The functional connectivity of the human claustrum according to the Human Connectome Project data

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Abstract

The claustrum is an irregular and fine sheet of grey matter in the basolateral telencephalon present in almost all mammals. The claustrum has been the object of several studies using animal models and more recently in human beings using neuroimaging. It has been involved in cognition and disease such as fear recognition, suppression of natural urges, multisensory integration, conceptual integration, seizures, multiple sclerosis and Parkinson´s disease. Nevertheless, the function of the claustrum still remains unclear. We present a high resolution functional connectivity study of the claustrum in order to identify its main networks. Resting state functional and anatomical MRI data from 40 healthy subjects were analyzed; taken from the Human Connectome Project (HCP, NIH Bleuprint: The Human Connectome Project), with 2x2x2 mm^3 voxel resolution, equivalent to the high resolution tractography studies. Positive functional connectivity was found ($p<0.05$, FDR corrected) between the claustrum and the insula, anterior cingulate cortex, pre-central and postcentral gyrus, superior temporal gyrus and subcortical areas. Our findings coincide with the results previously reported in both animal models and studies with humans. Showing the claustrum as a profusely connected structure not only structurally but also functionally. Evidencing the claustrum as a node participating in a plethora neural networks.

Keywords: Brain connectivity, resting state, HCP, insula, thalamus, cingulate cortex

Introduction

The claustrum is an irregular and fine sheet of grey matter in the basolateral telencephalon present in almost all mammals. The claustrum is separated from the insular cortex by the extreme capsule and medially from the lentiform nucleus by the external capsule (Edelstein and Denaro, 2004; Crick and Koch, 2005; Fernández-Miranda et al., 2008; Kapakin, 2011; Goll et al., 2015; Milardi et al., 2015). Figure 1 shows in an axial view the anatomical location of the human claustrum. Research in humans using diffusion tensor imaging (DTI) have revealed cortical connections with the claustrum, which possesses projections to A) prefrontal cortex, BA 8, 9, 10, 11, 12 and 34; B) visual cortex, BA 17, 18, 19 and 39; C) sensoriomotor cortex, BA 7, 5, 1/2/3, 4, 6 and 8; and D) language areas BA 44, 45 and 31; as well as with orbitofrontal cortex, temporal cortex, basal ganglia and amygdala (Fernández-Miranda et al., 2008; Milardi et al., 2015; Torgerson and Van Horn, 2014). These results are consistent with the input-output of the claustrum to cortical areas previously reported in animal model studies (Goll et al., 2015).

Based on its cellular composition and wide structural connectivity, the claustrum has been described as a "cornerstone of sensory integration" (Edelstein and Denaro, 2004). In a similar way, Crick and Koch (2005) proposed the claustrum as a crucial component integrating motor and sensory information coming from different modalities to assemble them in a single experience; in an analogy used by Crick and Koch, the claustrum is as an orchestra conductor, "[w]ithout the conductor, the players can still play but they fall increasingly out of synchrony with each other." (Crick and Koch, 2005); actually, this proposal has been one of the most influent in the claustum literature. In addition, the claustrum has been proposed as a relevant structure in the segregation of attention (Goll et al., 2015).

Claustrum have been involved in cognitive process such as fear recognition, suppression of natural urges, multisensory integration and conceptual integration. The involvement of the

claustrum in such processes is the result of a different research question more than the question of the function of claustrum by itself (Banati et al., 2000; Hadjikhani and Roland, 1998; Naghavi et al., 2007; Lerner et al., 2009). Although it is rarely reported in the medical literature the selective lesion of the claustrum; the claustrum has been involved in disease such as seizures, multiple sclerosis, Parkinson´s diseases and auditory hallucinations and delusions (Wada and Kudo, 1997; Kalaitzakis et al., 2009; Cascella et al., 2011; Cascella & Sawa, 2014; Klaver et al., 2015; Patru & Reser, 2015).

Resting-state functional connectivity has provided a useful tool to characterize the functional network of the claustrum. Examining resting state functional connectivity allows us to determine the correlation between the spontaneous activity of brain areas that are anatomically separated, observing if there is "(…) functional communication between brain regions (…)" (van den Heuvel and Pol, 2010) which is important in cognitive processes. A Recent study in humans, show the functional connectivity between the claustrum and anterior cingulate, prefrontal, visual cortex and parietal cortices; suggesting the association of the claustrum with cognitive control. This study also reported functional connectivity between the claustrum and posterior cingulate cortex, precuneus, angular gyrus, cuneus, visual cortex, and sensorimotor cortex, as well as with subcortical structures such as thalamus and nucleus accumbens among others (Krimmel et al., 2019).

