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Functional Magnetic Resonance Imaging Correlates of Ventral St

Pain

Running Title: fMRI Correlates of DBS for Pain

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Malone, and Machado designed and conducted the study, including pa
Drs. Jones, Beall, Lowe, Chen, Jian Lin and Xuemei Huang performed
data analysis. Drs. Jones and Machado prepared the manuscript draft w
input from Drs. Lempka, Gopalakrishnan, Beall, Bhattacharyya, Chen
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Abstract

Objective: Deep brain stimulation (DBS) for pain has largely been im
uncontrolled manner to target the somatosensory component of pain, v
mixed results. We have previously shown that patients with poststroke
treated with DBS targeting the ventral striatum/anterior limb of the int
demonstrated a significant improvement in measures related to the aff
this study, we sought to determine how DBS targeting the VS/ALIC n
response to pain.

Materials and Methods: Five patients with poststroke pain syndrome

status (ON/OFF) and six age- and sex-matched healthy controls under

Results: In response to pain, patients in the DBS OFF state showed si
0.001) in the same regions as healthy controls (thalamus, insula, and o
additional regions (orbitofrontal and superior convexity cortical areas)
reduced activation of these additional regions and introduced foci of s
activation ($p < 0.001$) in the hippocampi when painful stimulation was
side.

Conclusions: These findings suggest that DBS of the VS/ALIC modu
networks.

Keywords: Chronic pain, deep brain stimulation, DBS, fMRI, poststr

INTRODUCTION

Deep brain stimulation (DBS) has been explored as a potential treatme
pain since the 1970s. Traditionally, DBS is used to target the ascendin
or descending inhibitory pathways in an effort to modulate the sensory
pain. The most common target areas have been the sensory nuclei of t
endorphin-releasing areas, such as the periventricular gray area or the
Unfortunately, clinical outcomes associated with DBS of these traditio
mixed (1,2). Although some studies reported improvements in pain m
analog scale, large case series and industry-sponsored studies aimed a
effects of DBS found limited benefits (3,4). Many of these studies hav
mixed results due to limitations in the study design. Several of these st
during the early development of DBS with a lack of well-defined patie
surgical target identification, and electrode and stimulator technology
reviews suggest that future studies should focus on specific pain diagn
randomized placebo-controlled designs (6,7).

To potentially improve the success rate of DBS to treat chronic

change in how DBS is used to treat the chronic pain experience; this c

and pain-related disability without necessarily modulating pain intensi
with a Likert scale. There are many anatomical choices for DBS modu
affective/nonsensory pathways.

Cortical control of emotion is manifested through processing w
pallido-thalamocortical system and the circuit of Papez. In addition to
and prefrontal cortical areas into the dorsal striatum, there are direct p
frontal cortical areas and orbitofrontal cortical areas to the ventral stria
direct projections to the thalamus via the anterior limb of the internal c
previously demonstrated that acute stimulation of the VS and the venti
changes in mood and behavior (9). DBS of the ALIC has been shown
OCD (12,13) and was approved by the United States Food and Drug A
Humanitarian Device Exemption. In an uncontrolled study, our multic
also reported the long-term benefits of VS/ALIC DBS in patients with
depression (10). Our group has direct experience implanting DBS lead
experience titrating stimulation in a safe way to avoid side effects such
(1,2,10,11,13-15). It is also important to note that previous studies targ

cingulate cortex have demonstrated the potential of DBS of the affecti

poststroke pain syndrome (17). In this first-in-humans trial, patients tr
demonstrated a significant improvement in the Montgomery-Asberg D
and the Beck Depression Inventory, suggesting that DBS can indeed m
sphere of treatment-refractory pain. In addition, we learned that implan
safe in this patient population and is associated with improved quality

