the DBS implant.

Currently, patient selection is a risk-benefit equation which takes into account severity of symptoms, failure of response to non-invasive treatments, comorbidities, psychological state, risks of surgery and patient wishes.[6] The identification of biomarkers for treatment response to VTA DBS would be useful to better predict the individual risk-benefit ratio. If the 20-40% of non-responders could be identified prior to surgery, the rare but potentially serious risks of invasive DBS surgery in those who are unlikely to respond could be avoided. Moreover, a better understanding of the pathophysiology of CCH and the mechanism of action of VTA DBS is likely to contribute to better future diagnostics and therapeutics.

Objectives

To identify clinical and structural neuroimaging factors which are associated with response to VTA DBS in CCH.

Materials and methods

Population

This prospective observational cohort study investigates consecutive patients who were treated with VTA DBS between 2009 and 2019 at a single tertiary neuroscience centre, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. No sample size calculation was performed, and we included all patients treated during the study period. All patients included in the study met International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for CCH.[1] Patients were aged 18 and over, with no upper age limit. DBS was considered in all patients who had suffered from treatment refractory CCH for two or more years. Due to the invasive nature of the procedure, the criteria used for refractory chronic cluster headache were stricter than the European Headache Federation consensus criteria.[7] CCH was defined as treatment refractory if there had been treatment failure to adequate trial of verapamil and at least four of lithium, topiramate, melatonin, gabapentin, pregabalin, and sodium valproate. Many patients had also trialled one or more of methysergide, baclofen, and/or levetiracetam, and 18 patients had already failed to respond to occipital nerve stimulation. Patients who had attacks lasting less than 30 minutes or more than five attacks per day had also undergone a trial of indomethacin to exclude paroxysmal hemicrania. No headache treatments were changed for at least three months prior to DBS implantation.

All patients underwent magnetic resonance imaging (MRI) prior to DBS implant for surgical planning. Patients who had contraindications to MRI or refractory medical conditions that would increase the risk from surgery such as uncontrollable hypertension or anticoagulation (that could not be temporarily stopped) were excluded from surgery.

Surgical procedure

DBS was performed unilaterally in those with strictly unilateral attacks and bilaterally in those with a history of side-variable attacks. Surgery for electrode implantation was performed under general anaesthesia in the vast majority of patients. After attachment of the stereotactic frame (Leksell Coordinate Frame G), T1 and T2 weighted stereotactic MRI was obtained (Magnetom Espree, 1.5 T).

Targeting the VTA was performed using commercially available surgical planning software (Framelink, Medtronic). The VTA was defined at a level immediately above the mammillary

bodies, anteromedial to the red nucleus and posterolateral to the mammillothalamic tract.[8] Medtronic 3389 electrodes were implanted in the initial subjects, and Boston Scientific Vercise Cartesia directional leads in a smaller subset of the most recent 7 patients. Electrode location was verified intraoperatively with stereotactic MRI scan in patients without occipital nerve stimulation, and with a stereotactic CT scan in patients with implanted occipital nerve stimulation hardware.

DBS programming commenced within a few weeks of the surgical procedure. Settings were adjusted based on patient clinical response and lack of adverse effects. Start of stimulation was postponed in those patients experiencing a stun effect (i.e., a temporary resolution of symptoms for days or weeks after implantation without stimulation), until symptoms returned to baseline.[4]

Assessment of treatment response

Patients were instructed to complete a headache diary for a baseline period of one month prior to surgery, for a one-month period every three months for the first year following surgery, then annually thereafter. Clinical outcomes were collected and entered prospectively onto a database. Data were collected on attack frequency (number of attacks per month); typical headache severity (on 0-10 verbal rating scale (VRS)); typical headache duration (in minutes); headache load (a composite measure calculated as the monthly sum of headache VRS multiplied by headache hours for each day); the Headache Impact Test-6 (HIT-6) measure of headache-related disability;[9] and the Hospital Anxiety and Depression Scale (HADS) questionnaire.[10]

Statistical analysis of the clinical data was performed using IBM SPSS Version 28. Normality assumptions were based on visual inspection of histograms and Kolmogorov–Smirnov test. Missing data were not imputed. Descriptive data were summarised as means with standard deviation (SD) or medians with ranges depending on the distribution of data.

Data were compared from baseline to the point of last follow up, and unless otherwise specified are stated as percentage improvement. The last available observation was used for participants who were lost to follow up or died during the study period. Whole group comparison of follow up to baseline data was performed using Wilcoxon signed-rank test. P values shown are uncorrected for multiple comparisons.