The claustrum literature – including studies in animal model and in humans – has evidenced the vast anatomical connections between the claustrum and the entire cerebral cortex as well as with the subcortical structures (Eldestein & Denaro, 2004; Fernández-Miranda et al., 2008; Torgerson and Van Horn, 2014; Mathur 2014; Milardi et al., 2015; Goll et al., 2015; Qadir et al., 2018); and more recently Krimmel et al., (2019) contributed to this goal, examining the functional connectivity of the claustrum. Nevertheless, we do not have a clear or complete

understanding on the function of the claustrum beyond of the theoretical proposals (Eldestein & Denaro, 2004; Crick & Koch, 2005; Goll et al., 2015).

One of the most challenging issues to study the human claustrum is its intricated anatomical location and its irregular form. Technical constrains have limited the detailed study of the claustrum. We propose overcome these challenge by assessing the whole brain resting state functional connectivity of the claustrum using the high-resolution WU-Minn Human Connectome Project (HCP) dataset, which, differs qualitatively from the standard neuroimgen data, due to its higher spatial and temporal resolution and differing distortion. The functional datasets were acquired with a spatial resolution of 2 mm isotropic and a temporal resolution of 0.7 s at 3T, which in a non usual high spatial or temporal resolution for whole brain coverage. (HCP; Van Essen et al., 2012; Van Essen et al., 2013; Glasser et al., 2013; Smith et al., 2013)

Materials and methods

Subjects

The study included data from 40 healthy young adults (20 females) with ages between 22 and 35 years old. Subjects were selected from the public WU-Minn Human Connectome Project (HCP NIH Blueprint: The Human Connectome Project) (Van Essen et al., 2012). HCP excluded subjects having history of psychiatric, neurological or neurodevelopmental disorder or substance abuse. A full and detailed description of the recruitment criteria is provided by Van Essen et al., (2013). Our selection was restricted to subjects with complete resting-state functional magnetic resonance imaging (rfMRI) and anatomical MRI datasets. The full informed consent from all participants was obtained by the WU-Minn HCP Consortium. The protocols of the data

acquisition and distribution of the dataset complied with the Code of Ethics of the World Medical Association (Van Essen et al., 2013).

Image acquisitions and preprocessing

The HCP acquired anatomical and resting-state functional MRI data at Washington University using a customized Siemens 3T "Connectome Skyra" with a standard 32-channel head coil. Structural dataset acquisitions included high resolution T1-weighted (T1w) and T2-weighted (T2w) images with 0.7 mm isotropic resolution, FOV = 224x224 mm, matrix = 320, 256 sagittal slices in a single slab TR = 2400 ms, TE = 2.14 ms, TI = 1000 ms, FA = 8°. Resting-state fMRI were acquired at 2 mm isotropic resolution, TR=720ms, TE = 33.1 ms, slice thickness of 2.0 mm, 72 slices. Uğurbil et al., (2013) and Glasser et al., (2013) provide a full and detailed description of the HCP acquisition protocols. We include in our study the HCP dataset preprocessed by the HCP which due its higher spatial and temporal resolutions and differing distortions must be processed differently from standard neuroimaging data in order to achieve optimal results. (Glasser et al., 2013; Ugurbil et al., 2013). Pipelines developed by HCP include spatial distortion correction, motion correction, spatial registration and normalization to MNI coordinates, highpass filtering (cutoff=2,000s) and denoising of rfMRI. In addition, we use as confound regressors the motion outlier volumes during the analysis, and we spatially smoothed the rfMRI data to 3 mm full width half max (FWHM = 3) using conn toolbox (V18b, Functional connectivity toolbox, NITRC) (Whitfield-Gabrieli and Nieto-Castañón, 2012), and SPM 12 software (Friston et al., 1994).

Mask of claustrum and functional connectivity

The T1 anatomical volumes were used to manually delineate right and left claustrum masks for each subject, in an axial plane, in a superior-to-inferior manner to identify the body of the claustrum and edited in the coronal and sagittal plane for accuracy. We transformed them into the rfMRI space, spatially averaged the claustrum masks and established the threshold the mask to transform it into a binary mask. All these processes were carried on with FSL tools v5.0. The claustrum mask constituted our seed to perform a seed-based functional connectivity analysis.