To investigate the neural substrates of pain affect and its modu
ventral striatum, we previously studied the same patient cohort using a
magnetoencephalography (MEG) paradigm (18-20). Our findings wer
that in patients with poststroke pain, anticipatory brain response to a n
different than pain anticipation, indicating a loss of salience (18-23). S
DBS treatment, the abnormal anticipatory brain response to nonpainfu
was resolved, predominantly in the medial prefrontal and anterior cing
present work expands on this previous investigation to include a comp
oxygen level–dependent (BOLD) functional magnetic resonance imag
context of the same randomized, placebo-controlled clinical trial. Whi
temporal resolution, fMRI yields excellent spatial resolution and allow

and corroborate our earlier MEG findings. To our knowledge, this is th

MATERIALS AND METHODS

Ten patients were enrolled in a randomized controlled trial of VS/ALI
poststroke pain syndrome (17). All patients had at least 6 months of co
pain following a stroke involving the sensory thalamic area or white m
sensory thalamic area. Ten healthy controls were also specifically recr
fMRI findings only; these controls were age- and sex-matched to the s
patients, bilateral DBS leads (Model 3387, Medtronic, Minneapolis, M
the VS/ALIC area (Fig. 1) using neurosurgical techniques described pr
study procedures were approved by the institutional review board (IRI
sponsored Investigational Device Exemption from the US Food and D
enrollment, all patients provided written informed consent.

The prospective, randomized, double-blind, placebo-controlled
of an initial 6-month double-blind stimulation phase in which patients
months of active stimulation (ie, DBS ON) or sham stimulation (ie, DB
month crossover to the other treatment allocation. The blinded phase w
18-month open stimulation phase (ie, unblinded active DBS, no sham

fMRI images 2 months after randomization and 2 months after crosso

up of a complete DBS system. During MRI scans, temperatures near t
contacts were measured using fluoroptic temperature sensors as previo
Testing was performed in both DBS ON and OFF conditions and with
heating stimulus hardware both active and inactive. None of the scan
significant heating near the electrodes (ie, < 1°C for all scans).

Participants were imaged under an IRB-approved protocol on a
MRI scanner (Erlangen, Germany). After a standard anatomic T1-weig
prepared rapid gradient-echo sequence was obtained (axial acquisition
time/echo time/inversion time = 1900/1.71/900 ms; voxel size = 1 × 1
min 5 s), 2 BOLD sensitive echo-planar imaging (EPI) scans for fMRI
acquisition with 31 slices; repetition time/echo time = 2000/29 ms; vo
field of view = 64 × 64; 224 volumes; total scan time = 7 min 28 s).

The fMRI paradigm consisted of painful heat stimuli to the aff
area delivered using a contact heat-evoked potential stimulator of the
(Medoc Ltd, Ramat Yishai, Israel). During each scan, the heat stimuli
design comprising 5 cycles of heat (44.8 s) followed by no heat (44.8

necessary (e.g., because of excessive movement of the participant or f

Image analysis began with removal of the first 4 volumes to en
Each scan was then retrospectively volume- and slice-wise motion-cor
using SLOMOCO (26). Total displacement was calculated using volu
translation parameters and used as the motion quality parameter. The
motion corrupted if the maximum displacement of any voxel was grea
displacement of parenchymal voxels was more than 0.2 mm. Scans ex
were not included in the group analysis. Using the heating paradigm,
3dDeconvolve in Analysis of Functional NeuroImages (AFNI) softwa
maps, the specific output of which were voxel-based Student's t-score
images were aligned to their concurrent anatomic T1 image using the
from AFNI. The anatomic T1 image was then aligned to the template
brain was used after transforming it into Talairach coordinates using s
normalization (Syn) in Advanced Normalization Tools. The EPI imag
transformed to final template space using the Advanced Normalizatio
acquired in the previous step. A single participant had left-sided pain;
normalized brain maps were left-right flipped so that data from all of t

aligned to a common side reflecting the affected hemisphere. The map

combination of the 2 condition variables (DBS ON versus DBS OFF)
(affected side versus unaffected side) (Fig. 2). The final Bonferroni-co
(3dClustsim) after cluster analysis with single-voxel threshold, $p < 0.0$
requirement of 300.

