Allostatic Interoceptive Overload in Frontotemporal Dementia

Supplementary Information

Table of contents

1. Power estimation
2. Atrophy results
3. Hd-EEG methods: preprocessing steps and number of trials of the hdEEG samples
4. MRI data acquisition, preprocessing, and analysis
5. Supplementary Table 4 (Table S4)
6. Supplementary rsHEP modulations results
7. Supplementary rsHEP source localization results
   7.1. bvFTD activation results
   7.2 HC activation results
   7.3 AD activation results
   7.4. Activation differences between HC and bvFTD
   7.5. Activation differences between HC and AD
   7.6 Activation differences between bvFTD and AD
   7.7: Source split analysis results
8. bvFTD specific associations of rsHEP and multiple socio-cognitive measures
   8.1 Socio-cognitive split analysis results
   8.2 bvFTD associations of rsHEP and multiple socio-cognitive measures: bootstrapped models
9. SBM associations with rsHEP modulations
   9.1. SBM results for bvFTD patients
   9.2. SBM results for HCs
   9.3. SBM results for AD patients
   9.4 Split analysis of the associations between brain structure and rsHEP modulation
10. Functional connectivity supplementary analyses
    10.1. Functional connectivity split analysis:
    10.2. Bayes factors’ analyses
11. Machine learning analysis
    11.1. Machine learning methods
    11.2. Machine learning results
12. Supplementary references
1. Power estimation

To determine the sample size required for our multivariate multiple linear regression analyses, we ran a power estimation on \( R \) with the pwr library. We established an alpha level of 0.05, an effect size of \( \eta^2 = 0.15 \), and a power of 0.8. The final sample size of our study (with the smallest group featuring 19 participants) reaches a power of .96.

2. Atrophy results

To establish patterns of structural brain alteration in each patient group, we assessed gray matter integrity via voxel-based morphometry (VBM) relative to controls. To do so, we estimated and used w-score maps of the normalized and smoothed DARTEL outputs in order to analyze the images of each center together and avoid a resonator effect in our results. We accounted for the global atrophy pattern via a \( t \)-test between groups, corrected by TIV and sex (SPM12). Statistical significance was set at \( P < 0.001 \) (FDR-corrected, extent threshold = 50 voxels). We found significant atrophy patterns for bvFTD and AD patients, but not for PD patients. Results are presented in Table S1.

### Table S1. VBM atrophy of patients compared to HCs.

| Atrophy   | Cluster | Brain region          | Peak Coordinates | t    | P       | x    | y    | z  |
|-----------|---------|-----------------------|------------------|------|---------|------|------|----|
| bvFTD     | 391     | L Tri. Inferior Frontal | 4.69 < 0.001     | -34.5| 21      | 25.5 |
|           | 72      | R Precuneus (BA31)    | 3.79 < 0.001     | 13.5 | -61.5   | 57   |
|           | 106     | R Postcentral         | 3.74 < 0.001     | 51   | -16.5   | -21  |
|           | 75      | L Supramarginal       | 3.62 < 0.001     | -60  | -33     | 31.5 |
|           | 150     | R MiddleTemporal      | 3.61 < 0.001     | 43.5 | 4.5     | -30  |
|           | 59      | L Posterior frontal   | 3.54 < 0.001     | -34.5| 6       | 40.5 |
| AD        | 10954   | R Amygdala            | 5.02 < 0.001     | 30   | -3      | -28.5|
|           |         | R Hippocampus         | 4.97 < 0.001     | 27   | -25.5   | -7.5 |
|           | 255     | R Angular             | 3.98 < 0.001     | 34.5 | -55.5   | 37.5 |
|           | 574     | R Inferior Parietal   | 3.47 < 0.001     | 37.5 | -52.5   | 48   |
|           | 209     | L Superior Frontal    | 3.97 < 0.001     | -24  | 28.5    | 31.5 |
|           | 53      | R Middle Temporal     | 3.73 < 0.001     | 39   | -64.5   | 15   |
|           | 237     | R Precuneus           | 3.52 < 0.001     | 1.5  | -55.5   | 46.5 |
|           | 96      | R Precuneus           | 3.49 < 0.001     | 10.5 | -60     | 51   |
|           | 150     | R Superior Parietal   | 3.39 < 0.001     | 18   | -55.5   | 49.5 |
|           | 74      | L Medial Superior Frontal | 3.46 < 0.001    | -7.5 | 55.5    | 9    |
|           | 10954   | R Amygdala            | 5.02 < 0.001     | -7.5 | 55.5    | 9    |
|           | 51      | R Hippocampus         | 4.97 < 0.001     | 27   | -25.5   | -7.5 |
|           | 255     | R Angular             | 3.98 < 0.001     | 34.5 | -55.5   | 37.5 |

