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Theme: IV Taller internacional de Matemática Computacional y Bioinformática

Title in Spanish: Registro de imágenes de fuentes electrofisiológicas con BigBrain utilizando herramientas compatibles con el HCP

Title in English: Registration of electrophysiological source imaging with the BigBrain using the HCP compatible pipelines

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Abstract

Structural and functional features, and their integration at the different levels of brain organization, are the key to explain all brain states observed in normal or abnormal conditions. Invivo imaging modalities such as functional MRI (fMRI), MEG and EEG capture functional features of neural populations at level that can be situated in structural MRI (sMRI) tissue-contrasts. However, function emerges locally due to the cortex columnar organization of cellular layers and axonal fibers, at a level only accessible through high resolution structural imaging, such as histology. Invivo multimodal-imaging adopting surface-based processing pipelines, which acknowledge such cortical organization, has been proposed by the Human Connectome Project (HCP) to improve the accuracy in determining the cortical multimodal features. We introduce a pipeline that bridges the gap between levels through sMRI HCP compatible processing of BigBrain high resolution histology, which is integrated with MEG and EEG source processing. This is denominated BigBrain-HCP-MEEG, which maps simultaneously onto BigBrain, and HCP native and FSAverage structural spaces the MEG and EEG electrophysiological source spectral topographies and topologies. This can be done following two paths: 1) BigBrain-ICBM152 HCP compatible source model and lead field template

2) HCP-MEEG subject-specific source model and lead field, to then map topographies and topologies using the BC-VARETA pipeline. With our pipelines we have obtained high-quality mapping of electrophysiology onto the BigBrain, which renders HCP standards and is extensible to general databases as well as other types of histological volumes. This promises a strong asset in the study of the causes for the local properties of spectral activity and connectivity, that characterize the neural processes underlying brain function.

Key words: Multimodal imaging**,** Human Connectome Project**,** Electrophysiological Source Imaging**,** Big Brain.

Introduction

Structural and functional features, at different levels of brain organization, are the key to explain all neural processes underlying behavior. Such features are investigated in vivo through imaging techniques that can produce signals (fMRI, MEG, EEG), that are sensitive to function at the mesoscopic level of neural populations, or structural images, based on tissue-contrasts (MRI). However, actual function emerges locally from the disposition of cellular layers and their connectivities at the microscopic columnar level (Valdes-Sosa, 2009). Therefore, responding to questions about brain function must be through in vivo functional imaging informed with a high-resolution substrate, such as histology. Here, we introduce the registration of Electrophysiological Source Imaging (ESI) in the structural space of BigBrain (Amunts, K., 2013), which follows Human Connectome Project (HCP) compatible pipelines that can be widely adopted to process databases (Van Essen, D.C., 2013). Our pipelines are freely available open-source tools, emplaced in Cuba-China-Canada (CCC) neuroinformatic facility.

We have performed an initial test of concept on the registration of electrophysiology with the Big Brain structural space (Paz-Linares, D., 2018). As it was elaborated in the introduction this aims at explaining the origin of electrophysiological signals and their spectral properties in terms of the distribution of cellular content across columnar layers, microscopical distribution of cell fibers and their mesoscopic connectivities (Amunts, K., 2013). Our strategy will be based on layer specific analysis of source activity and connectivity in the spectral domain of electrophysiological signals. For now, we center the attention on the specific design that is compatible with the Human Connectome Project (Glasser, M.F., 2016), for the registration of electrophysiology. Therefore, this is based in the registration with a midthickness layer that is extracted from the Big Brain histological volume, that is weighted in T1 contrasts. Our contribution is the compatibilization of Big Brain with the HCP-MEEG pipeline and the

subsequent processing with the BC-VARETA pipeline. This is denominated BigBrain-HCP compatible MEG and EEG source processing pipeline (BigBrain-HCP-MEEG).

To achieve this, we design a hybrid T1w template by leveraging the recent high-quality image registration between Big Brain and ICBM152 T1 structural template, via the Advanced Normalization Tools (ANTs) software that is designed to produce the accurate registration of images with different contrast.

See in Figure 1 the histological Big Brain volume and cortical surface in the original histological space obtained by 3D reconstruction and registered to the ICBM152 structural template space with T1w contrast.

Creating the hybrid, which provides the Big Brain volume with the T1w contrast resembling the contrast of the average ICBM152 template, makes possible to process BigBrain like histological volumes with common processing pipelines for T1w images, such as SPM. However, we shall follow an HCP compatible scheme in the design of a pipeline for the registration of electrophysiological source imaging or connectivity with the Big Brain.