RESULTS

Of the 10 patients enrolled in the study, 8 consented to the fMRI proc
participants met the motion criteria during all 4 fMRI sequences (right
DBS ON and DBS OFF conditions). Four participants had pain on the
participant had pain on the left side. The chronic stimulation paramete
five participants are shown in Table 1. Six of the 10 healthy controls h
images during both the right and left arm heating sequences. Among t
controls, all were right handed, with no significant differences in sex c

Statistical maps of the BOLD response in study patients and he
in the top row of Figure 2. A predominant BOLD pattern seen in healt
activation of foci within the insula and along the frontoparietal opercu

functional region S2 (label 1). Although activation was bilateral, we n

In response to pain, patients with poststroke pain syndrome in
row of Fig. 2) exhibited significant activation in the same regions as h
7), with more pronounced activation of the thalamic (label 5), insular,
4). Patients also showed activation in additional regions not significan
controls, including in the orbitofrontal region (label 3) and diffusely o
(magenta rectangle) cortical region. Also in contrast to healthy contro
small foci of negative or inhibitory activation in the subgenual cortica
to healthy controls, patients showed more foci of activation, both posi
DBS OFF state.

In the DBS ON state (third row in Fig. 2), patients with poststr
fewer regions of positive BOLD activation than in the DBS OFF state
significant activation were seen in the superior convexities with painfu
affected and unaffected sides (see the 5 superior axial slices correspon
rectangle in the second row of Fig. 2). In the DBS ON state, during pa
affected side, foci of orbitofrontal activation (labels 3 and 4) and thala
were smaller than these foci in the DBS OFF state. In the DBS ON sta

stimulation of the unaffected side, significant increased activation was

(label 10), and multiple other locations. This was present predominant
with the unaffected side showing persistence of inhibition in the subge

DISCUSSION

DBS of the VS/ALIC has been proposed by our group as a method for
sphere of chronic pain, thus improving quality of life in patients with i
Poststroke pain syndrome is an excellent model in which to study the
intervention, as the pain involved in this syndrome is unlikely to resol
associated with a clear, imaging-identifiable etiology. The fMRI data
collected during the double-blind phase of a randomized, controlled tr
patients with intractable unilateral poststroke pain syndrome. The clin
supported our initial hypothesis that DBS of the VS/ALIC can success
sphere of pain and promote changes in quality of life (17). The present
fMRI to examine the mechanisms underlying the effects of VS/ALIC
sphere of pain.

In this study, activation patterns in healthy controls indicated i

networks in response to acute and expected painful stimuli and corrob

consistent with previous research (28). As expected for somatosensory activation of the thalami.

Relative to healthy controls, patients with poststroke pain synd showed more foci of positive and negative activation, suggesting that greater response in patients than in healthy controls. Patients showed l cortical regions in response to painful stimuli; this activation extended to the parietal cortical regions and also involved the opercular areas an there was marked activation of the insula and orbitofrontal areas, sugg involvement of affective and associative networks in response to patho

When fMRI scans were performed in the DBS ON state, we no in the broad pattern of cortical overactivation seen in the DBS OFF sta the strong orbitofrontal activation noted in the DBS OFF state. This fi reduces abnormal cortical activation associated with the chronic pain s activation pattern to more closely resemble that seen in healthy contro effects were greatest for heat stimulation of the affected side, with the in the convexity and regions of the insula, thalamus, and inferior front

affected side during DBS ON also led to robust negative BOLD activa

also noted strong BOLD activation of the cingulate cortex in response unaffected side during DBS ON, a finding that is unique in this data se