High resolution functional connectivity maps were estimated using the Conn toolbox (V18b, Functional connectivity toolbox, NITRC), (Whitfield-Gabrieli and Nieto-Castañón, 2012). Pearson correlation coefficients were calculated within each subject in MNI space taking the seed time course and the time course of all other voxels. The resultant correlation coefficient maps were converted to normally distributed scores using Fisher transform to permit a second-level analysis, in which, a one-sample t-test was performed. The resultant connectivity maps were corrected at map level $p<0.05$ using False Discovery Rate (FDR).

Results

The claustrum was delimited by our averaged mask whose dimensions are 31mm x 1 mm x 17 mm. We closely coincide with the dimension described by Kapakin (2011); figure 2 shows on an axial view the average mask used in the analysis.

We identified functional connectivity of the left claustrum ($p<0.05$ p-FDR corrected) with precentral gyrus, postcentral gyrus, insular cortex, superior temporal gyrus, supramarginal gyrus, opercular cortex, frontal cortex and anterior cingulate cortex (Fig. 3). We found functional connectivity between the right calustrum and precentral gyrus, postcentral gyrus, insular cortex, temporal cortex supramarginal gyrus, opercular cortex, frontal cortex, cingulate gyrus and occipital cortex (Fig. 4).

We performed a ROI-to-ROI (region of interest) analysis using as region of interest the claustrum and the CONN atlas cortical ROIs (Harvard-Oxford and the CONN network cortical ROIs (HCP-ICA). We obtained a positive correlation between the left claustrum and subcortical areas such as caudate nucleus, putamen, accumbens, thalamus, hippocampus, amygdala and brainstem. In same way when using the right claustrum as ROI we obtained positive functional connectivity with caudate nuecleus, putamen, thalamus, hippocampus, amygdala and brainstem, but not accumbens nucleus as in left claustrum. ($p<0.05$ p-FDR corrected) (Fig. 5).

Finally, functional connectivity was also found with network cortical ROIs. The claustra are functionally connected with nodes of the default mode network such as medial prefrontal cortex, lateral parietal cortex, salience network, including anterior insula, rostral prefrontal cortex, anterior cingulate cortex, supramarginal gyrus, language network whose areas are the inferior frontal gyrus, posterior superior temporal gyrus, frontoparietal network including the lateral prefrontal cortex, areas of the dorsal attention network, such frontal eye field, the intraparietal sulcus. The superior and lateral areas pertaining to the sensoriomotor network, the cereberal anterior area, and visual areas such as medial, lateral and occipital visual area (Fig. 6).

Discussion

The claustrum is located deep within the insular cortex, and investigating its function and connections is difficult due to its size and shape. Despite the inherent difficulty, it has been investigated using animal models (rodent, cat and non-human primate) and invasive techniques such as retrograde neuronal tract tracer labeling (Mathur et al., 2009) and electrophysiological studies (Remedios et al., 2014). In a recent review, Goll et al. (2015) presented the anatomical

connectivity of the claustrum in the rodent brain; the primary inputs and outputs to the claustrum are from the cerebral cortex, – which are reciprocal connections – such as prefrontal cortex, motor cortex, somatosensory cortex, auditory cortex and visual cortex. The claustrum also maintains connections with the striatum, amygdala, cingulate area, prelimbic area and hippocampus. The study of structural connections in human claustrum has advanced with the use of Diffusion Tensor Imaging (DTI) and the results are consistent with those in animal models, i. e. frontal, parietal, temporal and occipital areas (Fernández-Miranda et al., 2008; Milardi et al., 2015; Torgerson and Van Horn, 2014).

One of the most important hypotheses regarding the function of the claustrum was proposed by Crick and Koch (2005), who proposed the claustrum as an important hub which integrates stimuli from different sensory modalities. Hadjikhani et al., (1998) researching neural bases of tactile–visual cross-modal transfer of shape in humans using neuroimaging, found that the claustrum has an important role in cross-modal matching. Their results suggest that the cross-modal adaptation is associated with multimodal converging brain areas such as anterior cingulate cortex, inferior parietal lobe, superior and mid temporal cortex, dorsolateral prefrontal cortex and insular cortex. Banati et al., (2000) also found activation by tactile-visual stimuli in anterior cingulate cortex, dorsolateral prefrontal cortex, mid and superior temporal cortex and insula cortex. These results are consistent with our findings that anterior cingulate cortex, superior, temporal cortex and insular cortex are functionally connecting with the claustrum.

