Brief Communication

Identifying therapeutic targets from spontaneous beneficial brain lesions

(Running head: Paradoxical functional facilitation revisited)

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ABSTRACT

Brain damage can occasionally result in paradoxical functional benefit, which could help identify therapeutic targets for neuromodulation. However, these beneficial lesions are rare and lesions in multiple different brain locations can improve the same symptom. Using a technique called lesion network mapping, we show that heterogeneous lesion locations resulting in tremor relief are all connected to common nodes in the cerebellum and thalamus, the latter of which is a proven deep brain stimulation target for tremor. These results suggest that lesion network mapping can identify the common substrate underlying therapeutic lesions and effective therapeutic targets.

INTRODUCTION

Brain damage such as stroke usually results in problematic symptoms and an overall decrement in function. Rarely, brain damage can lead to improvement in function, referred to as paradoxical functional facilitation.[1] Ideally, these spontaneously occurring lesions would help identify therapeutic targets for neuromodulation, allowing for relief of similar symptoms in other patients. However, translating spontaneous lesion cases into therapeutic targets has been challenging because these lesion cases are rare and tend to occur in multiple different brain locations, leaving the therapeutic target unclear. Further, symptomatic benefit may depend on the effect of the lesion on remote but connected brain regions, obscuring the target altogether.[1, 2] Due to these challenges, spontaneously occurring therapeutic lesions have played little role in identifying neuromodulation targets in use today.[3]

A recently validated technique termed lesion network mapping is ideally suited to address these problems.[4] By integrating a map of brain connectivity into lesion analysis, lesions in different locations can be linked to common neuroanatomy. This approach has proven broadly applicable for clinical symptoms or syndromes caused by focal brain lesions.[5] Here, we apply this same technique to lesions providing symptomatic benefit. For proof of concept, we focus on spontaneously occurring lesions that improve upper limb function in patients with essential tremor. This focus is motivated by the relatively high prevalence of essential tremor, especially in the age group at risk for stroke, and the presence of an established therapeutic target in the ventral intermediate nucleus of the thalamus (VIM).[6, 7] We test the hypothesis that this therapeutic target can be identified from case reports of spontaneously occurring beneficial lesions and a publicly available map of the human brain connectome.

SUBJECTS/MATERIALS AND METHODS

Cases of paradoxical functional facilitation of essential tremor

Cases of individuals with essential tremor who had relief of tremor following a focal brain lesion were identified using PubMed search terms "tremor", "essential tremor", "stroke", and "ischemic stroke". The search was performed in September 2016. A total of 1119 articles were found. Inclusion criteria were (i) a clear description of pre-stroke essential tremor, including postural and action tremor of the upper limbs, (ii) acute relief of tremor attributed to an ischemic event, and (iii) a published figure showing the location of the focal ischemic lesion. Exclusion criteria included: (i) cases of tremor relieved by hemorrhage, tumor, infection or other structural lesion; (ii) poor description of pre-existing tremor; (iii) parkinsonian tremor or obvious presence of parkinsonism; (iv) poor image resolution such that lesion boundaries could not be delineated. All case reports were evaluated by a movement disorders specialist (L.C.S.) for compliance with the above criteria.

Lesion network mapping

Lesion network mapping was performed in three steps using previously validated methods (Figure 2A).[4, 8] (i) published images of each lesion were traced by hand onto a common reference brain; (ii) the lesion volume (combination of all 2D slices) was used as a seed region of interest in a resting state functional connectivity MRI analysis that used normative data from 1000 subjects (http://neuroinformatics.harvard.edu/gsp/), as described earlier [8]; and (iii) the resulting network associated with each lesion volume was thresholded at a t-value of 7 (corresponding to voxel-level FWE-corrected $P<10^{-6}$ for whole brain search volume) and overlaid across lesions to identify common sites of network overlap.

Refinement of lesion network topography

Ideally, we would have liked to compare lesion networks improving essential tremor to lesion networks that failed to improve essential tremor, however identifying an adequate number of these lesion cases was not feasible. Instead, we compared our lesion networks to those derived from 486 consecutive stroke patients [9] using Bayesian Spatial Generalized Linear Mixed Model (BSGLMM, https://warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/software/bsglmm/).[10] This analysis

identified voxels most predictive of tremor relief, correcting for bias that could come from lesion locations in general.