For analysis of responders versus non-responders, response was defined as a ≥50% improvement in attack frequency. Comparison of clinical characteristics of responders to

non-responders was performed using multivariable logistic regression, with the variables included defined a priori.

DBS target

Volumes of tissue activation were estimated using field simulation software (GuideXT TM, Brainlab). Virtual electrodes were modelled and adjusted into the lead artifact using postoperative T1-weighted MR images. Parameters of stimulation from the most recent clinical visit were applied. All devices were programmed with a frequency of 185 Hz and a pulse width of 60 ms. Amplitudes were variable among subjects and determined the volume of activated tissue. Ventral contacts were most often stimulated. When monopolar configuration was employed, the implantable pulse generator acted as anode, and the single contact as cathode. All volumes of tissue activation were exported into a NIfTI format and co-registered to the symmetrical MNI ICBM152 1mm nonlinear template as previously described.[8] Right sided volumes of tissue activation were flipped to the left using the fslswapdim tool – an advanced tool that re-orders the data storage to permit changes between axial, sagittal, and coronal slicing, when used in this mode the same left-right convention will be maintained. Group averages were created using the fslmaths tool for the responders, and non-responders.

Voxel-based morphometry

Pre-implantation 3D T1-weighted MRI images (MPRAGE) were used for voxel-based morphometry (VBM) analysis. All scans were acquired on a single 1.5T Siemens Espree MRI scanner with a spatial resolution of 1 mm^3. Structural data was analysed with FSL-VBM,[11] an optimised VBM protocol[12] using FSL tools.[13] Firstly, brain-extraction and grey matter-segmention was performed on structural images, before non-linear registration to the MNI 152 standard space.[14] The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Secondly, native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion or contraction due to the non-linear component of the spatial transformation. Then, the modulated grey matter images were smoothed with an isotropic Gaussian kernel with a sigma of 2 mm. Finally, voxelwise general linear model was applied using permutation-based non-parametric testing and threshold free cluster enhancement (TFCE), correcting for multiple comparisons across space. Two-group difference (two-sample unpaired T-test) was carried out with the groups being "responders" and "non-

responders" with contrasts showing increased voxels in each group when tested against the other.

Standard Protocol Approvals, Registrations, and Patient Consents

Clinical data collection and MRI scans were performed as part of clinical practice under supervision of our organisations Clinical Effectiveness Supervisory Committee on the basis of a humanitarian intervention; with arrangements for clinical governance, consent and audit or research as advised by National Institute for Health and Care Excellence guidelines.[15] Ethical approval for the radiological analysis was granted by West London REC 3 (REC reference number: 10/H0706/68). Written informed consent for the procedure and collection of anonymised clinical and radiological data was obtained from all participants in the study.

Data availability

De-identified data are available upon reasonable request from the corresponding author

Results

Population

Forty-three patients with treatment-refractory CCH were treated with VTA DBS during the study period. Four additional patients met criteria and were offered the procedure but declined. Fifteen patients received right, 16 left, and 12 bilateral DBS implantation. The mean age at the time of implant was 53.4 years (SD 11.9, range 25-77) and 30 (70%) were male. The mean duration of chronic headache at the time of implant was 12.0 years (SD 7.4). Patients had previously failed a mean of 8.4 preventive medications (SD 1.3, range 6-11), including verapamil (43/43 of the patients), lithium (41/43), topiramate (42/43), gabapentin (40/43), pregabalin (38/42), melatonin (36/43), sodium valproate (27/43), methysergide (29/43), baclofen (15/43), levetiracetam (19/43). Seven patients had failed to respond to non-invasive vagus nerve stimulation.Eighteen (42%) of the patients had previously been treated with invasive occipital nerve stimulation, from which ten had no response and eight had a partial response. Almost all patients (41/43, 95%) were within the highly disabled range on the HIT-6 questionnaire.

Clinical outcomes

Twenty-nine (67%) patients experienced a stun effect following the procedure, of whom 15 were temporarily rendered pain free.

The mean duration of follow up was 6.1 years (SD 3.1, range 1.0-11.7). Overall, at time of last follow up, there was a statistically significant improvement in attack severity, frequency, duration, headache load, but no statistically significant improvement in HIT-6 score, or anxiety or depression measured by the HADS score (see Table 1). Twenty-nine (67.4%) of patients were classed as responders (50% or greater improvement in attack frequency), and four (9.3%) were pain free.