On the other hand, another important hypothesis about the function of the claustrum is related to segregation of attention (Goll et al., 2015). The claustrum is considered as a hub for attention, according to this model, the prefrontal cortex modules to the claustrum in a top down process and the output of the claustrum modules the cortical representation of the sensory modalities. The claustrum controls which cortical output will be attended amplifying the

preferred modality and reducing the other ones. This process would be modulated by additional subcortical inputs related to the context and emotion hippocampus and amygdala respectively. Our results are compatible with this model, since we found a positive correlation between the claustrum and the prefrontal cortex, anterior cortex cingulate, pre y postcentral gyrus, amygdala and hippocampus, which, according to the model of Goll et al. are implied in the segregation of attention (Goll et al., 2015).

We found functional connectivity with specific nodes of the characterized networks such as salience, default mode, dorsal attention, frontoparietal, language, sensoriomotor, visual an cerebelar anterior, which imply that the claustrum is not only well connected structurally but also functionally.

Our findings reveal that the claustrum maintains a functional connectivity with regions of the salience network, this could be justified not only due to the anatomical closeness of the claustrum with the insula, but also because they share ontogeny. Pirone *et al*., (2012) using immunohistochemistry technique and samples of insular and temporal subunits of the human claustrum, revelead that the claustrum share ontogeny with the insular cortex, but not with the putamen. Additionally, Remedios et al., 2014, analized the neurons located in the auditory zone of the primate claustrum and arrived to the conclusion that the clausturm detects the occurrence of novel or salient stimulus.

On the other hand, we found functional connectivity between the claustrum and executive networks brain, which evidence that the claustrum participate in cognition. Claustral activation is reported in a fMRI study about the neuronal bases of the integration of auditory and visual stimuli, which, were conceptually related (congruent). The author of this study concluded that the

contribution of the claustrum was related to the congruence of stimuli, not only to the matching of these (Naghavi *et al*., 2007).

We are confident that our study contribute to the understanding of this thin but well connected structure: the claustrum. The use of the high quality HCP dataset provide us of advantages to our study, because of its high spatial and temporal resolution; and to the standardized preprocessing accomplished by the HCP members. Additionally the age range chosen (22-35 years-old) permit an unbiased analyses due to it represent healthy adults who are not experimenting the major neurodevelopmental changes nor neurodegenerative changes (Essen et al., 2012).

In conclusion, the claustrum is a highly connected brain structure, hardly to study due its anatomical location and irregular form. Neuroimaging offers a powerful tool to explore its function non invasively, despite its limited resolution. Making use of open access high resolution datasets, we have characterized the functional connectivity of the human claustrum, which mainly include positive relations with insular, frontal, temporal and cingulate cortex. These findings evidence the close relationship of the claustrum with the salience network, strongly supporting its proposed role to mediate the salience value of sensory stimuli.