BvFTD: behavioral variant frontotemporal dementia; HC: healthy controls; AD: Alzheimer’s disease patients. R: right. L: left.
3. Hd-EEG methods: preprocessing steps and number of trials of the hdEEG samples

We instructed participants not to think about anything in particular while remaining still, awake, and with eyes closed—which avoids artifacts and other noisy visual signals(1). Data was recorded via a Biosemi Active-two 128-channel system at a sampling rate of 1024 Hz and down-sampled offline 512 Hz. We corrected the hdEEG for eye movements, eyeblink artifacts, and heart with independent component analysis(2) and with a visual inspection protocol(3-11). We set analog filters at 0.03 and 100 Hz. We also applied a digital bandpass filter between 0.5 and 40 Hz offline to remove unwanted frequency components. The reference was set to linked mastoids for recording and re-referenced offline to the average of all of the rest electrodes. We replaced malfunctioning channels via statistically weighted spherical interpolation (based on neighboring sensors)(12). R-values from ECG signal were identified with pan Tompkins function on HEPLAB toolbox(13).

Spatiotemporal clustering

Spatiotemporal cluster analyses was repeated 5000 times, with recombination and randomized resampling of the subject-wise averages before each repetition using the Monte Carlo method(14). After each repetition, we retained the t-value of the largest cluster identified. The proportion of t-values obtained after randomization that were greater than the initially identified cluster-level t-value was used to calculate a nonparametric P-value for the cluster. This approach addresses the problem of multiple comparisons across the dimensions of the electrode, time, and space(15, 16). The reported latencies of HEPs in EEG vary significantly(17). In consequence, the cluster analysis was applied at the sensor level in the time window between 200 to 800 ms after the R-peak, to avoid cardiac artifacts(18, 19) and following HEP contamination(8, 20-22). In addition, we calculated the effect size for all comparisons following Cohen’s method (23). Considering that bvFTD and AD groups were different in terms of age and years of education, we used a control-group-derived Z parameter (i.e., patients versus controls). For each bvFTD and AD patient, we calculated normalized Z-scores using the parameters (mean and SD) derived from the respective control group. Then, we compared Z-scores across the two groups through a 5000 point-by-point Monte Carlo permutation test with bootstrapping(24), with Benjamini and Hochberg false discovery rate (FDR) correction(25). To ensure that different sample sizes did not drive the results in the AD and HC groups relative to bvFTD patients, we repeated all analyses on subsamples of AD and HCs and the full sample of bvFTD (all groups with equal numbers of subjects), with equal numbers of subjects, selected with a randomized procedure (randperm function).

Source localization

The PCD maps were obtained using a head model of three concentric spheres, in a predefined source space of 21,926 voxels (voxel size of 4 x 4 x 4 mm$^3$) of the Montreal Neurological Institute average brain. A brain segmentation of 116 anatomic compartments was implemented using the automated anatomical labeling atlas (AAL atlas(26)). BMA images were subject-wise normalized (total average power over all images equal to unity) and baseline-corrected (relative to a window between 300 and 50 ms preceding the heartbeat). Then, we selected the inverse solutions corresponding to the time window at which rsHEP modulations significantly differed between groups in the cluster analysis (see hdEEG results section for details). The mean activation map of each group was obtained for each hdEEG scalp distribution. We computed 161 activation maps (161 time points, sampling the time interval between 270 and 584 ms following the peak of the R wave of the heartbeat). For each set of images (obtained at a particular time point), the mean PCDs computed in each voxel were compared between group pairs via two-tailed non-parametric permutation tests ($\alpha = .05$; 20000 randomizations). Results were corrected for multiple comparisons through the Benjamini and Hochberg FDR method(25). For statistical analyses, we used in-house MATLAB codes (MathWorks, USA). BMA images were visualized using the software Neuronic Tomography Viewer. To control for sample sizes differences across groups,
we repeated all analyses on subsamples of AD and HCs and the full sample of bvFTD (all groups with equal numbers of subjects), selected with a randomized.

**Table S2. Number of trials of the hdEEG subsamples.**

| Variable | bvFTD | HC | AD | Statistics (all groups) |
|----------|-------|----|----|-------------------------|
| Number of trials | 198 (30) | 184 (22) | 162 (22) | F(2,86) = 0.52 P = .60 |

Data presented as mean (SD). BvFTD: behavioral variant frontotemporal dementia; HCs: healthy controls; AD: Alzheimer’s disease.