Demographics and baseline clinical characteristics were similar between responders and non-responders, with the possible exception of right-side attacks being more likely to respond than either left-sided or side-variable attacks (see Table 2).

Adverse events

There were no serious adverse events. The most common side effects were discomfort or pain around the battery site (seven patients), diplopia and/or oscillopsia (six patients) and neck stiffness (four patients) (see Table 3). Diplopia or oscillopsia could be resolved by altering stimulation amplitude in all patients other than one who had a pre-existing trochlear nerve palsy following a previous head injury. Four non-responders had the DBS system explanted, two of them secondary to infection of the peripheral hardware and one due to post-surgical neuropathic pain around the head wound site. Two patients were lost to follow up and four patients died from unrelated conditions during the study period, all at least one year after the DBS implant.

Voxel-based morphometry results

VBM showed differences in several brain regions between responders and non-responders. Prior to correction for multiple comparisons, responders showed increased neural density in the posterior cingulate cortex, lingual gyrus, corpus callosum, posterior insula, habenula, striatum, ventral tegmental area, hypothalamus and periaqueductal grey, however the TFCE clusters did not survive multiple comparison correction. Non-responders had increased neural density in the dorsal anterior cingulate cortex, anterior insula, amygdala, visual cortex and the orbitofrontal cortex which was statistically significant after multiple comparison correction (1-p corrected = 0.999) (see Figures 1 and 2).

DBS target

All active electrodes were placed in the target in the VTA with a mean targeting error of 0.9 mm (SD=0.6 mm). Group average volumes of tissue activation for the entire group, the responders and non-responders are presented in Figure 3. Table 4 shows the coordinates for the maximum intensity voxels and centre of gravity for the group average volumes. There was no difference between the responder and the non-responder groups although the non-responder group had a tendency of being more lateral, posterior, and inferior.

Discussion

In the population studied in this prospective observational cohort study, VTA DBS showed no serious adverse events, was effective in approximately two-thirds of patients with treatment refractory CCH, and remained effective at long-term follow up. VBM analysis has been used to show that neural density differs between responders and non-responders in several brain regions which are commonly linked to pain processing and central processing of autonomic function, both of which are relevant to the pathophysiology CCH.

The pathophysiology of cluster headache is imperfectly understood but thought to involve interactions between the hypothalamus and the trigemino-vascular system. The circadian and circannual periodicity of cluster headache attacks and bouts suggest hypothalamic involvement. Positron-emission tomography and functional MRI studies have demonstrated activation in the region of the posterior hypothalamus during attacks of cluster headache.[16-18] Based on this finding, DBS was first used in a patient with treatment refractory CCH in 2001.[19] Although initially described as the posterior hypothalamic region, the DBS target has been more precisely located at the VTA.[20] Published case series suggest it is effective in 60-80% of patients, and remains effective with long term follow-up.[3-5] A single randomised sham-controlled trial including 11 patients with CCH was negative. However, the study was limited by the short blinded phase of only one month that overlaps with the possible stun period, and at one year follow up six (55%) were responders with no safety concerns.[21] A randomised sham controlled trial with a longer blinded phase is required to exclude a placebo effect, although this appears unlikely given the patients' lack of response to multiple other treatments including occipital nerve stimulation surgery, and recognition that attack recurrence is often seen in patients who are unaware that the battery has run flat or stimulation has been turned off.[3,22]

Given the good response to treatment in approximately two-thirds of this highly disabled population, we therefore recommend considering DBS in similarly treatment refractory patients with CCH; providing it is performed in centres which are experienced in it's use and where there are arrangement for clinical governance, consent, and audit; as per National Institute for Health and Care Excellence guidelines.[15] In the future there may be newer less invasive treatments which should be trialled before considering DBS. Non-invasive vagus nerve stimulation and monoclonal antibodies to calcitonin-gene related peptide are two newer treatments for headache disorders, but both appear to only be effective in episodic and not CCH.[23,24]

Previously, no clinical characteristics have been identified that reliably predict VTA DBS response in CCH, although the presence of bilateral (side-variable) attacks has been suggested to be a possible predictor of poor response.[5] The increased likelihood of right sided attacks responding to VTA DBS in this study is not easily explained. There is a slight preponderance for right sided attacks in cluster headache.[25] Taken together with better responses in those with right sided attacks, it suggests that the pain neuromatrix may have some form of lateralisation which both makes patients more prone to right sided attacks and more likely to respond to treatment if attacks are right sided. We hypothesised that patients with comorbid affective disorders or other chronic pain conditions may be less likely to respond, as these has been shown to be negative predictive factors of response to occipital nerve stimulation for chronic headache disorders, but this was not borne out by the results.[26]