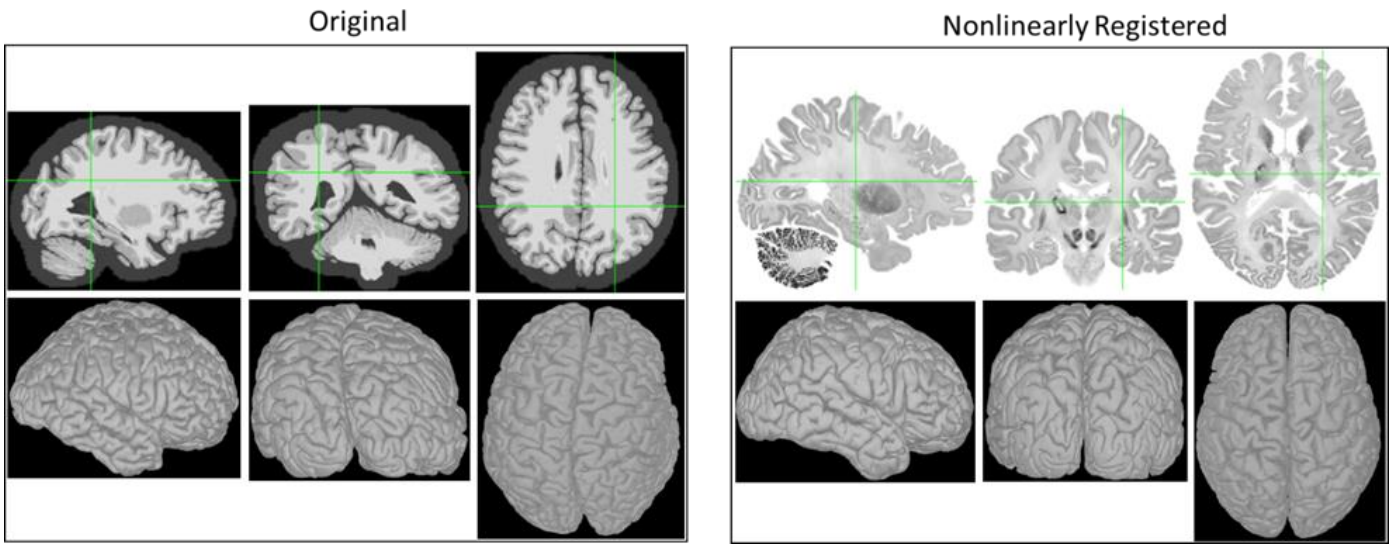


Figure 1 Conformal registration of BigBrain T1 contrast and ICBM152 volume/cortices

This is designed in 6 steps outlined below and illustrated in Figure 2:

Step 1) Processing with our T1alone pipeline (Freesurfer and Ciftify) the Big Brain volume at 1mm resolution that was registered to the ICBM152 structural space and provided with ICBM152 T1w non-brain tissue. This provides the standard HCP structural outputs for the Big Brain volume, such as the native and FSAverage registered 32K midthickness surface that is reduced to 8K for the use of electrophysiological source imaging.

Step 2) Head model inversion using the hybrid template of Big Brian FSAverage and the ICBM152 head tissue layers obtained with FSL. This allows to perform "average" electrophysiological source imaging, onto the Big Brain, to obtain, for instance the source spectra, in the 8K down sampled FSAverage Big Brian midthickness.

Step 3) Interpolation of the results for average electrophysiological source imaging with Big Brian – ICBM152 hybrid template, obtained in the low resolution 8K Big Brain cortex, to the high resolution 300K Big Brian histological (native) cortex.

Step 4) Head model inversion using the individual HCP compatible low resolution 8K structural space and head model. These results can be mapped to the individual FSAverage registered 32K superficial space and therefore to the HCP compatible an analogous BigBrain structural output.