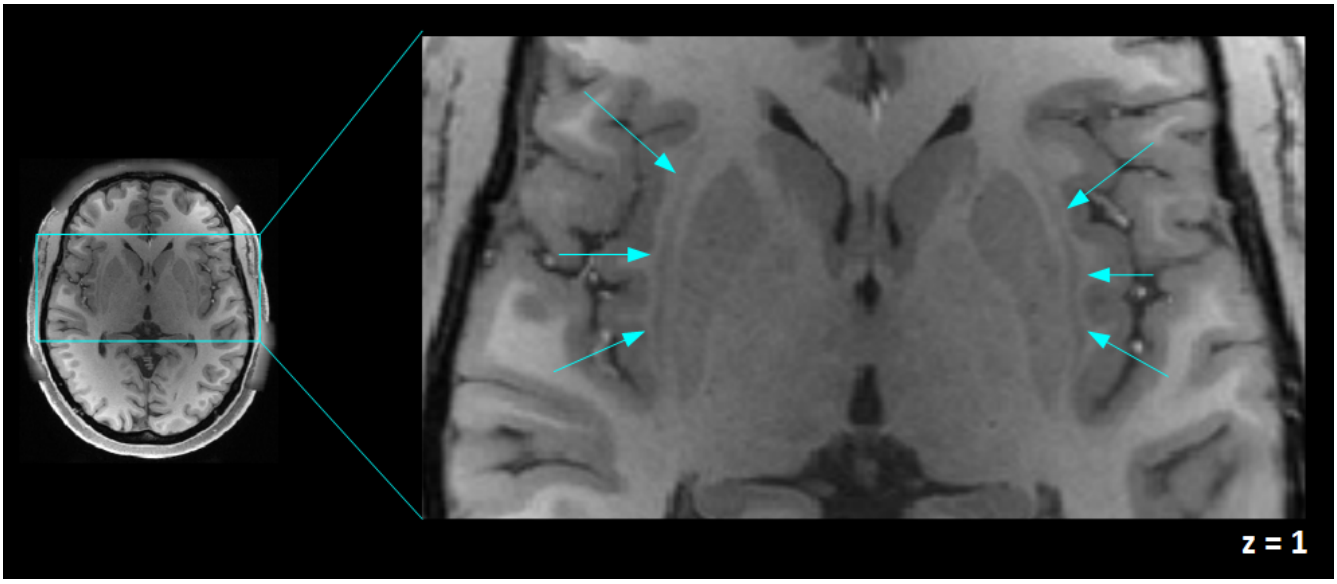

Figure 1. An axial view of the human claustrum. The human claustra are shown between the external and extreme capsule (signaled by blue arrows), left and right claustra in a T1-weighted image of one of the participants are shown in MNI coordinates.

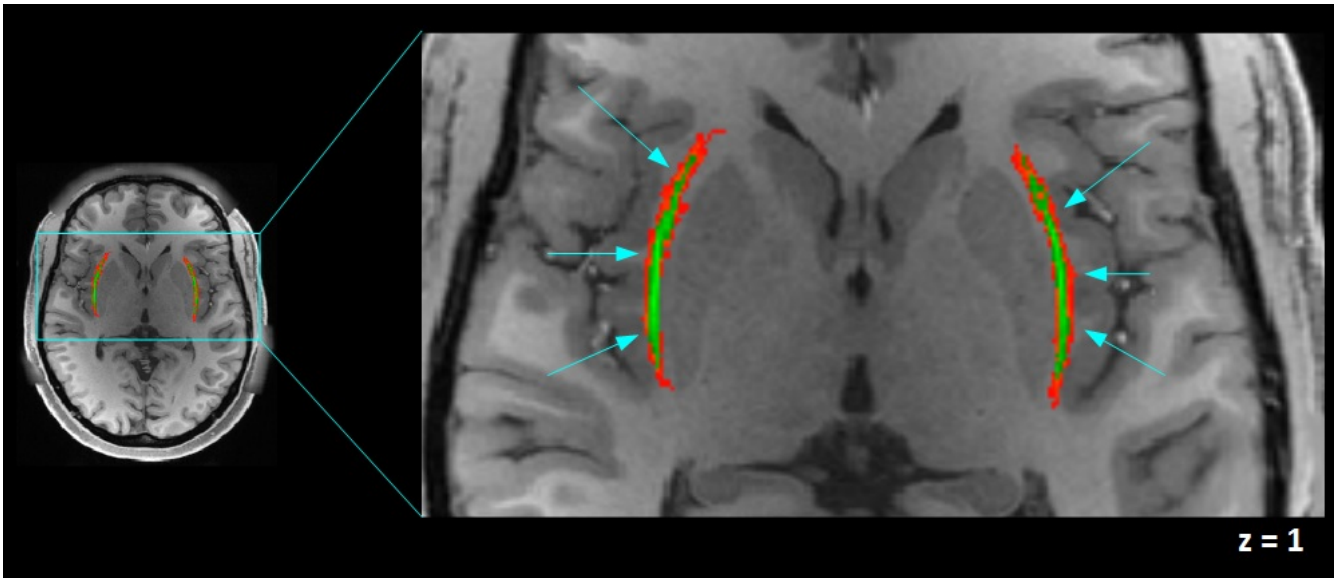

Figure 2. On an axial view, the averaged mask of the claustrum is shown in green, left and right claustra mask on a T1-weighted image of one of the participants are shown in MNI coordinates. In our analisys we include only the green area.