4. MRI data acquisition, preprocessing, and analysis

**Center 1:** Using a 3-T Phillips scanner with a standard head coil, we acquired whole-brain T1-rapid anatomical 3D gradient echo volumes, parallel to the plane connecting the anterior and posterior commissures, with the following parameters: repetition time (TR) = 8300 ms; echo time (TE) = 3800 ms; flip angle = 8º; 160 slices, matrix dimension = 224 x 224 x 160; voxel size = 1 mm x 1 mm x 1 mm. Also, functional spin echo volumes, parallel to the anterior-posterior commissures, covering the whole brain, were sequentially and ascendingly acquired with the following parameters: TR = 2640 ms; TE = 30 ms; flip angle = 90º; 49 slices, matrix dimension = 80 x 80 x 49; voxel size in plane = 3 mm x 3 mm x 3 mm; slice thickness = 3 mm; sequence duration = 10 minutes; number of volumes = 220.

**Center 2:** Using a 3-T Siemens Skyra scanner with a standard head coil, we acquired whole-brain T1-rapid gradient ecAo volumes, parallel to the plane connecting the anterior and posterior commissures, with the following parameters: repetition time (TR) = 2400 ms; echo time (TE) = 2000 ms; flip angle = 8º; 192 slices, matrix dimension = 256 x 256 x 192; voxel size = 1 mm x 1 mm x 1 mm. Finally, functional EP2D-BOLD pulse sequences, parallel to the anterior-posterior commissures, covering the whole brain, were acquired sequentially intercalating pair-ascending first with the following parameters fMRI parameters: TR = 2660 ms; TE = 30 ms; flip angle = 90º; 46 slices, matrix dimension = 76 x 76 x 46; voxel size in plane = 3 mm x 3 mm x 3 mm; slice thickness = 3 mm; sequence duration = 10.5 minutes; number of volumes = 240.

**Surface-based morphometry (SBM) pre-processing and analysis**

We processed all T1 images via SBM on the FreeSurfer software suite (v 6.0 [https://surfer.nmr.mgh.harvard.edu/](https://surfer.nmr.mgh.harvard.edu/)). SBM metrics included sensitive measures of atrophy (volume and thickness). SBM offers reliable region-specific metrics to analyze structural(27) and functional connectivity(28) changes by overcoming registration errors and therefore improving the parcellation process. Preprocessing included removal of nonbrain tissue, an automatic Talairach transformation, segmentation of the subcortical white matter (WM) and deep GM volumetric structures (including the hippocampus, amygdala, caudate, putamen, and ventricles), intensity normalization, tessellation of the GM-WM boundary, an automatic topology correction, and surface deformation following
intensity gradients to optimally place the GM/WM and GM/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class(29). Full details on the implemented methods can be found in a previous report(29). Finally, we quantified the volume and thickness from each segmentation of the Desikan-Killiany atlas(30). To control the variability of images acquired with different scanners, the volume of both HC and patients was z-scored based on the mean and SD of the corresponding center’s HC(31-33). The plain-text output of the FreeSurfer’s pipeline was post-processed on Python (v 3.7.4, Python Software Foundation) and restructured for statistical analysis. To avoid potential biases stemming from differences among the participant’s head size(34), we normalized the volume measures of each area relative to the estimated total intracranial volume (eTIV, also provided in FreeSurfer’s results).

To test our predictions, we assessed the association of the rsHEP modulation with the cortical volume and thickness measures from whole-brain parcellation through Kendall correlations with Pingouin statistics packages (v 0.3.6) on Python (v 3.7.4, Python Software Foundation) (Figure 1B). Statistical significance was set at $P < .05$, FDR-corrected. Again, we repeated all analyses on subsamples of AD and HCs and the full sample of bvFTD (all groups with equal numbers of subjects), selected with a randomized procedure.

Preprocessing of fMRI data for rsFC analysis

First, to ensure that magnetization achieved a steady-state, we discarded the first five volumes of each subject’s resting-state recording. Images were then preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF V2.3)(36), an open-access toolbox that generates an automatic pipeline for fMRI analysis. DPARFS works by calling the SPM12 and the Resting-State fMRI Data Analysis Toolkit (REST V.1.7). As in previous studies(6, 8), preprocessing steps included slice-timing correction (using the middle slice of each volume as the reference scan) and realignment to the first scan of the session to correct head movement (SPM functions)(21, 37-42). We regressed out six motion parameters, cerebrospinal fluid (CSF) and white matter (WM) signals to reduce potential effects of movement-related, physiological, and cardio-respiratory effects (REST v.1.7 toolboxes). Motion parameters were estimated during realignment, and CSF and WM masks were derived from the tissue segmentation of each subject’s T1 scan in native space with SPM12 (after co-registration of each subject’s structural image with the functional image). None of the participants showed head movements greater than 3 mm and/or rotations higher than 3º(43) and no differences in head motion among groups were found (Supplementary Table 2). Finally, images were normalized to the MNI space using the echo-planar imaging (EPI) template from SPM12(44), smoothed using an 8-mm full-width-at-half-maximum isotropic Gaussian kernel, and bandpass filtered between 0.01–0.1 Hz to correct and remove low-frequency drifts from the MRI scanner. Finally, we excluded recordings with movements greater than 3 mm and/or rotation movements higher than 3º(43). Motion parameters did not differ significantly among groups (Table S2)