VBM has been used to show that gray matter concentration in an area in lobule VI of the cerebellum is associated with treatment responsiveness to verapamil.[31] Brain morphometry studies have revealed neuroimaging predictors of response to DBS in Parkinson's disease,[32,33] and obsessive compulsive disorder.[34] Therefore, we posited that differences in brain structure may be associated with treatment response to VTA DBS in CCH. Indeed, several brain regions were identified which differ between responders and non-responders. The regions with increased neural density in responders (thalamus, periaqueductal gray, hypothalamus) are known to be involved in modulation of peripheral pain signals, whereas the regions with increased neural density in non-responders (anterior cingulate cortex, anterior insula, frontal cortex) are involved in the perception and expectation of pain and potentially the placebo effect, as well as the cortical representation of the autonomic nervous system.[35,36]

A variety of brain areas have been found to differ in patients with cluster headache compared to healthy controls in previous neuroimaging studies. The first published study in cluster headache using VBM found increased bilateral posterior hypothalamic gray matter volume, but this has not been confirmed by other studies.[27,28] In our study there was a small area of increased neural density in the left hypothalamic region in responders to DBS, however the difference to non-responders was not statistically significant. Another study using VBM found that patients with cluster headache had decreased grey matter volume in several brain regions involved in pain processing, possibly suggesting deficient top-down modulation of antinociceptive circuits in cluster headache patients.[29] However, other than the left insula, these areas do not overlap with the regions in which we found to correlate with response to VTA DBS.

Our finding of increased neural density in the amygdala and frontal cortex of non-responders may suggest dysfunction in the corticolimbic system. Increased volumes of these brain regions and associated connectivity abnormalities have been shown in a previous study of chronic cluster headache.[37] Interestingly the opposite finding of smaller amygdala volume has been shown to be a predictor of persistence in other chronic pain syndromes.[38] This could be further investigated in future studies using connectivity measures, quantitative analysis of amygdala volume, and or cortical thickness measures of the relevant frontal brain regions.

Our finding of morphometric brain differences between responders and non-responders to VTA DBS suggests that with larger datasets in the future, structural neuroimaging may be able to improve prediction of likelihood of response for an individual patient. This may allow the identification of likely non-responders prior to surgery and thereby avoid an invasive and costly operation, and conversely to consider offering this treatment at an earlier stage in those who are highly likely to respond.

Identifying predictors of response may shed light on the mechanism of action of DBS, which is currently uncertain. A probabilistic tractography study in seven patients who underwent DBS for CCH showed that the largest treatment response was associated with activation in an area which lay on a tract which connects the hypothalamus, prefrontal and mesial temporal regions in the forebrain, with brainstem regions including the nucleus of the solitary tract, periaqueductal gray, trigeminal nucleus and tract.[8] This tract may correspond with the trigemino-hypothalamic tract that has been demonstrated in rats.[39] The often-delayed response to DBS, and previous findings that acute stimulation is unable to abort acute attacks, suggest that DBS may act by modulating the process of central sensitisation, rather than the

process of attack generation.[5,40] More than half of the patients in our study experienced between 50-99% improvement. The fact that most patients did not have complete symptom resolution may support this mechanism of action. A previous PET study has shown stimulation induced changes in a variety of cortical regions involved in pain processing, including deactivation in the middle temporal gyrus, posterior cingulate cortex and contralateral anterior insula.[41] These brain regions overlap with the regions we found to have increased neural density in non-responders to VTA DBS, and the increased neural density in these regions may reflect a greater degree of central sensitisation in the non-responders which is more difficult to reverse by DBS.