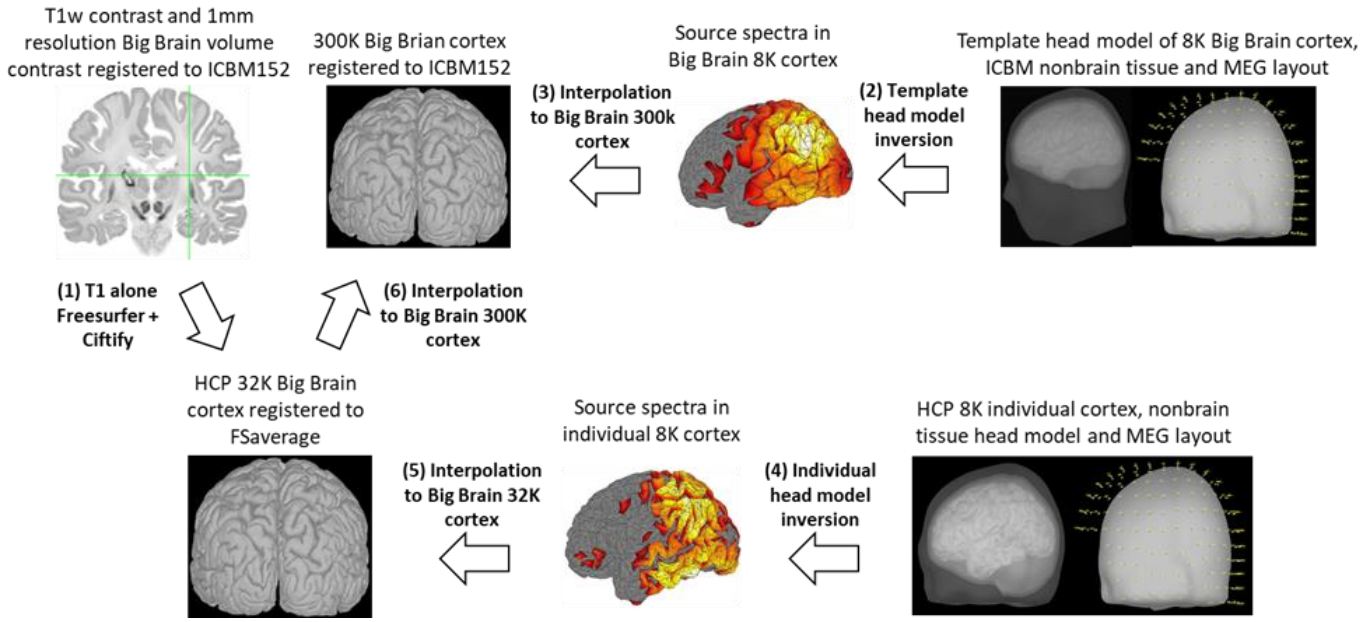


Figure 2 Steps for the registration of HCP compatible electrophysiological source imaging with the Big Brain

Step 5) Interpolation of the results for HCP compatible individual electrophysiological source imaging to the FSAverage registered 32K superficial space that can be mapped to the analogous space in the Big Brian HCP compatible structural outputs. analogous to the high resolution 300K Big Brian histological (native) cortex.

Step 6) Interpolation of the results for individual HCP compatible electrophysiological source imaging to the high resolution 300K Big Brian histological (native) cortex.

Materials and Methods or Computational Methodology

Leveraging the former nonlinear registration of BigBrain and ICBM152 (Xiao, Y., 2019) via Advanced Normalization Tools (ANTs), we designed their hybrid image, based on T1w contrasts using a workbench of FSL commands (Smith, S.M., 2016). This makes it possible to process BigBrain like histological volumes with common processing pipelines for T1w images, such as the SPM Computational Anatomy Toolbox (CAT) (Gaser, C. and Dahnke, R., 2016). Using HCP compatible structural processing for T1w images, based on Freesurfer and Ciftify (Dickie, E.W., 2019), we obtain the HCP cifty standard native and FSAverage (grand average of thousands of images) spaces for the BigBrain-ICBM152 hybrid. We based the source modeling for MEG (alternatively EEG) in our HCP compatible lead field pipeline (https://github.com/CCC-members/BrainStorm_Protocol) designed in the BrainStorm suit (Tadel, F., 2011), using two substrates: 1) BigBrain-ICBM152 HCP compatible source model template and 2) subject-specific source models, that are then mapped to the HCP standard BigBrain FSAverage space. Registration of electrophysiology with the BigBrain is then performed by our ESI pipeline BC-VARETA for the estimation of activations (Gonzalez-Moreira, 2020) and connectivity (Paz-Linares, D., 2018) in the spectral domain (https://github.com/CCC-members/BC-VARETA_Toolbox).

Using HCP compatible structural processing for T1w images, based on Freesurfer and Ciftify, we obtain the HCP cifty standard native and FSAverage structural spaces for the BigBrain-ICBM152 hybrid. In Figure 3 we show the result of this type of processing that shall be extended in the future to Big Brain like histological volumes registered to the ICBM152 template and to produce HCP compatible T1w structural outputs. The steps accompanying the results in Figure 3 are outlined below.