Analysis of rsFC fMRI data

Based on the fMRI resting-state recordings, we evaluated associations between the rsHEP modulations and FC patterns. Images were pre-processed on the Data Processing
Assistant for Resting-State fMRI (DPARSF v 2.3)(45), an open-access toolbox which generates an automatic pipeline for fMRI analysis by calling SPM 12 and the Resting-State fMRI Data Analysis Toolkit (REST v.1.7). To control the variability of images acquired with different scanners, the connectivity measures of both HCs and patients were z-scored based on the mean and SD of the corresponding center’s HCs(31-33).

Our hypothesis predicted that rsHEP modulations in bvFTD would correlate with AIN connectivity. Therefore, we implemented a seed analysis to examine associations between the HEP modulation and FC of the AIN(46) (Figure 1B). To test the specificity of our predictions for these networks, we also examined associations of the rsHEP modulation with the connectivity of five additional functional networks: the SN, the executive network (EN), the DMN, the visual network (VN), and the motor network (MN). By testing the specificity of rsHEP as a marker of interoceptive allostatic overload in bvFTD, we expected non-significant associations between rsHEP modulations and the control networks. In order to compare with relevant works in neurodegenerative diseases, we planted seeds on cubic regions of interest (ROIs) with a size of 7x7x7 voxels(32, 47, 48) for each network. Each group of seeds was located on different coordinates to capture each network’s connectivity. For the AIN, we selected three regions, used to estimate the unified allostasis/interoceptive system and the connections between cortical, amygdalar, visceromotor regions, and primary interoceptive regions(46). These regions were: the right dorsal middle insula (dmlns, MNI coordinates: 41, 2, 3 and -41, 2, 3), the right anterior midcingulate (aMCC, MNI coordinates: 9, 22, 33), and the right dorsal amygdala (dAmy, MNI coordinates: 27, 3, −12)(46). Specific nodes, and their connectivity with the rest of the brain, were selected for the control networks, namely: the bilateral dorsal anterior cingulate (ACC) for the SN(49) (MNI coordinates 10, 34, 24 and -10, 34, 24), the right and left superior frontal gyri for the EN(32, 48, 50) (MNI coordinates 30, -2, 62 and -30,-2,62), the posterior cingulate (PCC) for the DMN(51) (MNI coordinates: 3,-54,27 and -3,-54,27); 5), the primary visual cortex for the VN(52), and the primary motor cortex (M1) for the MN(53) (MNI coordinates: 32,-30,68 and -32, 30,68). To calculate the networks, we employed a non-linear dynamic connectivity fluctuation analysis (DCFA)(32), which includes Dynamic Functional Connectivity (DFC)(54) and takes into account BOLD signal fluctuations. This analysis allows measuring the connectivity in the time domain, by segmenting the BOLD signal into non-overlapping time windows. DCFA proved to be robust against parameter and scanner acquisition heterogeneity. The symbolic weights capture transient brain activity that conventional methods may disregard as noise. Moreover, DFCA measure outperformed linear measures across in the discrimination and classification of patients with bvFTD and AD(55).

Then we used standard masks(56) to isolate the voxels typically involved in each resting-state network. Finally, data were spatially averaged across all included voxels to obtain a resting-state time series per network. The resulting connectivity maps were compared between group pairs with two-tailed non-parametric permutation tests (P = .05 FDR-corrected). Furthermore, connectivity maps in each group were correlated with the respective rsHEP modulations through the SPM12’s multiple regression module (FDR-corrected P = .05). Once again, we repeated all analyses on subsamples of AD and HCs and the full sample of bvFTD selected with a randomized procedure.

5. Supplementary Table 3 (Table S3)
Table S3. Movement parameters for the fMRI subsamples.

| Variable | BvFTD | HC | AD | Statistics (all groups) |
|----------|-------|----|----|-------------------------|
| Translation | .09 (.05) | .09 (.05) | .09 (.05) | $F = 1.04$ $P = 0.38$ |
| Rotation   | .06 (.03) | .04 (.05) | .06 (.03) | $F = .94$ $P = 0.42$ |

bvFTD: behavioral variant frontotemporal dementia; HC: healthy controls; AD: Alzheimer's disease.

6. Supplementary rsHEP modulations results

To ensure that the results were not driven by the more significant number of subjects in the AD and HC groups relative to bvFTD, we repeated the analyses selecting an equal number of subjects. The MATLAB's function randperm was used to determine the random samples. The resulted sample was demographically matched (Table S4). rsHEP comparisons between bvFTD and HC revealed a significant cluster over right centro-temporal regions in the 290-430 ms post R-peak period ($t$-sum= -50512.61, cluster-level $P = .01$, $d = 0.62$ corrected for multiple comparisons in space and time, Figure S1A), with its maximum $t$-value at 330 ms. Specifically, bvFTD patients presented increased negative amplitude than HC, meaning larger negative rsHEP modulation. In the normalized bvFTD vs AD subsample comparison, the rsHEP modulation difference was higher for bvFTD than for AD between 190 and 310 ms ($P < .05$, FDR-corrected, $d = .50$, Figure S1B).

