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Bridging Scales to Map the Human Claustrum: BigBrain, Julich, and 7-Tesla MRI

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Background. The claustrum is a thin, sheet-like grey matter structure nestled between the putamen and insula, wrapped by the capsulae externa and extrema. It is among the most highly connected brain regions, with reciprocal projections spanning the cortical mantle. But claustral function is underinvestigated in living humans, as its complex three-dimensional architecture is poorly understood, and its thinness and proximity to neighboring structures challenge the effective resolution of MRI. Consequently, few *in vivo* studies exist, and those that do report radically inconsistent characteristics—for example, volume estimates differ by up to fivefold **[FIG.1A]**—raising concerns about the reliability of findings on connectivity, function, and case-control differences.

Objective. To illuminate the claustrum's three-dimensional anatomy and characterise mapping challenges, our work establishes a multi-scale reference linking micrometre histology to (sub)millimetre MRI, quantifies resolution-dependent distortions and inter-individual variability, and defines the practical limits for reliable *in vivo* measurement.

Methods. We manually segmented the bilateral claustrum across three scales. First, we derived a continuous three-dimensional "gold-standard" reference from BigBrain (n=1; 100µm isotropic, MNI ICBM-152 space) (Amunts et al. 2013) **[FIG.1B]**. Second, in ten Julich postmortem brains (5 female; 37–85 years), we mapped the claustrum in native space on every ~60th Merker-stained coronal section (1µm in-plane, ~1.2mm spacing; >400 sections per brain) to validate boundaries and assess population variability relative to BigBrain (Amunts et al. 2020). Finally, we quantitatively compared three 7-Tesla MP2RAGE datasets (n=30; 10 per resolution at 0.5mm, 0.7mm, 1.0mm isotropic) with the BigBrain reference and its resolution-matched downsamplings to benchmark MRI's capacity to resolve claustral morphology.

Results. The BigBrain gold standard provides the first continuous three-dimensional model of the human claustrum from histology. It is broadly consonant with prior two-dimensional histological descriptions but resolves the claustrum in greater detail than recent three-dimensional post-mortem MRI references (Coates and Zaretskaya 2024; Mauri et al. 2024) and whole-brain anatomical atlases (Mai et al. 2015; Ding et al. 2016). Comparison of BigBrain with Julich brains confirmed that while the gold standard is broadly representative, cellular-level resolution suggests direct abutment with the olfactory tubercle, amygdaloid complex (Kedo et al. 2018), and piriform cortex (Kedo et al. 2024) **[FIG.1C]**, with substantial intersubject variability in the ventral claustrum. MRI-to-BigBrain comparisons revealed resolution-dependent distortions that scaled with voxel size (1.0mm > 0.7mm > 0.5mm): mediolateral thickness was inflated, producing paradoxical volume overestimation; anteroposterior length was truncated with anterior portions often missing; and superoinferior extent was underestimated due to largely unresolved ventral "puddles" **[FIG.1D]**.

Discussion. This work resolves a critical methodological bottleneck in claustrum research by providing the first comprehensive validation framework linking histology to MRI. By leveraging BigBrain's unmatched three-dimensional continuity alongside cellular-level validation in the Julich brains, our findings establish minimum resolution requirements and morphological benchmarks for reliable *in vivo* measurement. In particular, submillimeter resolution at ultra-high field consistently recovers the claustrum's dorsal core and achieves over 50% spatial agreement with the gold standard, establishing a satisfactory foundation for *in vivo* studies that may test long-standing hypotheses about claustral connectivity, function, and clinical relevance.

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