Our prior investigation with MEG showed that patients with pe neurophysiologically distinguish cues that represent pain versus those stimuli (19). This trend was predominantly evident in the prefrontal ar indicating a cortical overactivation to incoming nonpainful stimuli. Th clinical presentation of allodynia, a condition in which all sensory stim whether they are painful or not, are interpreted as painful. With DBS O were able to differentially anticipate nonpainful stimuli, evidenced by overactivation, indicating an "affective benefit" that restored salience, emotional regulation (18). The findings of the current fMRI study corr investigation, both in terms of cortical overactivation in the DBS OFF reduction in the spread of cortical activation in the DBS ON state, pote partial restoration of the distinction between normal and pathological p speculate that improved cognitive and emotional regulation restored b the widespread cortical activation in the pain matrix areas, including th area linked with fear and emotion (29).

volunteers who underwent the same painful stimulation procedures du
helped us to interpret the data, as results from the controls provided a
regarding what we should expect in the pain-free brain. In addition, al
same well-characterized pain syndrome, improving the homogeneity o

Limitations of the work include its small sample size. Only 9 o
completed the randomized phase of the clinical trial, and of these, only
in the fMRI experiments. In addition, the techniques for acquisition of
are substantially affected by motion artifacts; because of motion artifa
include only 5 patients with poststroke pain syndrome and 6 healthy c
analysis to achieve reliable statistical maps. Another limitation is the
as patients exhibiting strong or exaggerated movements in response to
have met the inclusion criterion regarding minimal movement. Thus, t
patients who might have had a differential response.

In conclusion, these findings suggest that DBS of the VS/ALIC
neural networks, corroborating our original hypothesis. DBS significa
overactivation of cortical regions seen in patients with chronic pain bu

Future studies in patients with more common pain syndromes are need

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Table 1. Chronic stimulation parameter settings

Patient	Lead hemisphere	Active electrodes	Pulse amplitude (V)	Puls
1	Right	10(-) 11(+)	2	
	Left	2(-) 3(+)	2	
2	Right	C(+) 10(-)	6	
	Left	C(+) 1(-)	6	
3	Right	C(+) 11(-)	1	
	Left	N/A	N/A	
4	Right	C(+) 10(-) 11(-)	4	
	Left	C(+) 2(-) 3(-)	4	
5	Right	C(+) 8(-)	3.5	
	Left	C(+) 0(-)	3.5	

For the active electrodes, '+' and '-' refer to the electrode polarity. 'C' r

implantable pulse generator. For right-side leads, the electrodes are nu

the most distal electrode. For the left-side leads, the electrodes are nur

the most distal electrode.

Figure 1. Axial oblique T1-weighted magnetization-prepared rapid gr
in-plane with bilateral deep brain stimulation electrodes targeting the v
limb of the internal capsule. The deeper contacts include the nucleus a
contacts are seen as small rounded enlargements at the end of the elec

Figure 2. Statistical maps of blood oxygen level–dependent (BOLD) a
heating stimulus for normal healthy controls (NHC, top row), patients
syndrome with deep brain stimulation (DBS) OFF (second row), and p
pain syndrome with DBS ON (third row). These maps represent differ
state (healthy controls vs DBS ON vs DBS OFF) and side of heating s
side of the body affected by chronic pain from a contralateral chronic
unaffected side). Each map displays 18 axial slices spaced 8 mm apart
orange indicate positive BOLD response to heating stimulus (activatio
blue indicate negative BOLD response to heating stimulus (suppressio
Bonferroni-corrected *p* value was 0.05 for positive and negative activa
0.001 with a cluster size of 300). Images are displayed using radiologi
indicate the specific brain regions described in the Results section.

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Drs. Machado, Beall, Bhattacharyya, Lowe, Lempka, Gopalakrishnan, Malon and conducted the study, including patient recruitment. Drs Jones, Beall, Lo Xuemei Huang performed the data collection and data analysis. Drs Jones a manuscript draft with important intellectual input from Drs. Lempka, Gopalak Bhattacharyya, Chen, and Lowe. All authors approved the final manuscript. access to the study data. Megan Griffiths, helped with editorial assistance.