Correspondence to known therapeutic targets

We compared our lesion network mapping results to established therapeutic targets for essential tremor using two approaches. First, we computed the spatial overlap between our results and a previously-derived optimal thalamic deep brain stimulation (DBS) target for essential tremor (MNI coordinates +/-13.05 -18.38 -2.01 mm).[11] Second, we compared our lesion network mapping results to a publicly available high resolution thalamic atlas.[12, 13] Lesion network targets in the left and right thalamus were averaged together for atlas overlay and visualization of DBS leads using Lead DBS software (www.lead-dbs.org).[14]

The study was approved by the institutional review board at Beth Israel Deaconess Medical Center (protocol #2018P000128) and conducted according to the principles of the Declaration of Helsinki.

RESULTS

Our search identified 11 cases of ischemic stroke causing relief of pre-existing essential tremor (**Figure 1, Supplementary Table 1**). Although lesion locations were heterogeneous, they were part of a common network, with functional connectivity to a common set of brain regions (**Figure 2)**. All 11 lesion locations were connected to the bilateral thalamus, bilateral cerebellum, left globus pallidus, and left putamen (**Figure 2B, Table 2**). The connectivity most predictive of tremor relief was to the right thalamus (peak MNI-coordinate 12 -18 -2 mm), followed by the left thalamus and right dorsal cerebellum (**Figure 2C, Supplementary Table 2**). Results were nearly identical when excluding four cases that involved lesions to the thalamus itself (Figure 2D).

Lesion network mapping results aligned well with the existing therapeutic target for essential tremor, with near perfect overlap (**Figure 3A).** In fact, our peak coordinate for tremor relief derived from spontaneous

brain lesions was identical to the peak coordinate for targeting DBS, within the constraints of our 2x2x2mm spatial resolution (12 -18 -2 mm vs 13.05 -18.38 -2.01 mm). When our lesion network results were overlaid on a high-resolution thalamic atlas, they overlapped the VIM nucleus (**Figure 3B**).

DISCUSSION

There are three main findings. First, lesions improving pre-existing essential tremor occur in multiple different brain locations. Second, these heterogeneous lesion locations are all part of the same functionally connected brain network. Finally, the peak of this lesion network is in the VIM, a proven therapeutic target for essential tremor. These findings suggest that lesion network mapping might be used to identify therapeutic targets from spontaneous beneficial brain lesions.

The search for locations to surgically induce therapeutic lesions has been guided in large part by trial-and-error and serendipity. For example, the first surgical lesions to improve tremor were not to the thalamus, but to nerve roots, the spinal cord, cerebral peduncle and the motor cortex.[3] These lesions improved tremor, but also caused paralysis. One of the first lesions to improve tremor without weakness was discovered when the thalamus was inadvertently damaged during an operation aimed at other brain structures. Here we provide evidence that spontaneously occurring brain lesions providing paradoxical functional benefit might inform this process.

This is the first study to use lesion network mapping for brain lesions that provide functional benefit. Previous lesion network mapping studies have been restricted to lesions that *cause* specific symptoms.[5] By investigating lesions that *improve* pre-existing symptoms, we show that lesion network mapping can help identify therapeutic targets. As spontaneously occurring brain lesions can improve other symptoms including other movement disorders, depression, migraine, and addiction, this technique may prove broadly applicable.[1] Unfortunately, there are not enough published cases displaying the lesion location to readily apply this technique to these other symptoms. We hope that the current paper, demonstrating the value of such cases, will motivate increased reporting moving forward.