Table S4. Subsamples’ demographic data

| bvFTD | HC | AD | Statistics (all groups) |
|-------|----|----|-------------------------|
| $N = 19$ | $N = 19$ | $N = 19$ | $\chi^2 = 3.61$ $P = .16^a$ |
| Sex (F:M) | 5:14 | 10:9 | 12:7 |
| Years of age | 68.57 (1.92) | 68.89 (7.48) | 73.16 (6.11) | $F = 0.84$ |
| Years of education | 14.57 (0.91) | 14.77 (3.42) | 12.9 (5.36) | $F = 1.26$ |

Data presented as mean (SD), with the exception of sex. bvFTD: behavioral variant frontotemporal dementia; HC: healthy controls; AD: Alzheimer's disease.

$^a$ $P$-values calculated via independent measures ANOVA.

$^b$ $P$-values calculated via chi-squared test ($\chi^2$).
Figure S1: Split analysis results. A. rsHEP modulations during resting-state for the subsample of HC (green line) and bvFTD patients (violet line). Gray shaded boxes show statistically significant differences at \( P = .05 \) cluster corrected (from 290 to 430 ms). Scalp topographies show the significant electrodes of the cluster and the differences in amplitude (microvolts) between ERPs at 400 ms. B. Subtraction of the mean rsHEP modulations between bvFTD and HC (violet line), and AD and HC (pink line) in the cluster significant electrodes. Gray shaded boxes show statistically significant differences at \( P = .05 \) FDR-corrected (between 190 and 310 ms). Scalp topographies show the differences in amplitude (microvolts) at 250 ms and the electrodes used for the analysis.

7. Supplementary rsHEP source localization results

7.1. bvFTD activation results

Figure S2: BMA images were visualized using the software Neuronic Tomography Viewer (Neuronic, Cuba) and segmented with the AAL atlas. BvFTD: behavioral variant of frontotemporal dementia. INS: insula; AMY: amygdala; HPC: hippocampus; BG: basal ganglia; THAL: thalamus; ITG: inferior temporal gyrus.
Table S5. Voxels with maximum activations in patients with bvFTD.

| Cortical region                        | MNI coordinates | BA |
|----------------------------------------|-----------------|----|
| Gyrus Rectus                           | x y z (right)   | 11 |
| Inferior Frontal Gyrus (pars orbitalis)| -4   17 -24 (left) | 47 |
| Middle Frontal Gyrus (orbital part)    | -23  27 -24 (right) | 10 |
| Anterior Cingulate Cortex              | 6    30 -8 (right) | 32 |
| Inferior Frontal Gyrus (pars triangularis) | -42  26 4 (left) | 45 |
| Inferior Frontal Gyrus (pars opercularis) | 44  13 16 (right) | 44 |
| Insula                                 | -50  13 8 (left) | 13 |
| Rolandic Operculum                     | -39  -14 8 (left) | 48 |
| Amigdala                               | 23   2 -16 (right) |     |
| ParaHippocampal Gyrus (PG)             | -24  -29 -16 (left) | 36 |
| Caudate                                | 9    4 8 (right)  |     |
| Putamen                                | -6   8 -4 (left)  |     |
| Thalamus                               | 26   3 8 (right)  |     |
| Superior Temporal Gyrus                | -23  9 8 (left)  |     |
| Inferior Temporal Gyrus                | 15   -24 4 (right) |     |
| Fusiform Gyrus                         | -14  -22 4 (left) |     |
| Supramarginal Gyrus                    | 58   -14 15 (right) | 22 |
|                                       | -18  27 12 (left) |     |
|                                       | 65   -38 -25 (right) | 20 |
|                                       | -53  -26 -20 (left) |     |
|                                       | 28   -54 -16 (right) | 37 |
|                                       | -32  -61 -8 (left) |     |
|                                       | 58   -22 28 (right) | 40 |

7.2 HC activation results

Figure S3: BMA images were visualized using the software Neuronic Tomography Viewer (Neuronic, Cuba) and segmented with the AAL atlas. HC: healthy controls; INS: insula; AMY: amygdala; HPC: hippocampus; BG: basal ganglia; THAL: thalamus; ITG: inferior temporal gyrus.
### Table S6. Voxels with maximum activations in HCs.