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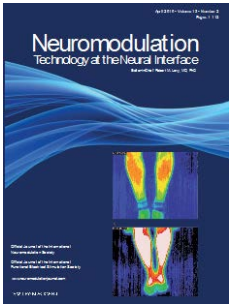

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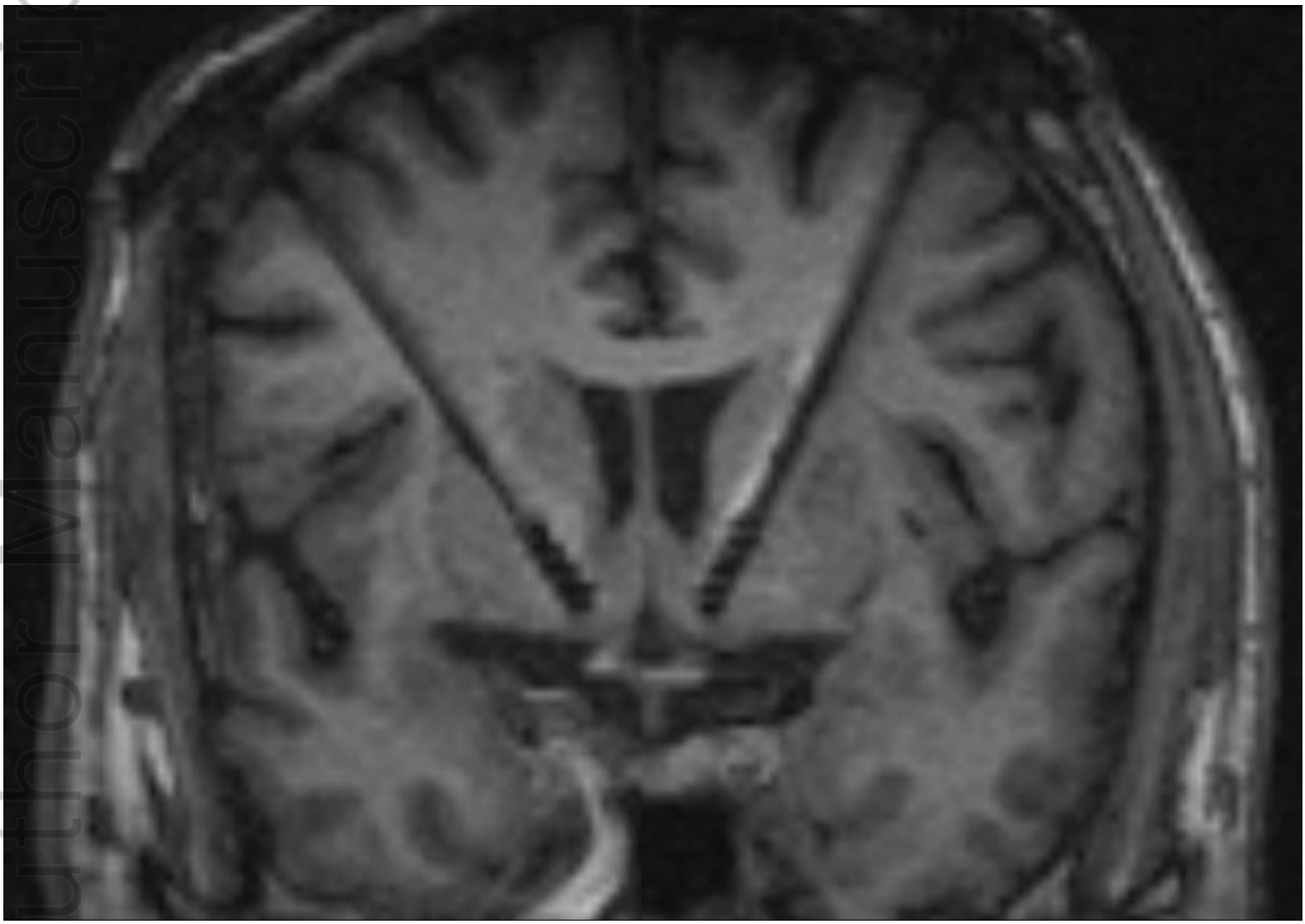