Interestingly, despite the improvement in headache frequency, severity, and duration, we did not find a statistically significant improvement in disability or affective scores following VTA DBS (see Table 1). The lack of a statistically significant (once multiple comparisons are taken into account) improvement in HIT-6 may be because it is not validated for use in cluster headache. The lack of improvement in HADS scores suggests than the mechanism of anxiety and depression in these patients may be different to that of cluster headache, although this is surprising given the association between central sensitisation disorders and depression and anxiety.[42]

A challenge to neuroimaging studies in CCH is accounting for the attack lateralisation. Cluster headache is a strictly unilateral disorder (although a minority of patients may have side-alternating attacks), Many previous neuroimaging studies in CCH have flipped the images along the x-axis so that brain regions are analysed as ipsilateral or contralateral to the side of pain.[16,28,43,44] Other studies have used the true left and right hemispheres regardless of the side of the headache, in order to take into account the lateralisation of brain functions.[45] Structural asymmetry has been shown in previous voxel-based morphometry MRI studies in healthy controls, the most right-handed persons having a larger left hemisphere.[12,46] The majority of our patients were right-handed, but five were left-handed (who may either have right hemisphere dominance and therefore larger right hemisphere or bilateral representation). A subset of our patients had bilateral side-variable attacks, with varying proportions of attacks on each side, therefore we elected not to flip scans so that the true left and right were preserved, and so that all treated patients could be included.

In conclusion, although it remains to be proven in clinical trials, VTA DBS appears to be an effective long-term treatment which may be considered in patients with CCH who are refractory to medical treatment. Neuroanatomical differences may explain why some patients

do not respond. A randomised sham controlled trial with a longer blinded phase is required to confirm the efficacy of VTA DBS for CCH.

Contribution statement

S. Cheema: collection of clinical data, statistical analysis of clinical data, interpretation of results, drafting and revision of manuscript

F. Ferreira: VBM analysis of neuroimaging data, revision of manuscript

O. Parras: analysis of DBS target, interpretation of results, revision of manuscript

S. Lagrata: collection of clinical data, revision of manuscript

S. Kamourieh: collection of clinical data, revision of manuscript

A. Pakzad: analysis of DBS target, revision of manuscript

L. Zrinzo: performing DBS procedure, interpretation of results, revision of manuscript

M. Matharu: conception of study, collection of clinical data, interpretation of results, revision of manuscript

H. Akram: conception of study, performing DBS procedure, VBM analysis of neuroimaging data, interpretation of results, revision of manuscript

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Tables

Table 1. Improvement in headache metrics following VTA DBS

	Baseline (median)	Follow up (median)	Z[a]	P value[a]
Attack frequency (per month)	140	56	-4.95	<0.001*
Attack severity (0-10 VRS scale)	10	8	-4.83	<0.001*
Attack duration (minutes)	110	60	-3.48	<0.001*
Headache load	700	229	-3.98	<0.001*
HIT-6	70	66	-2.16	0.03
HADS-A	11	10.5	-0.89	0.37
HADS-D	13	10.5	-0.96	0.34

[a] Wilcoxon signed-rank test

* Statistically significant results if Bonferroni correction used

Abbreviations: HADS-A, hospital anxiety and depression scale anxiety subscale; HADS-D, hospital anxiety and depression scale depression subscale; HIT-6, headache impact test-6; VRS, verbal rating scale

Table 2. Baseline patient characteristics in responders and non-responders

	Responders n=29	**Non-responders n=14**	**OR (95% confidence interval)**	**P value**
Age (years), mean (SD)	54.1 (12.3)	51.9 (11.3)	-	-
Gender (males)	21 (72%)	8 (57%)	0.54 (0.11-2.66)	0.451
Duration of CCH (years), mean (SD)	11.3 (7.7)	13.6 (6.5)	-	-
Number of oral preventive treatments failed, mean (SD)	8.3 (1.5)	8.6 (1.0)	-	-
Laterality of attacks:				
Right	13 (45%)	2 (14%)	9.78 (1.04-91.84)	0.046
Left	9 (31%)	7 (50%)	1.28 (0.24-6.85)	0.776
Side variable	7 (24%)	5 (36%)	Reference group	-
Baseline attack frequency (attacks per month), median, IQR	140 (91)	154 (91)	-	-
Baseline attack severity (0-10 on VRS scale), median, IQR	10 (1)	9.5 (1.5)	-	-
Baseline attack duration (minutes), median, IQR	120 (147.5)	105 (90)	-	-
Baseline headache load, median, IQR	700 (651.5)	685.5 (738.75)	1.00 (1.00-1.00)	0.238
Baseline HIT-6 score, median, IQR	71 (9.5)	68 (9.25)	-	-
Baseline HADS-A score, median, IQR	12 (8)	10.5 (7.75)	-	-
Baseline HADS-D score, median, IQR	13 (9)	12 (7)	-	-
Diagnosis of affective disorder (depression or anxiety)	14 (48%)	9 (64%)	0.56 (0.08-2.61)	0.378
Other pain disorder (including migraine and non-headache pain)	13 (45%)	7 (50%)	1.42 (0.31-6.48)	0.648
Smoking history	16 (55%)	6 (42%)	-	-

Triptan response[a]	23/28[c] (82%)	10/14 (71%)	-	-
Oxygen response[a]	18/24[c] (75%)	9/13[c] (69%)	-	-
GON block response[b]	16/27[c] (59%)	6/14 (43%)	-	-

Response defined as 50% improvement in attack frequency at the time of last follow up.