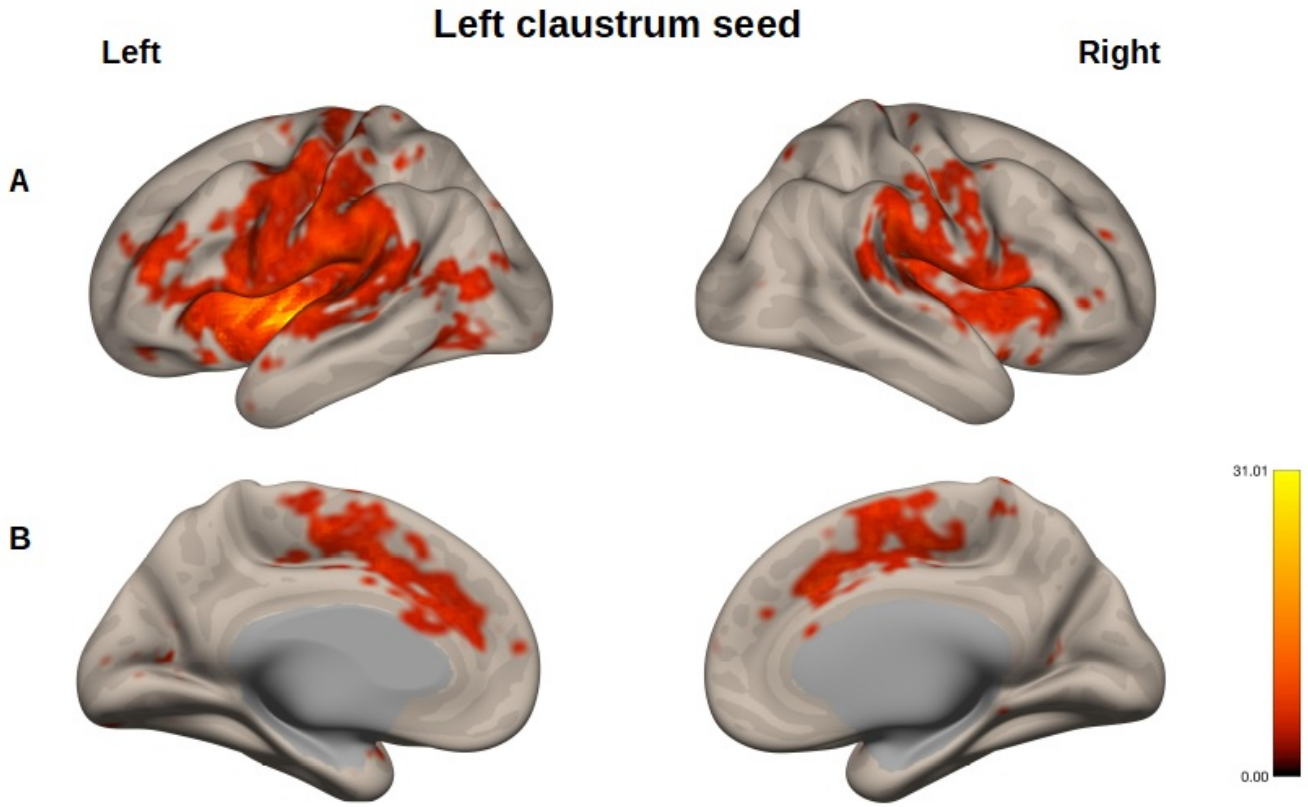

Figure 3. Seed-to-voxel functional connectivity with left claustrum as seed. ($p < 0.05$, p-FDR corrected) Row (A) Left, Insular cortex, temporal cortex, precentral gyrus, postcentral gyrus, supramarginal gyrus, opercular cortex, frontal cortex. Right, insular cortex, precentral and postcentral gyrus, supramarignal gyrus, temporal cortex (B) Left, cingulate gyrus (anterior division). Right, cingulate gyrus.