| Cortical region                              | MNI coordinates | BA |
|----------------------------------------------|-----------------|----|
| Gyrus Rectus                                 | 4 -5 47 21 24   | 11 |
| Inferior Frontal Gyrus (pars orbitalis)      | 36 -41 32 48 -12 | 47 |
| Middle Frontal Gyrus (orbital part)          | 28 -33 55 42 -8 | 10 |
| Orbitofrontal Cortex                         | 8 -6 55 42 -8   | 10 |
| Anterior Cingulate Gyrus                     | 8 -7 42 35 24   | 32 |
| Inferior Frontal Gyrus (pars triangularis)   | 48 -50 22 24 4  | 45 |
| Inferior Frontal Gyrus (pars opercularis)    | 55 -54 12 10 20 | 44 |
| Insula                                       | 43 -38 4 12 4   | 13 |
| Rolandic Operculum                           | 46 -43 -25 20   | 48 |
| Amigdala                                     | 28 -26 2 -15 -8 | 20 |
| Hippocampus (HPC)                            | 27 -25 -18 -15 -12 | 37 |
| ParaHippocampal Gyrus (PG)                   | 25 -29 -31 -15 -14 | 22 |
| Caudate                                      | 12 -11 17 -11 8 | 20 |
| Putamen                                      | 22 -27 13 2 4   | 20 |
| Pallidum                                     | 19 -18 -3 2 0   | 20 |
| Thalamus                                     | 8 -13 25 -13 4 | 20 |
| Superior Temporal Gyrus                      | 51 -59 -8 -20 -8 | 22 |
| Inferior Temporal Gyrus                      | 50 -53 -50 -33 -25 | 20 |
| Fusiform Gyrus                               | 41 -40 -33 -33 -24 | 37 |
| Supramarginal Gyrus                          | 63 -57 -32 -26 -28 | 40 |
7.3 AD activation results

Figure S4: BMA images were visualized using the software Neuronic Tomography Viewer (Neuronic, Cuba) and segmented with the AAL atlas\(^{(57)}\). AD: Alzheimer’s disease. INS: insula; AMY: amygdala; HPC: hippocampus; BG: basal ganglia; THAL: thalamus; ITG: inferior temporal gyrus.

Table S7. Voxels with maximum activations in patients with AD

| Cortical region                        | MNI coordinates | Hemisphere | BA |
|----------------------------------------|-----------------|------------|----|
|                                        | x   | y   | z   |          |    |   |
| Gyrus Rectus                           | 5   | 32  | -20 | Right    | 11 |
|                                        | -7  | 32  | -20 | Left     |    |
| Inferior Frontal Gyrus (pars orbitalis)| 35  | 35  | -20 | Right    | 47 |
|                                        | -31 | 34  | -20 | Left     |    |
| Middle Frontal Gyrus (orbital part)    | 39  | 34  | -4  | Right    | 10 |
|                                        | -31 | 34  | -10 | Left     |    |
| Orbitofrontal Cortex                   | 6   | 34  | -14 | Right    | 11 |
|                                        | -10 | 34  | -12 | Left     |    |
| Anterior Cingulate Gyrus               | 12  | 34  | -12 | Right    | 32 |
|                                        | -5  | 34  | 8   | Left     |    |
| Inferior Frontal Gyrus (pars triangularis) | 49  | 24  | 4   | Right    | 45 |
|                                        | -50 | 34  | 4   | Left     |    |
| Inferior Frontal Gyrus (pars opercularis) | 45  | 14  | 4   | Right    | 44 |
|                                        | -50 | 11  | 4   | Left     |    |
| Insula                                 | 43  | -1  | 4   | Right    | 13 |
|                                        | -40 | 5   | -8  | Left     |    |
| Rolandic Operculum                     | 55  | -6  | 12  | Right    | 48 |
|                                        | -56 | 5   | 4   | Left     |    |
| Amigdala                               | 25  | -4  | -14 | Right    |    |
|                                        | -25 | 1   | 20  | Left     |    |
| Hippocampus (HPC)                      | 31  | -24 | -12 | Right    | 20 |
|                                        | -30 | -19 | -14 | Left     |    |
| ParaHippocampal Gyrus (PG)             | 27  | -39 | -8  | Right    | 37 |
|                                        | -26 | -40 | -8  | Left     |    |
| Caudate                                | 14  | 10  | 12  | Right    |    |
|                                        | -12 | 13  | 12  | Left     |    |
| Putamen                                | 23  | 11  | -8  | Right    |    |
|                                        | -22 | 3   | 4   | Left     |    |
| Pallidum                               | 19  | 0   | 0   | Right    |    |
|                                        | -16 | 0   | 0   | Left     |    |
| Thalamus                               | 9   | -24 | 4   | Right    |    |
|                                        | -14 | -22 | 4   | Left     |    |
| Superior Temporal Gyrus                | 58  | -2  | 4   | Right    | 22 |
|                                        | -54 | -1  | -8  | Left     |    |
### 7.4. Activation differences between HC and bvFTD