Although the whole brain peak of lesion network mapping of tremor relief was in VIM, a secondary peak was present bilaterally in the cerebellum. The location of this peak falls in the motor cerebellum, in close proximity to the hand region.[15] The cerebellum is thought to play a key role in essential tremor, part of a cerebellar-thalamic circuit.[16, 17] Whether the cerebellar sites identified by lesion network mapping represent a secondary therapeutic target remains unknown, but could prove valuable for patients whose tremor is refractory to VIM DBS. Further, non-invasive stimulation of the cerebellum has shown some promise for treatment of essential tremor [18] and different therapeutic targets across neuromodulation methods tend to converge on common brain networks.[19]

There are some limitations. We used 2D instead of 3D lesions and used a normative connectome that was not age- or disease-matched to the lesion patients. However, these factors have been previously investigated and found to have little effect on lesion network mapping results.[4, 20] Second, our analysis was based on a relatively small number of lesions that improved tremor. Third, we did not have an optimal control group, namely patients with essential tremor and lesions that did not improve tremor. Instead, the topography of findings was refined using a large heterogeneous group of stroke patients, and some of these control lesions could conceivably also have provided tremor relief. However, these limitations should bias us against the present findings. Finally, our study was limited to a single syndrome, essential tremor. Whether the same approach can identify treatment targets in other conditions remains to be determined.

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AUTHOR CONTRIBUTIONS

Conception and design (JJ, LCS, MDF), acquisition and analysis of data (JJ, LCS, AH, MR, OW, NSR, MDF), drafting the manuscript or figures (JJ, LCS, AH, MDF). All authors reviewed and critiqued the manuscript.

POTENTIAL CONFLICTS OF INTEREST

MDF has submitted patents using connectivity imaging to identify brain stimulation targets. Other authors have nothing to disclose.

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FIGURE LEGENDS

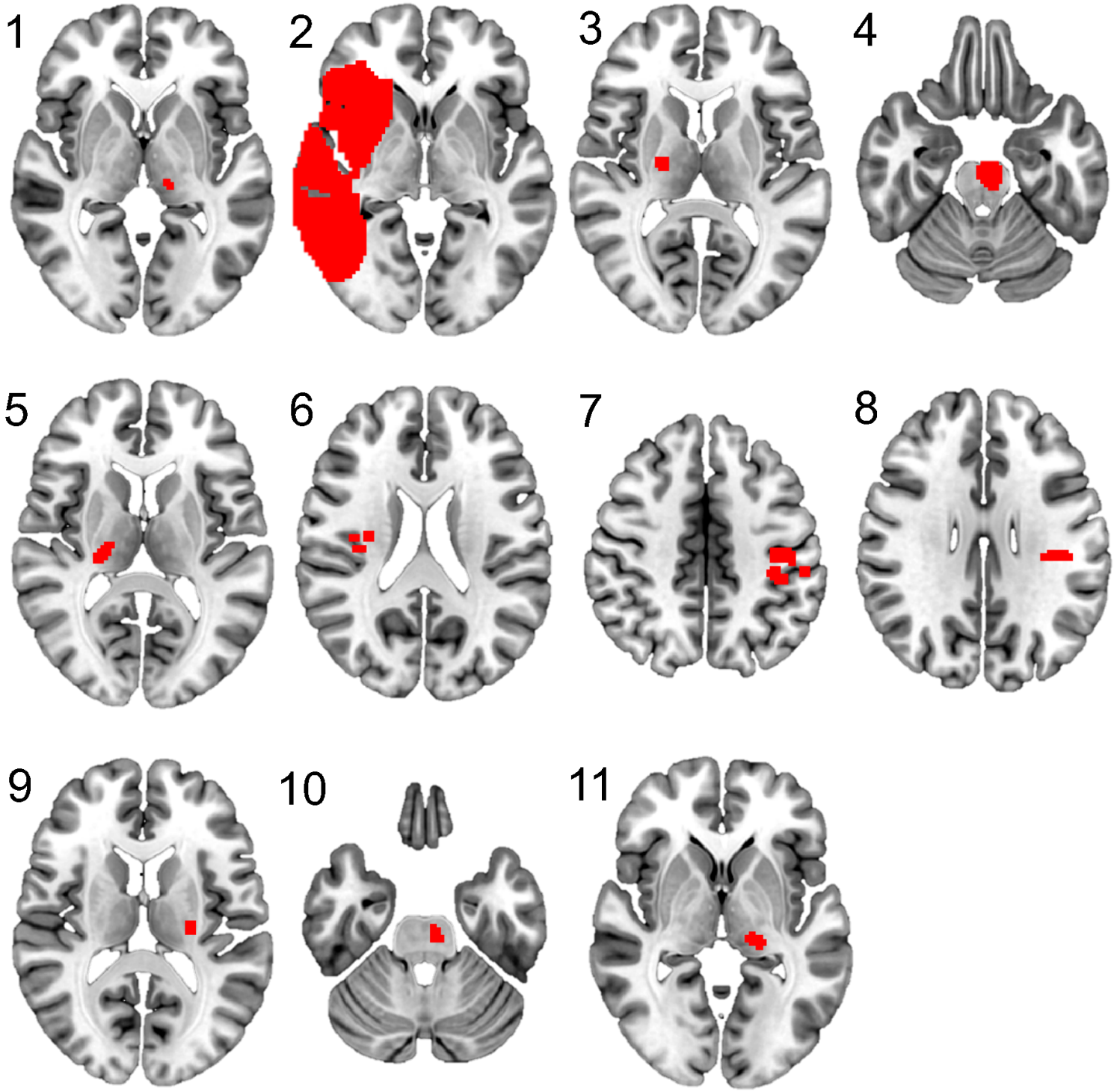
Figure 1. Lesion locations providing tremor relief in patients with essential tremor.