Step 1) Nonlinear registration of BigBrain into the ICBM152 template space obtained with Advanced Normalization Tools (ANTs) (Figure 3a).

Step 2) Hybrid image obtained by 1-normalization of the BigBrain contrast, resampling and linear registration to the ICBM152 template, 2-removing the brain from the ICBM152 image, that is then 3-substituted by the BigBrain (Figure 3b).

Step 3) Instance of BigBrain-ICBM152 hybrid processing with the SPM Computational Anatomy Toolbox (CAT) included in Brainstorm (Figure 3c).

Step 4) Cifty grayordinate conversion of the BigBrain that include HCP standard gray matter volumetric and cortical spaces, curvature, cortical thickness, volumetric and superficial atlases (Figure 3d).

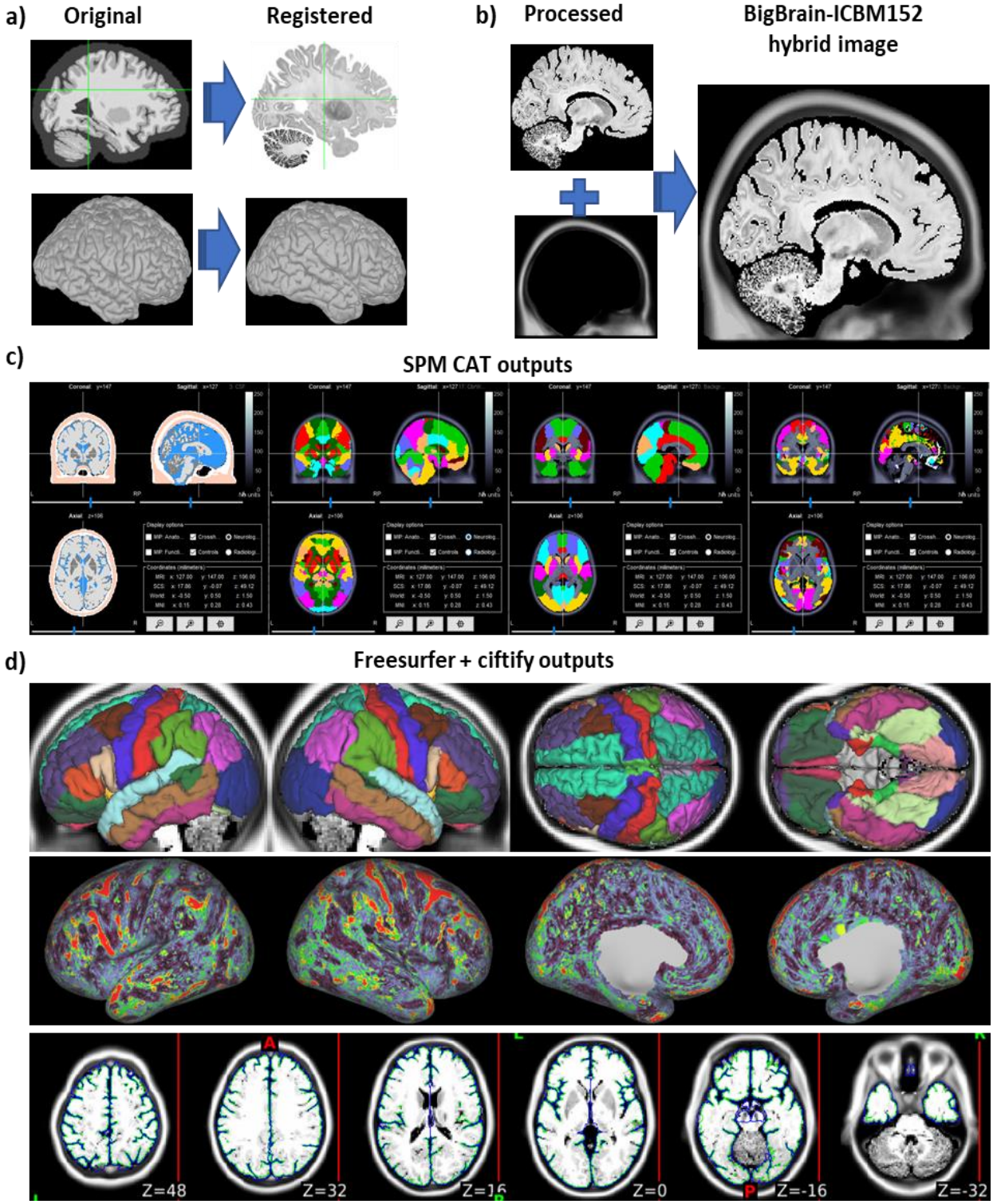
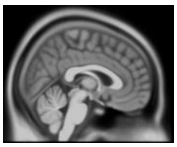
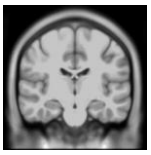
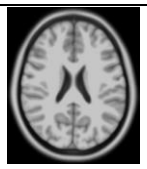
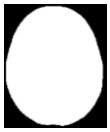
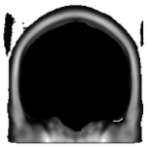
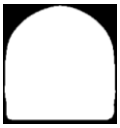
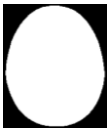
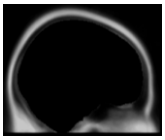
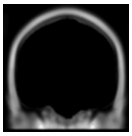
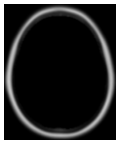
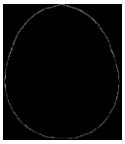
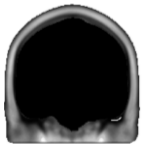
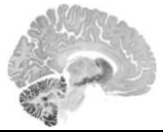
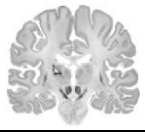
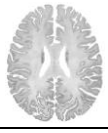
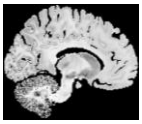
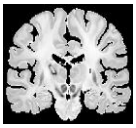
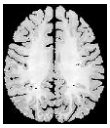
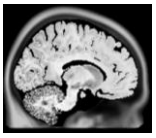
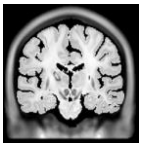
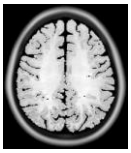