[a] defined as greater than 50% improvement in pain severity within 15 minutes

[b] defined as greater than 50% improvement in pain severity within two weeks

[c] not all patients had tried subcutaneous sumatriptan and/or oxygen due to contraindications, and two patients had not previously had a greater occipital nerve block

Abbreviations: CCH, chronic cluster headache; GON, greater occipital nerve; HIT-6, headache impact test-6; OR, odds ratio; V1/V2/V3, first, second, and third divisions of the trigeminal nerve respectively; VRS, verbal rating scale

Table 3. Adverse events

Adverse event	Number of patients	Proportion
Battery site discomfort or pain	9	21%
Transient diplopia or oscillopsia	6	14%
Neck stiffness	4	9%
Lead site pain	3	7%
Lead migration	1	2%
Swelling over battery site	1	2%

Table 4. DBS electrode position

	Maximum intensity voxel (MNI ICBM) mm			Centre of gravity voxel (MNI ICBM) mm		
	X	**Y**	**Z**	**X**	**Y**	**Z**
Group mean	-4	-13	-9	-4	-13	-8
Responders	-4	-13	-9	-4	-13	-8
Non-responders	-5	-14	-10	-5	-13	-8

MNI ICBM, Montreal Neurological Institute International Consortium of Brain Mapping standardised stereotactic space

Figure Legends

Figure 1. Increased neural density in responders

Differences shown did not survive multiple comparison correction at 1-p corrected = 0.999)

Abbreviations: MD, mediodorsal thalamus; P.CING, posterior cingulate cortex; LG, lingual gyrus; CC, corpus callosum; P.INS, posterior insula; HAB, habenula; SRT, striatum; STrT, spinal trigeminal tract; VTA, ventral tegmental area; HT, hypothalamus; PAG, periaqueductal gray

