Delineation of a Connection Between the Trigeminal Nerve and Central Amygdala via Lateral Parabrachial Nucleus in Humans: An Ultra-High Field Diffusion MRI Study

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Background

Orofacial pain is thought to be more unpleasant than pain elsewhere in the body due to the importance of the face in social, feeding, and exploratory behaviors[1-4]. Pain from the orofacial region is carried to the brain via the trigeminal nerve (CNV) and the trigeminal brainstem sensory nuclear complex (VBSNC). Recent pre-clinical evidence suggests that a monosynaptic circuit from CNV directly to the lateral parabrachial nucleus (latPB) underlies the greater unpleasantness elicited by pain in the orofacial region in rodents[5]. The latPB further projects to the central amygdala (CeA), which is thought to contribute to the affective component of pain[6]. **This circuit has yet to be delineated in humans.** With ultra high-resolution open-source neuroimaging databases, i.e., the Human Connectome Project (HCP), the presence of circuits identified in other species can be explored *in vivo* in humans. Diffusion-weighted imaging (DWI) and tractography can map white matter tracts and delineate such circuits.

Aims

- **Primary Objective:** Determine whether the CNV-latPB-CeA circuit can be resolved in humans *in vivo* in a pilot and an independent validation sample using probabilistic tractography on ultra-high field (7T) DWI scans from the HCP.
- **Secondary Objective:** Explore whether there are sex differences in the probabilistic connectivity metric for the CNV-latPB-CeA circuit in both samples.

Methods

Pilot Sample: 15 Healthy Adults:
- 8F (mean age ± SD: 31.8 ± 2.3)
- 7M (27.4 ± 1.7)

Validation Sample: 80 Healthy Adults:
- 52F (30.1 ± 2.7); 28M (28.0 ± 4.0)
- Power calculation based on: $\eta_p^2 = 0.043$ (factors*: tract target * sex*)
- After exclusions:
- 45F (30.1 ± 2.7); 22M (28.1 ± 3.8)

Neuroimaging data:
7T DWI
- 1.05 mm isometric
- 65 directions; 6 b0's

T1 at 3T (0.7 isometric)

Seeds: CeA[7], basolateral amygdala (BLAT)[7], periaqueductal gray (PAG)[8], latPB[8], motor nucleus of the trigeminal nerve (5M)[9], trigeminal root entry zone (REZ), trigeminal cisternal plane (CP)

Statistics: Connectivity strength was quantified by natural log normalized, seed size-corrected, averaged, and thresholded waytotal count per tractogram
- Repeated measures ANOVA with sex as a between subjects factor
- Factor 1: Target; Factor 2: Hemisphere

Guiding the Probabilistic Tractography

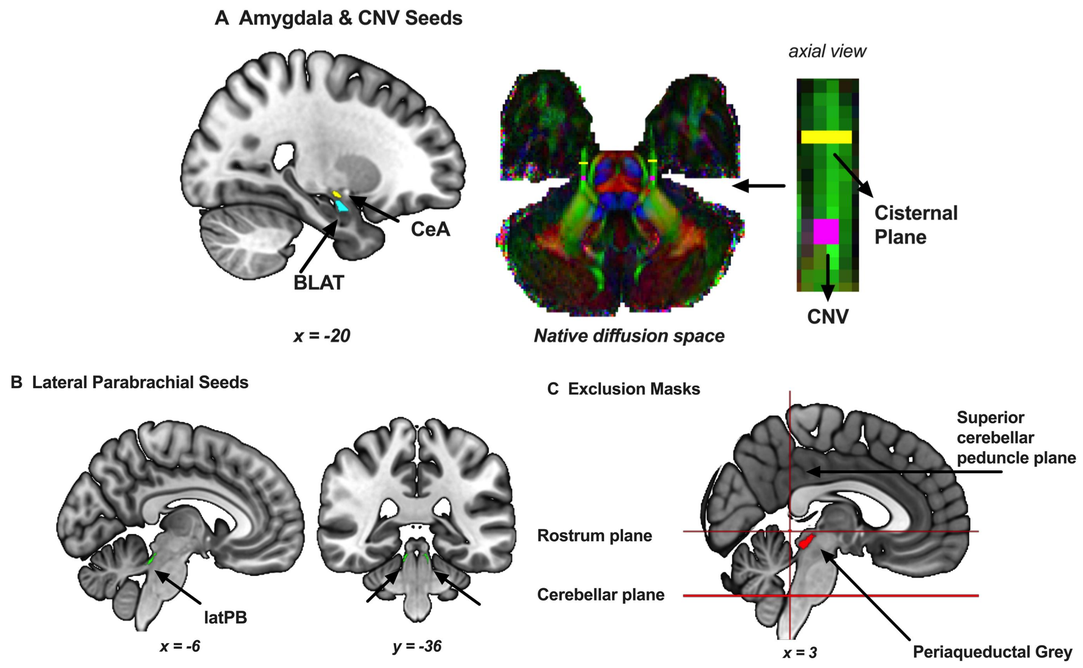

***Figure 1:* Seeds and exclusion planes used in tractography.**
Panel A: Amygdalar subnuclei from the Tyszka & Pauli atlas. CNV seeds are illustrated in a representative diffusion image from a study subject. *Panel B:* LatPB seeds from the Brainstem Navigator atlas. *Panel C:* Exclusion planes and the PAG seed were used to increase the specificity of tractography by eliminating streamlines crossing these regions.