Figure 3 Steps for the registration of HCP compatible electrophysiological source imaging with the Big Brain.

Table-1 Full process to obtain the ICBM-BigBrain hybrid model.

Name	X view	Y view	Z view	Description
ICBM152				ICBM 152-2009c T1w downloaded from MCGILL web site
ICBM152 Inner Skull mask				FSL bet get surfaces process
Inner Skull inverted mask				Inverting ICBM 152 Inner skull mask
ICBM152 without brain				Multiply the inverter inner skull with the ICBM 152 T1w and get the T1 without brain
Outer Skin mask				Getting outer skin mask from FSL bet command
ICBM152 cleaned				Multiply the ICBM 152 T1w without brain with the ICBM 152 outer skin mask to clean the noise
ICBM152 InnSk mesh				Inner skull mesh got from the ICBM 152 T1w using FSL bet command
ICBM152 T1w cleaned and InnSk				Sum the cleaned ICBM 152 T1w whit the inner skull mesh to obtain the completed template
BigBrain original				Original BigBrain co-registered to ICBM 152

BigBrain normalized				Normalize the BigBrain with the ICBM 152 T1w intensity
ICBM152-Bigbrain T1w hybrid				Sum the cleaned ICBM152 T1w whit the normalized BigBrain and getting the ICBM152-Bigbrain T1w

The design of the hybrid Big Brain - ICBM152 image required the preparation of an independent pipeline that is based on FSL and Linux batch commands. Below we outline the steps of this pipeline that are illustrated at every stage in Table 1.

Step 1) Extraction of the inner skull mask from the ICBM152 T1w template.

Step 2) Inversion of the mask, which sets to val=0 the inner skull tissue and val=1 the external volume.

Step 3) Multiplication of the ICBM152 template with inverted mask to remove the brain tissue and keep only nonbrain tissue.

Step 4) Extraction of the outer skin mask of the ICBM152 T1w template.

Step 5) Multiplication of the outer skin mask by the ICBM152 template to clean T1w artifacts in the periphery.

Step 6) Interpolation and smoothing of the ICBM152 T1w inner skull mesh.

Step 7) Addition of the inner skull mesh to the cleaned ICBM152 template to create the complete nonbrain tissue of the template head.