**Table S8.** Voxels with maximum difference activation between HCs and bvFTD patients.

| Cortical region | MNI coordinates | Hemisphere | BA |
|-----------------|-----------------|------------|----|
|                 | x   | y   | z   |               |             |             |
| Gyrus Rectus    | 8   | 38  | -24 | Right         | 11           |
|                 | -6  | 18  | 24  | Left          |              |
| Inferior Frontal Gyrus (pars orbitalis) | 38  | 24  | -16 | Right         | 47           |
|                 | -40 | 30  | -12 | Left          |              |
| Middle Frontal Gyrus (orbital part) | 27  | 58  | -16 | Right         | 10           |
|                 | -31 | 54  | -12 | Left          |              |
| Orbitofrontal Cortex | 5   | 38  | -12 | Right         | 11           |
|                 | -7  | 42  | -12 | Left          |              |
| Anterior Cingulate Gyrus | 7   | 35  | 20  | Right         | 32           |
|                 | -6  | 35  | -8  | Left          |              |
| Inferior Frontal Gyrus (pars triangularis) | 54  | 42  | 8   | Right         | 45           |
|                 | -49 | 46  | 8   | Left          |              |
| Inferior Frontal Gyrus (pars opercularis) | 56  | 18  | 8   | Right         | 44           |
|                 | -51 | 13  | 8   | Left          |              |
| Insula          | 34  | 18  | -11 | Right         | 13           |
|                 | -39 | 14  | -4  | Left          |              |
| Rolandic Operculum | 46  | -20 | 20  | Right         | 48           |
|                 | -53 | -6  | 8   | Left          |              |
| Amigdala        | 23  | 2   | -16 | Right         |              |
|                 | -26 | 2   | -21 | Left          |              |
| Hippocampus (HPC) | 25  | -14 | -20 | Right         | 20           |
|                 | -30 | -18 | -12 | Left          |              |
| ParaHippocampal Gyrus (PG) | 28  | -34 | -12 | Right         | 37           |
|                 | -24 | -30 | -16 | Left          |              |
| Caudate         | 14  | 10  | 16  | Right         |              |
|                 | -12 | 18  | -8  | Left          |              |
| Putamen         | 28  | 3   | 8   | Right         |              |
|                 | -21 | 13  | -4  | Left          |              |
| Pallidum        | -15 | 2   | -4  | Left          |              |
| Thalamus        | 14  | -15 | 16  | Right         |              |
|                 | -12 | 10  | 4   | Left          |              |
| Superior Temporal Gyrus | 57  | -6  | -4  | Right         | 22           |
|                 | -54 | -26 | 4   | Left          |              |
| Inferior Temporal Gyrus | 53  | -31 | -24 | Right         | 20           |
|                 | -53 | -34 | -24 | Left          |              |
| Fusiform Gyrus  | 37  | -30 | -24 | Right         | 37           |
|                 | -32 | -34 | -24 | Left          |              |
| Supramarginal Gyrus | 56  | -44 | 28  | Right         | 40           |
|                 | -57 | -28 | 32  | Left          |              |
### 7.5. Activation differences between HC and AD