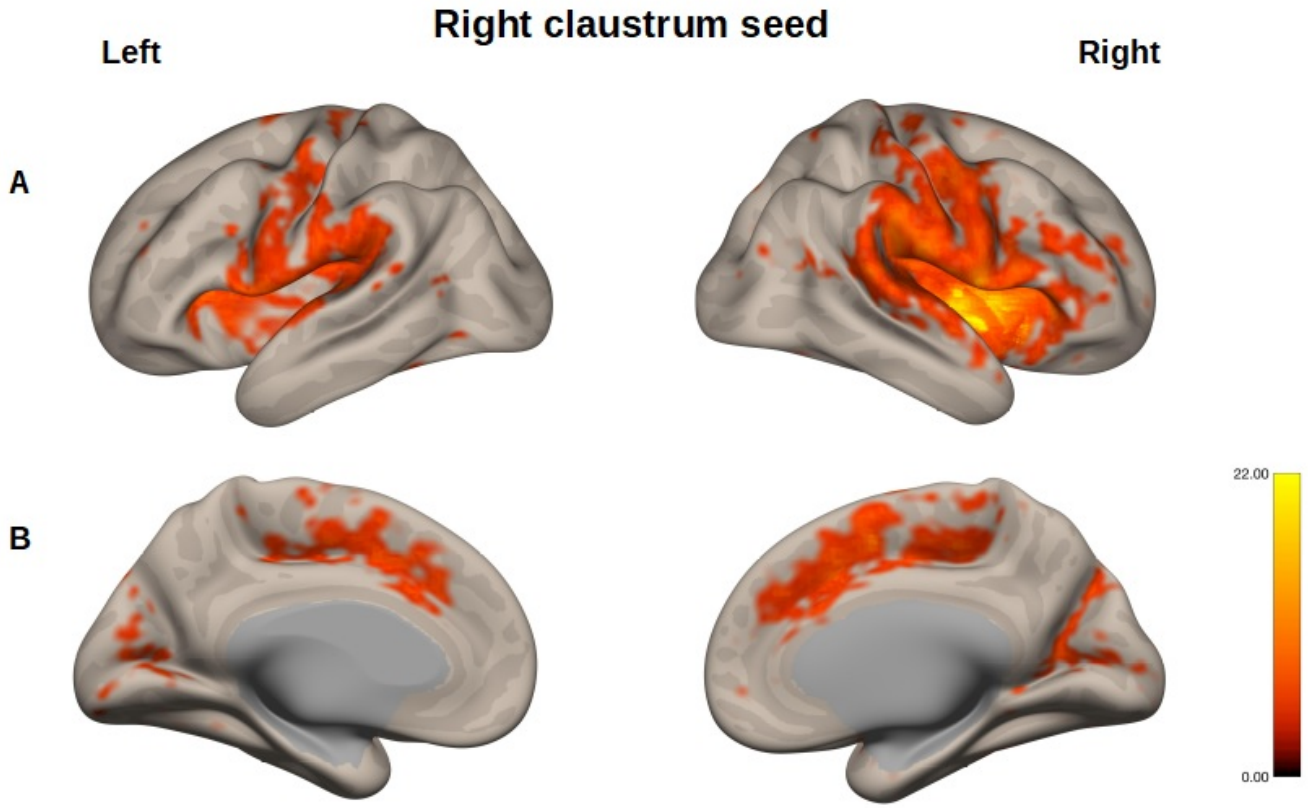

Figure 4. Seed-to-voxel functional connectivity with right claustrum as seed. ($p < 0.05$, p-FDR corrected) Row (A) Left, insular cortex, temporal cortex, precentral gyrus, postcentral gyrus. Right, insular cortex, precentral and postcentral gyrus, supramarginal gyrus, temporal cortex, opercular cortex, frontal cortex. (B) Left, cingulate gyrus. Right, cingulate gyrus, occipital cortex.