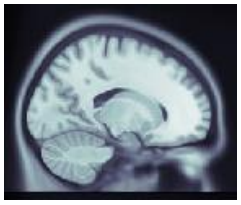
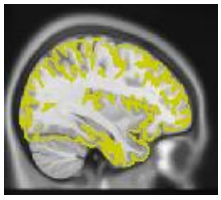
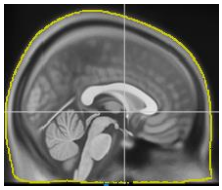
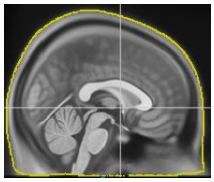
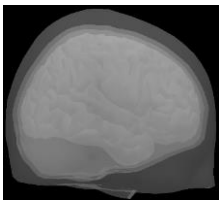
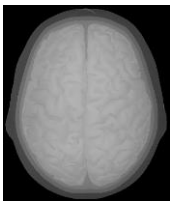
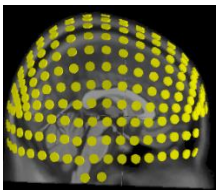
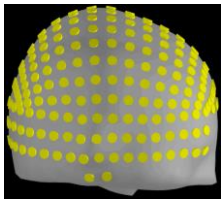
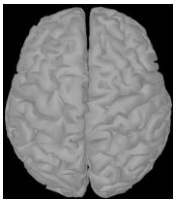
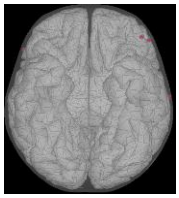
Step 8) Registration of the Big Brain volume to the ICBM152 brain using flirt and intensity normalization to achieve the contrast of the ICBM152 brain.

Step 9) Addition of the processed Big Brain to the processed ICBM152 nonbrain tissue to create the hybrid image.

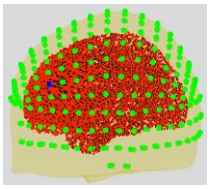
We have produced HCP compatible MEG/EEG source model, head model and lead field outputs based on the Big Brain and ICBM152 hybrid template, using the structural pipeline. Table 2 shows the outputs that are analogous to those of the Table 2 and comparable in terms of quality of the source and head model geometry and lead field. The files of this template, linked to our online GitHub repository, are according to Brainstorm format and therefore can be used to replicate any type of analysis based on electrophysiological source imaging. The users need only to register

with the head model a new sensor layout (in correspondence to the type of MEG or EEG dataset) or correct the position of the sensor layout using the Brainstorm visual interface. This is done modifying the configuration files, that can be later reloaded in bash mode and recognized in a loop as the second step for quality control after manual quality control, to perform lead field computation and geometrical corrections.

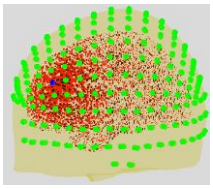
Table 2 Example report of the structural pipeline (ICBM-BigBrain hybrid model)

Description	View	Description	View
(1) MRI inspection		(2) Cortex - MRI registration	
(3) Scalp registration		(4) SPM Scalp Envelope - MRI registration	
(5) BEM surfaces registration		(6) BEM surfaces registration	
(7) Sensor-MRI registration		(8) Sensor-Scalp registration right view	
(9) Cortical mesh		(10) Cortical vertices that intercept the Inner Skull	

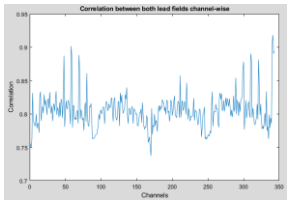
(11) Realistic Lead Field view



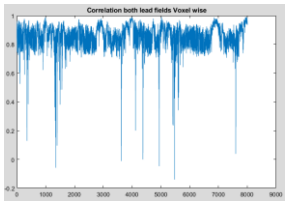
(12) Homogenous Lead Field view



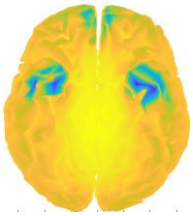
(13) Channel-wise correlation between the real and homogeneous Lead Fields



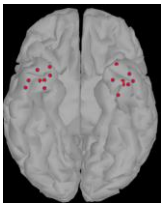
(14) Voxel-wise correlation between the realistic and homogeneous Lead Fields



(15) Correlation cortical map



(16) Voxels with low correlation (<0.3)



Results and discussion

Our strategy for the registration of electrophysiology with the Big Brain space unfolds into two different paths, which are differentiated in steps 2 and 4 included in the previous section. The two paths use HCP compatible structural outputs for the hybrid T1w image, the Big Brain volume registered to the ICBM152, following the T1 alone pipeline based on Freesurfer and Ciftify.