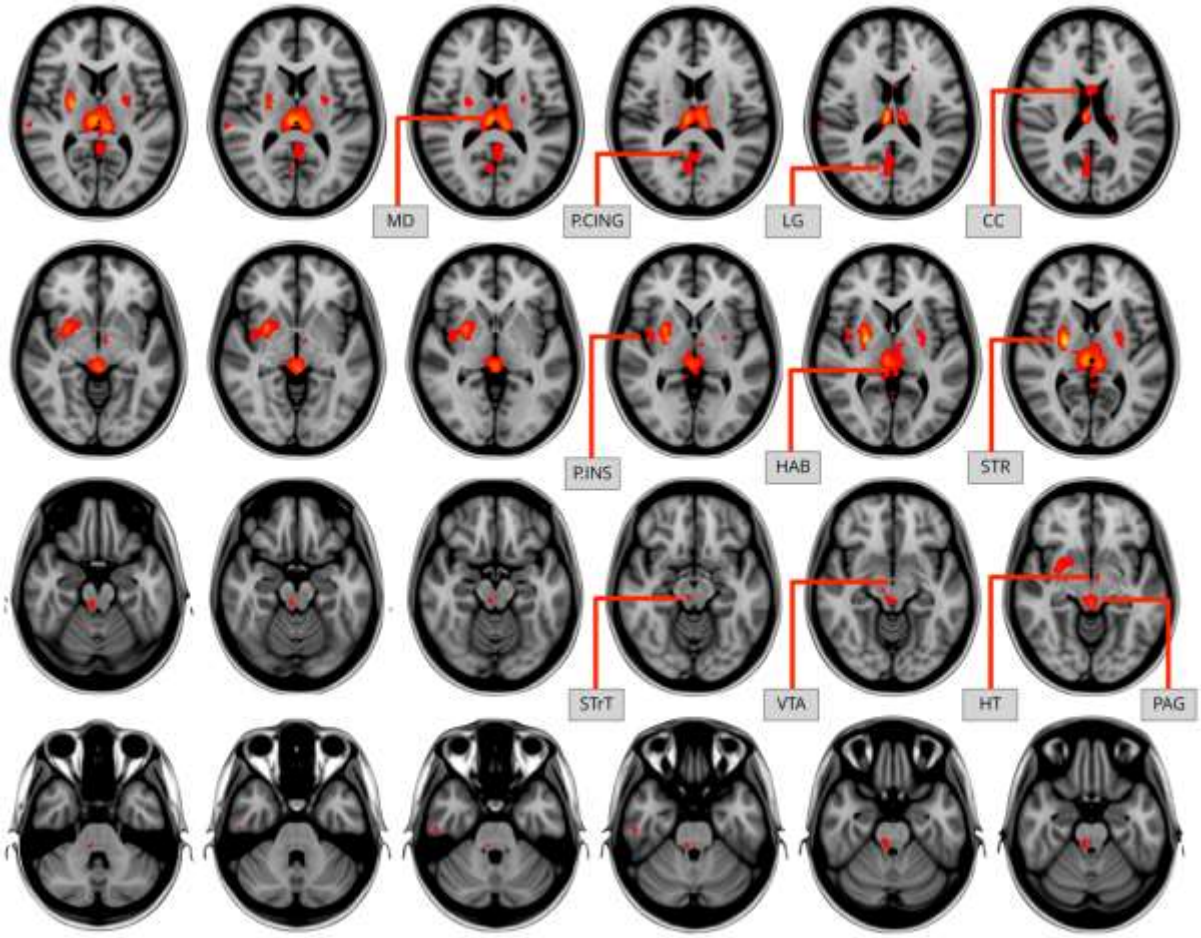
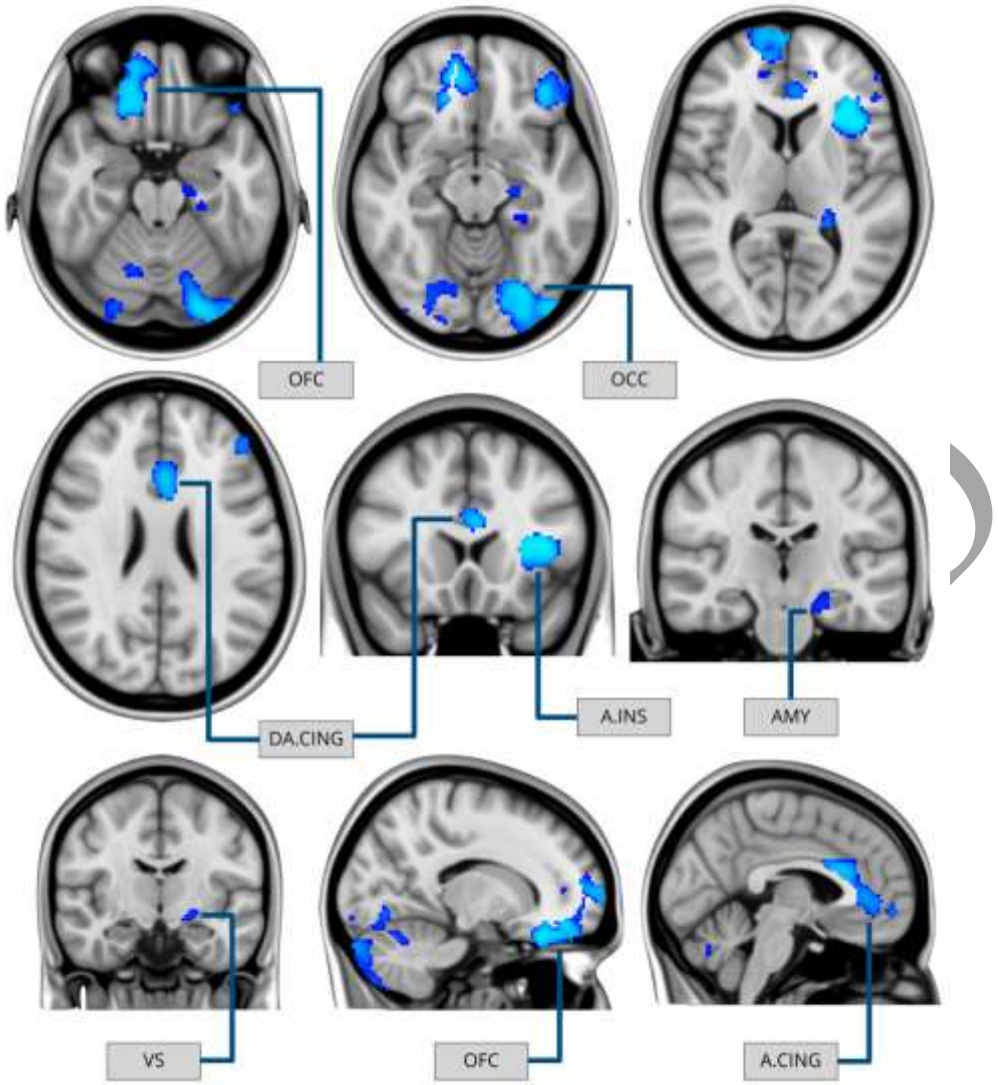