Figure 2. Lesion Network Mapping.

A. Each lesion location (3 examples shown) was converted into a lesion network using a large resting state functional connectivity database. B. Lesion network overlap showing voxels functionally connected to all 11 lesion locations. C. Posterior probability of voxels most associated (probability > 0.9) with tremor relief. D. Posterior probability when cases with thalamic lesions are excluded.

Figure 3. Lesion network mapping identifies the VIM DBS target for essential tremor.

A. Lesion network map (left panel), probabilistic coordinates of the ventral intermediate nucleus (VIM) target for DBS (middle), and their overlap (right). B. Bilateral average of the lesion network map overlaid on a high-resolution thalamic atlas. C. Example of the DBS electrode position in a patient with essential tremor with good therapeutic response. Note that the electrodes are run immediately next to the lesion network overlap clusters (shown also in panel B) and are likely to be within the activation field with multiple lead contacts. Note that he brain is slightly tilted to enable visualization of the lead trajectories within the 3D brain volume. Abbreviations follow Hassler nomenclature as equally used in the Schaltenbrand-Wahren stereotactic atlas (Schaltenbrand et al, 1977). V.im.i = ventral intermedius internus. V.im.e = ventral intermedius externus. For other abbreviations, see Ewert et al. (2017).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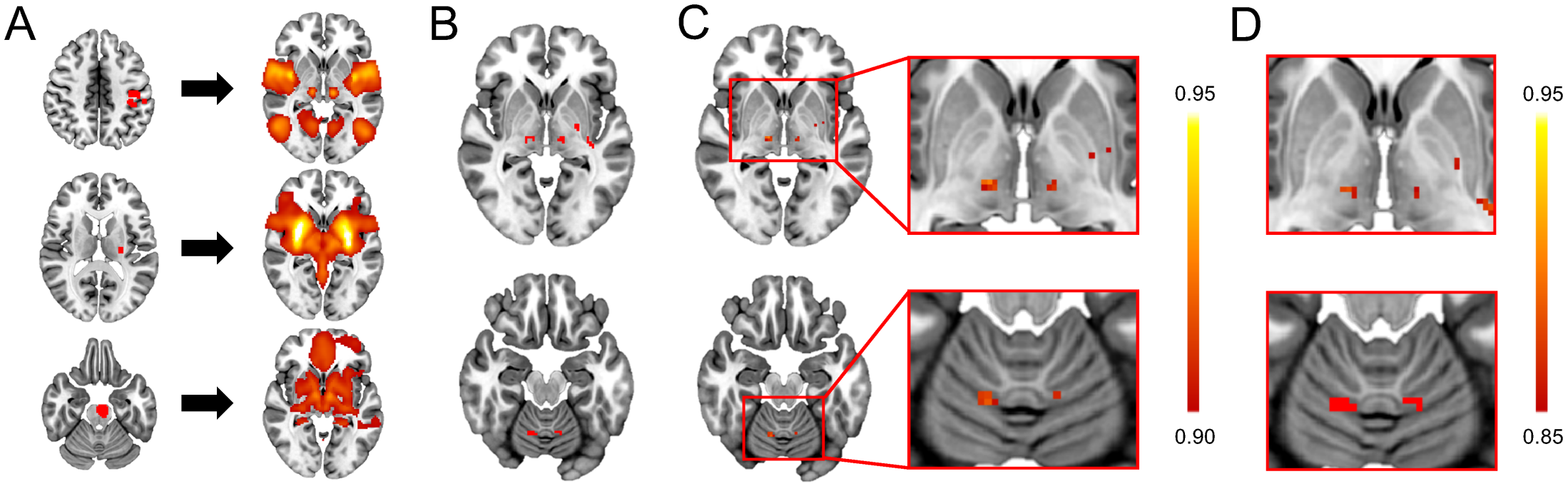
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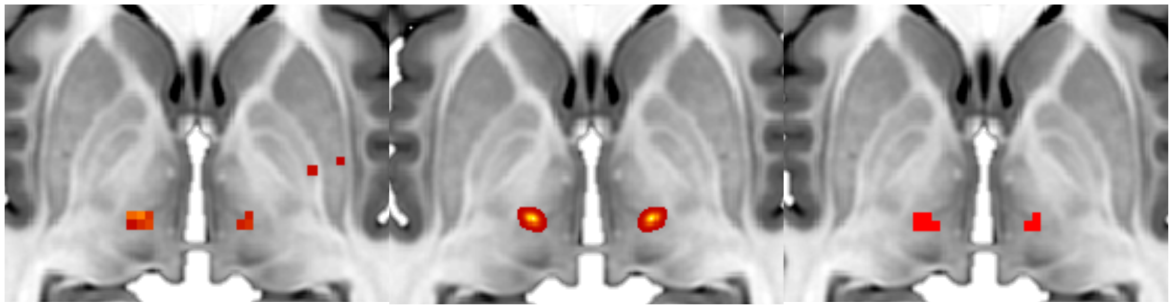

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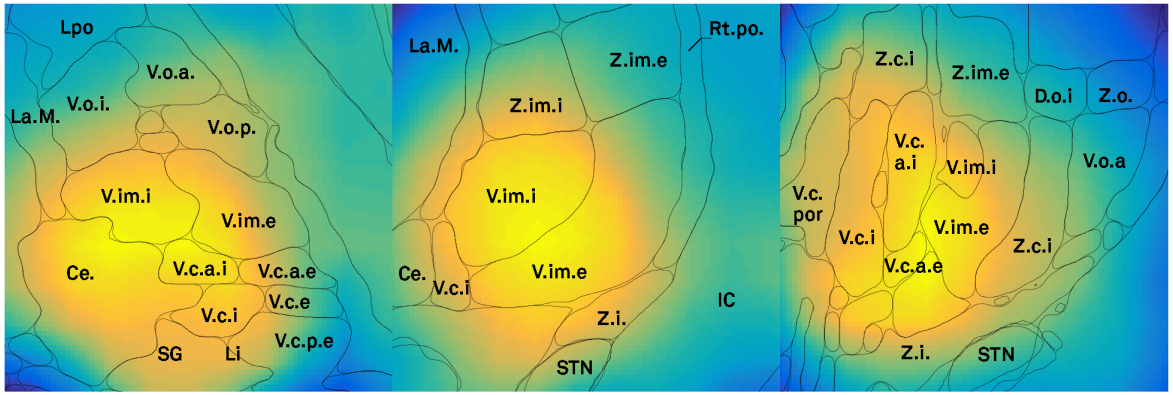

AXIAL *(z = 2.3 mm)* **CORONAL** *(y = -14.5 mm)* **SAGITTAL** *(x = ±14.5 mm)*

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