Path 1) By construing a template source model based on the Big Brain FSAverage midthickness, reduced to 8K from the FSAverage 32K surfaces, and head model of the ICBM152 nonbrain tissue (inner-skull, outer-skull and scalp) obtained with FSL for the hybrid image. This process provides the Big Brain template source model with an ICBM152 template head model with the purpose to produce HCP compatible lead fields. The head model geometric files are included as template for the registration of different types of MEG/EEG sensor layout and the computation of the lead field. Our HCP compatible source modelling, head modelling and lead field pipeline produces outputs that can be used by our BC-VARETA pipeline for electrophysiology.

Path 2) The structural outputs of the T1 alone HCP compatible pipeline produces volumetric and superficial spaces for the Big Brain that are analogous to the FSAverage template and any HCP compatible individual structural outputs, and therefore can be mapped homomorphically to any database. Therefore, we map the BC-VARETA HCP

compatible functional outputs, obtained for any individual and interpolated to 32K resolution, onto the Big Brain FSAverage midthickness. Then, these can be mapped onto the Big Brain native cortical surface at 300K, drawn from histological data, since the FSAverage registered, and the histology based (native) Big Brian cortical surface live in a common space.

Figure 4 shows the results obtained by following these two paths, 1) Inversion of the lead field that is obtained using the subject individual head model (Figure 4a), for an instance that corresponds to HCP subject 175237 and 1) Inversion of the lead field that is obtained from Big Brain ICBM152 hybrid (Figure 4b). The outputs illustrated in Figure 4 are outlined below:

Output 1) Overlapping spheres MEG lead field computed in the geometry for the BigBrain-ICBM152 hybrid template, based into an 8K source model (cortex), from HCP compatible structural processing for T1w images, and a head model (inner-skull, outer-skull, and scalp), obtained with FSL. Figure 4a.

Output 2) The same type of MEG lead field for HCP subject 175237. Figure 4b.

Output 3) Estimated activity with the BigBrain-ICBM152 and subject individual geometry, that are registered in the BigBrain and FSAverage space. Figure 4c.

Output 4) QC indicators selected for corrections of the template ICBM152-BigBrain hybrid. Figure 4d.

As usual these types of outputs are obtained by our pipelines: HCP-MEEG for modelling sources, head and lead field, and for BC-VARETA electrophysiological source imaging and connectivity. The HCP compatible source models based on the BigBrain-ICBM152 hybrid template geometry can be used in any dataset by modifying the sensor layout (that corresponds to the datasets), which is then recognized by our pipeline to perform lead field computation or geometrical corrections. Concurrent registration of BC-VARETA outputs corresponding to the alpha band (cross-spectrum and connectivity) with BigBrain, was obtained for the HCP MEG resting-state dataset (Figure 4c), at 64K resolution, by interpolation of the 8K solution given in substrates 1) and 2).

We can perform the manual quality control of the registration by the visual inspection of these outputs, using the images of Figure 4 that are generated automatically within our pipeline. To rule out possible interactions of external QC factors with the quality control of the registration we have used here cases (subject HCP 175237 and CHBMP MC00009) that, after expert inspection, were classified as high quality. This classification was given in terms of quality for their HCP structural (individual and FSAverage space) and head modelling (individual space) outputs obtained with our pipeline, as well as the functional data outputs of our pipeline for electrophysiology in the individual sensor and source spaces.

Quality Control (QC) indicators produced by our pipelines, either for manual or automatic corrections, evaluate this co-registration (Figure 4d): in terms of the sensor or cortical topographies expected for each band, which must be similar in BigBrain, FSAverage or native spaces, geometry of the source, and head models, the layout of MEG/EEG sensors and 3D distribution of the source lead fields.