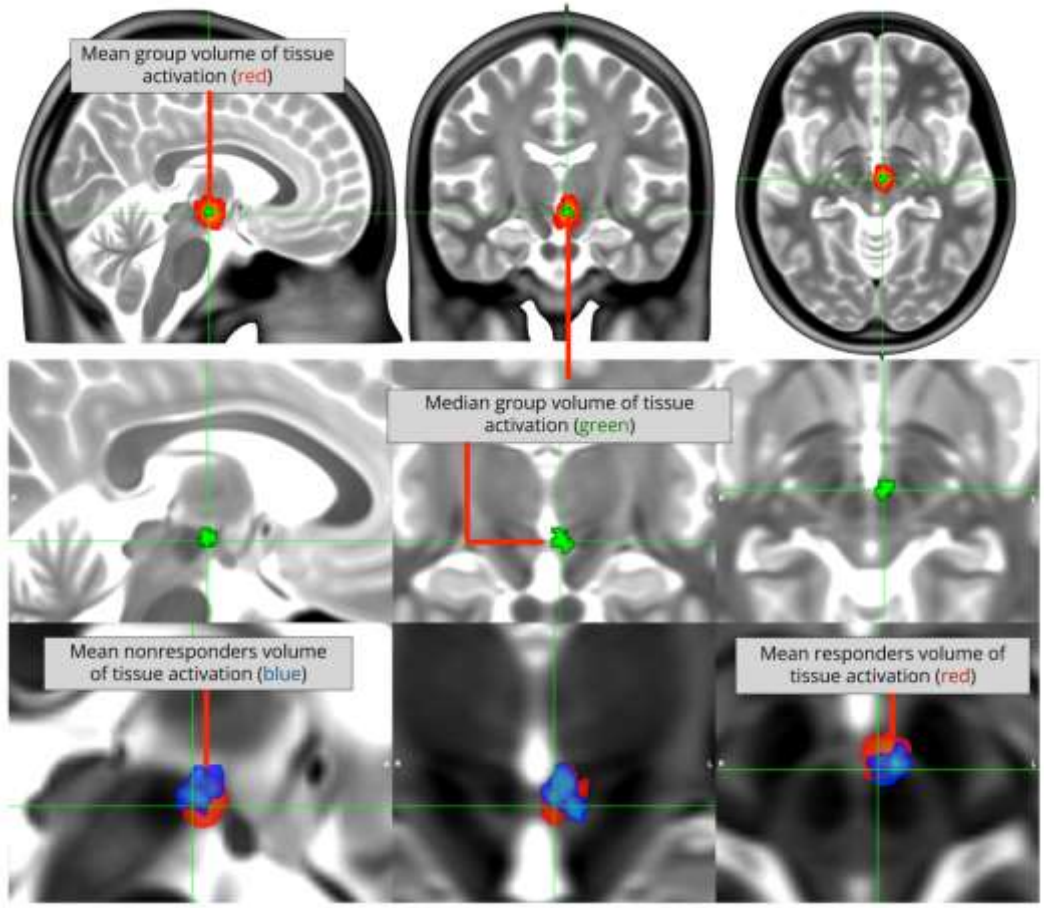
Figure 2. Increased neural density in non-responders



Differences shown are statistically significant after multiple comparison correction (1-p corrected = 0.999)

Abbreviations: OFC, orbitofrontal cortex; OCC, occipital love; DA.CING, dorsal anterior cingulate cortex; A.INS, anterior insula; AMY, amygdala; VS, ventral striatum; OFC, orbitofrontal cortex; A.CING, anterior cingulate cortex

Figure 3. Volumes of tissue activation



Group average volumes of tissue activation for the entire group (green), responders (red), and non-responders (blue)

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