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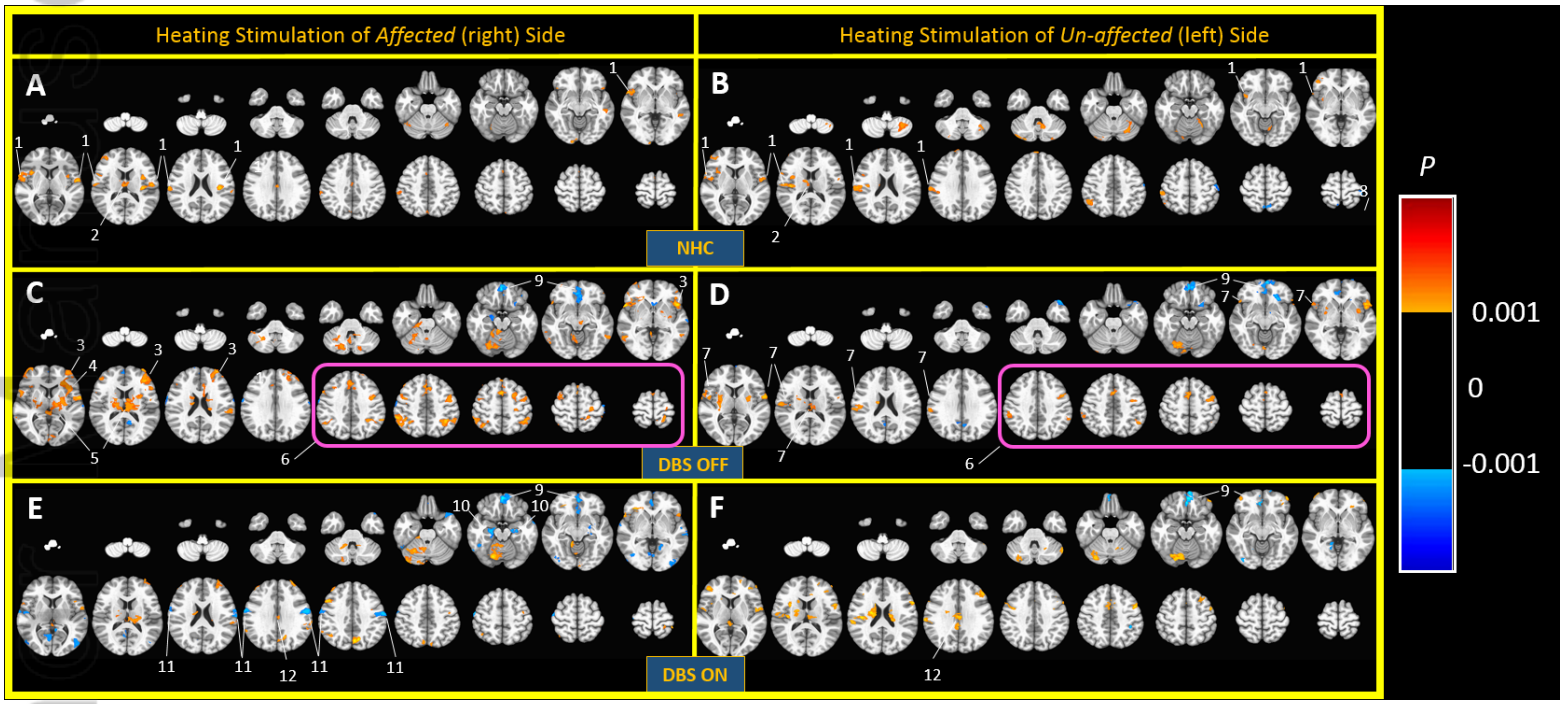

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