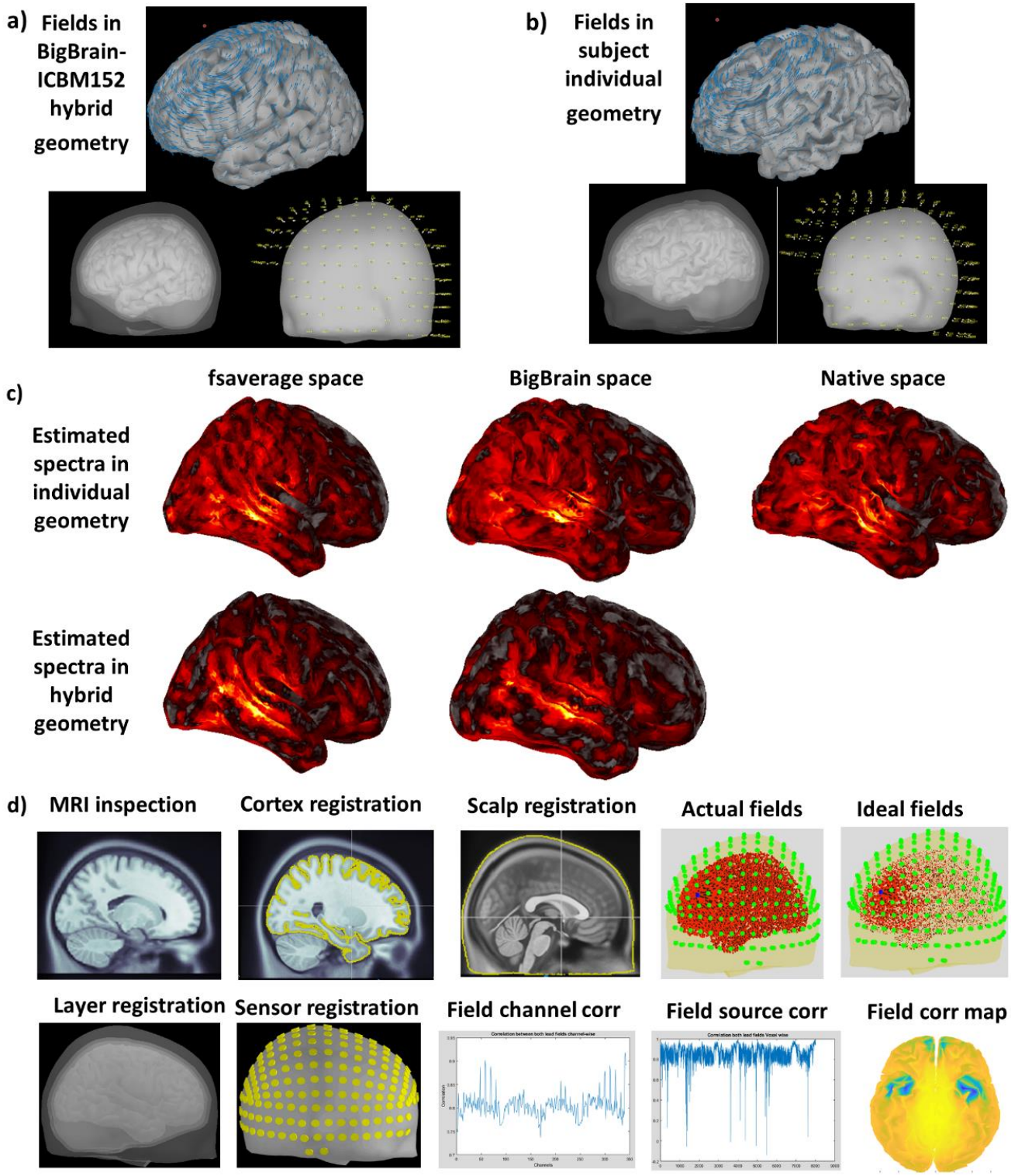


Figure 4 BC-VARETA outputs for the HCP MEG resting-state dataset and QC indicators

Conclusions

We have introduced an HCP compatible pipeline for the registration of electrophysiological source imaging and connectivity onto the structural space of the Big Brain, which can be widely adopted to process legacy databases. This was possible due to our processing pipelines (https://github.com/CCC-members/HCP_BST_source_head_modeler), and the design of a new pipeline to produce HCP compatible hybrid processing of the BigBrain and the ICBM152, which can be extended to other types of histological volumes.

We have obtained a high-quality registration of electrophysiology with the Big Brain, which renders HCP standards. This promises a strong asset in the study of the causes for the local properties of spectral activity and connectivity, that characterize the neural processes underlying brain function. Structural and functional features, at different levels of brain organization, are the key to explain all neural processes underlying behavior. Such features are investigated in vivo through imaging techniques that can produce signals (fMRI, MEG, EEG), which are sensitive to function at the mesoscopic level of neural populations, or structural images, based on tissue-contrasts (sMRI). However, actual function emerges locally from the disposition of cellular layers and their connectivities at the microscopic columnar level. Therefore, responding to questions about brain function must be through in vivo functional imaging informed with a high-resolution substrate, such as histology.

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