Results

The CNV-latPB-CeA circuit can be resolved at 7T

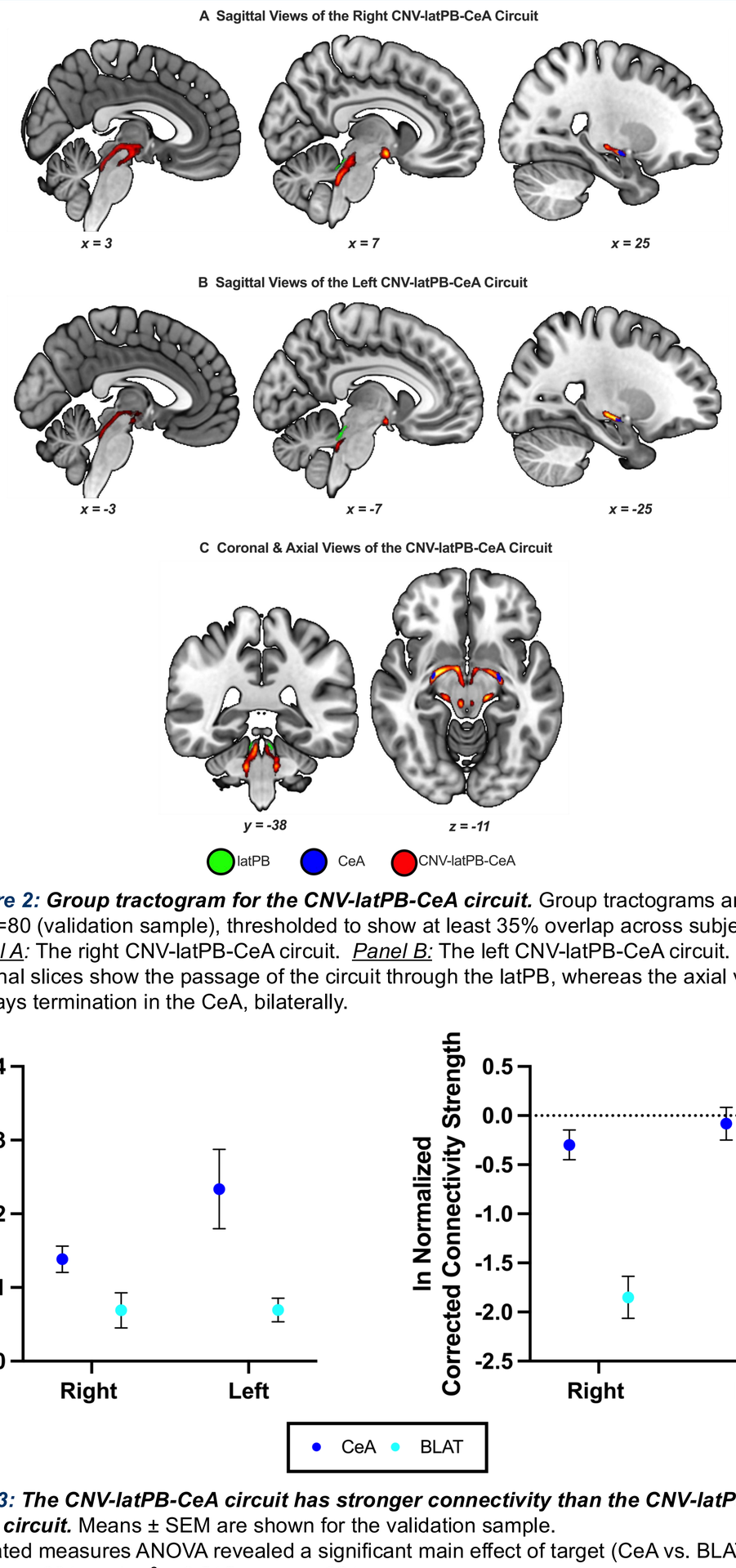

***Figure 2:* Group tractogram for the CNV-latPB-CeA circuit.** Group tractograms are based on N=80 (validation sample), thresholded to show at least 35% overlap across subjects. *Panel A:* The right CNV-latPB-CeA circuit. *Panel B:* The left CNV-latPB-CeA circuit. *Panel C:* Coronal slices show the passage of the circuit through the latPB, whereas the axial view displays termination in the CeA, bilaterally.

***Figure 3:* The CNV-latPB-CeA circuit has stronger connectivity than the CNV-latPB-BLAT control circuit.** Means ± SEM are shown for the validation sample.
A repeated measures ANOVA revealed a significant main effect of target (CeA vs. BLAT); $F_{1,65} = 69.113$, $p < .001$, and $\eta_p^2 = 0.515$; $p_{Tukey} < .001$

We found no sex differences in the study samples

Discussion

We show:

❖The first *in vivo* delineation of the direct monosynaptic CNV-latPB-CeA circuit in humans in a pilot and an independent, sufficiently powered validation sample.

❖This circuit bypasses trigeminal brainstem sensory nuclear complex synapses to provide unmodulated nociceptive input to the latPB and, further, to the CeA.

Significance:

❖The CNV-latPB-CeA circuit may provide a neural basis for enhanced suffering in orofacial pain.

❖Therefore, the CNV-latPB-CeA may serve as a potential therapeutic target for chronic pain disorders that are accompanied by increased levels of fear of pain and suffering, such as trigeminal neuralgia[10].

Conclusion

The monosynaptic CNV-latPB-CeA circuit exists in humans and can be resolved using 7T diffusion weighted imaging.

Data Availability

All procedures were approved by the University of Toronto's Human Research Ethics board (Protocol number: 00040458). We have no conflicts of interest to declare. The data that support the findings of this study are openly available in the Human Connectome Project database at https://db.humanconnectome.org, HCP S1200 Release (February 2017).

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