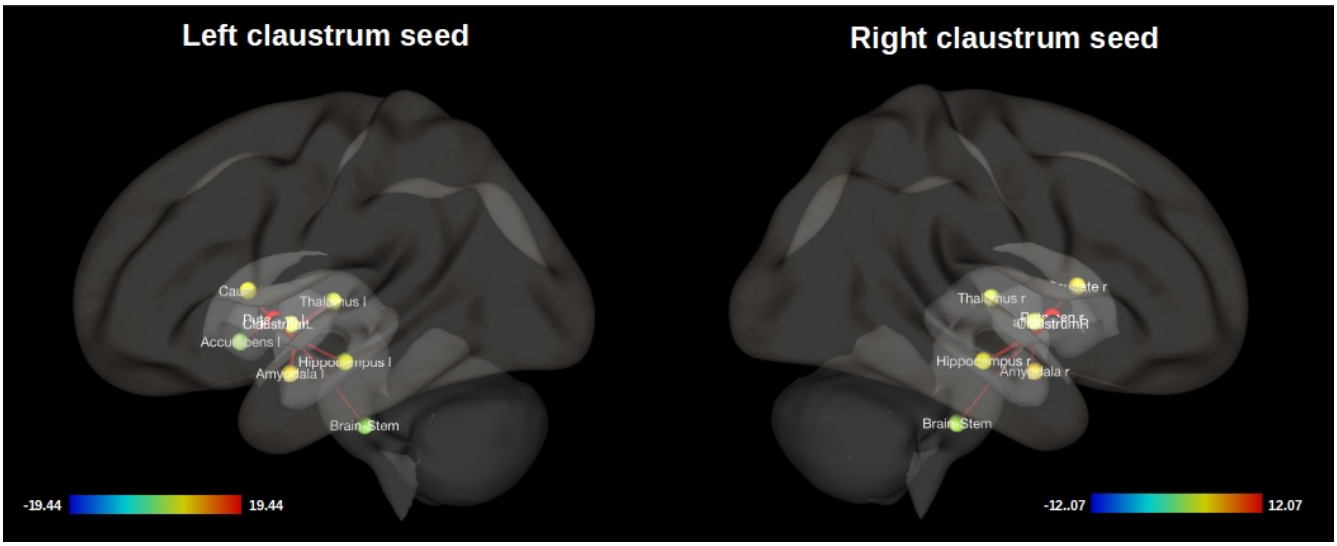

Figure 5. ROI-to-ROI functional positive connectivity between the claustra as seed area and subcortical structures. We found a positive functional connectivity between the claustra and the caudate nucleus, putamen, thalamus, hippocampus, amygdala and brainstem. Positive functional connectivity is present between the left claustrum and the accumbens nucleus, but not with the right claustrum. The results are thresholded ($p < 0.05$, p-FDR corrected).

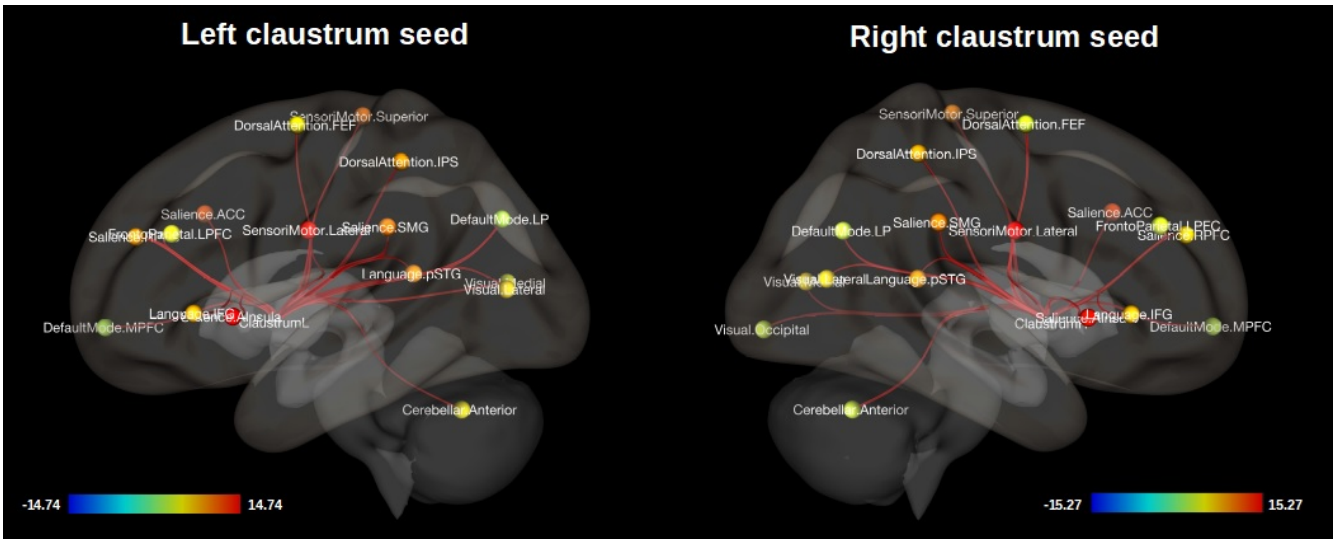

Figure 6. ROI-to-ROI functional positive connectivity between the claustra as seed area and conn network cortical ROIs. The results are thresholded ($p < 0.05$, p-FDR corrected).
In our analysis functional connectivity is similar when we use the left or right claustrum as seed. We found a functional connectivity between the visual area (occipital) and the right claustrum, but not with left claustrum. MPFC medial prefrontal cortex, LP lateral parietal, IFG inferior frontal gyrus, pSTG posterior superior temporal gyrus, A. insulae anterior insula, RPFC rostral prefrontal cortex, ACC anterior cingulate cortex, SMG supramarginal gyrus, LPFC lateral prefrontal cortex, FEF frontal eye field, IPS intraparietal sulcus.

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