**Table S9.** Voxels with maximum difference activation between HCs and AD patients.

| Cortical region                          | x    | y    | z    | Hemisphere | BA |
|------------------------------------------|------|------|------|------------|----|
| Gyrus Rectus                             | 8    | 38   | -24  | Right      | 11 |
|                                          | -6   | 18   | 24   | Left       |    |
| Inferior Frontal Gyrus (pars orbitalis)  | 38   | 24   | -16  | Right      | 47 |
|                                          | -40  | 30   | -12  | Left       |    |
| Middle Frontal Gyrus (orbital part)      | 27   | 58   | -16  | Right      | 10 |
|                                          | -31  | 54   | -12  | Left       |    |
| Orbitofrontal Cortex                     | 5    | 38   | -12  | Right      | 11 |
|                                          | -7   | 42   | -12  | Left       |    |
| Anterior Cingulate Gyrus                 | 7    | 35   | 20   | Right      | 32 |
|                                          | -6   | 35   | -8   | Left       |    |
| Inferior Frontal Gyrus (pars triangularis)| 54  | 42   | 8    | Right      | 45 |
|                                          | -49  | 46   | 8    | Left       |    |
| Inferior Frontal Gyrus (pars opercularis)| 56  | 18   | 8    | Right      | 44 |
|                                          | -51  | 13   | 8    | Left       |    |
| Insula                                   | 34   | 18   | -11  | Right      | 13 |
|                                          | -39  | 14   | -4   | Left       |    |
| Rolandic Operculum                       | 46   | -20  | 20   | Right      | 48 |
|                                          | -53  | -6   | 8    | Left       |    |
| Amigdala                                 | 23   | 2    | -16  | Right      |    |
|                                          | -26  | 2    | -21  | Left       |    |
| Hippocampus (HPC)                        | 25   | -14  | -20  | Right      | 20 |
|                                          | -30  | -18  | -12  | Left       |    |
| ParaHippocampal Gyrus (PG)               | 28   | -34  | -12  | Right      | 37 |
|                                          | -24  | -30  | -16  | Left       |    |
| Caudate                                  | 14   | 10   | 16   | Right      |    |
|                                          | -12  | 18   | -8   | Left       |    |
| Putamen                                  | 28   | 3    | 8    | Right      |    |
|                                          | -21  | 13   | -4   | Left       |    |
| Pallidum                                 | -15  | 2    | -4   | Left       |    |
| Thalamus                                 | 14   | -15  | 16   | Right      |    |
|                                          | -12  | 10   | 4    | Left       |    |
| Superior Temporal Gyrus                  | 57   | -6   | -4   | Right      | 22 |
|                                          | -54  | -26  | 4    | Left       |    |
| Inferior Temporal Gyrus                  | 53   | -31  | -24  | Right      | 20 |
|                                          | -53  | -34  | -24  | Left       |    |
| Fusiform Gyrus                           | 37   | -30  | -24  | Right      | 37 |
|                                          | -32  | -34  | -24  | Left       |    |
| Supramarginal Gyrus                      | 56   | -44  | 28   | Right      | 40 |
|                                          | -57  | -28  | 32   | Left       |    |
### 7.6 Activation differences between bvFTD and AD

**Table S10.** Voxels with maximum difference activation between AD and bvFTD

| Cortical region                  | MNI coordinates | BA |
|----------------------------------|-----------------|----|
|                                  | x   | y   | z   |     |
| Anterior Pre-frontal cortex      | 5   | 52  | 20  | (right) |
|                                  | -5  | 18  | 20  | (left)  |
| Anterior Cingulate Gyrus         | 1   | 45  | 20  | (right) |
|                                  | -5  | 23  | 20  | (left)   |
| *Middle Temporal Gyrus           | 64  | -34 | -12 | (right) |
|                                  | -59 | -8  | -12 | (left)   |
| *Inferior Temporal Gyrus        | 60  | -39 | -16 | (right) |
|                                  | -56 | -54 | -16 | (left)   |
| *Fusiform Gyrus                 | 28  | -7  | -40 | (right) |
|                                  | -39 | -82 | -16 | (left)   |
| *Inferior Occipital Gyrus       | 40  | -82 | 16  | (right) |
|                                  | -40 | -83 | -12 | (left)   |
| *Ligual Gyrus                   | 29  | -91 | -16 | (right) |
|                                  | -35 | -87 | -16 | (left)   |

Note: Areas at which activation in bvFTD patients was increased in comparison with that of Alzheimer’s patients are denoted with an asterisk (*).

### 7.7 Source split analysis results

**Table S11.** Voxels with maximum difference activation between HC and bvFTD

| Cortical region                  | MNI coordinates | BA |
|----------------------------------|-----------------|----|
|                                  | x   | y   | z   |     |
| Gyrus Rectus                     | 4   | 52  | -16 | (right) |
|                                  | -4  | 54  | -16 | (left)  |
| Inferior Frontal Gyrus (pars orbitalis) | 45  | 45  | -8  | (right) |
|                                  | -54 | 37  | -4  | (left)   |
| Middle Frontal Gyrus (orbital part) | 5   | 50  | -4  | (right) |
|                                  | -6  | 56  | -8  | (left)   |
| Orbitofrontal Cortex            | 39  | 55  | 4   | (right) |
|                                  | -28 | 59  | 4   | (left)   |
| Anterior Cingulate Gyrus         | 5   | 47  | 20  | (right) |
|                                  | -5  | 45  | 16  | (left)   |
| Inferior Frontal Gyrus (pars triangularis) | 52  | 36  | 4   | (right) |
|                                  | -55 | 33  | 8   | (left)   |
| Inferior Frontal Gyrus (pars opercularis) | 54  | 14  | 20  | (right) |
|                                  | -61 | 16  | 20  | (left)   |
| Insula                           | 45  | 18  | -4  | (right) |
|                                  | -32 | 20  | -8  | (left)   |
| Rolandic Operculum               | 59  | 7   | 12  | (right) |
|                                  | -54 | 2   | 12  | (left)   |
| Amigdala                         | 27  | 1   | -16 | (right) |
|                                  | -24 | 3   | -12 | (left)   |
| Hippocampus (HPC)                | 29  | -34 | -4  | (right) |
|                                  | -30 | -18 | -12 | (left)   |
| ParaHippocampal Gyrus (PG)       | 14  | -15 | -16 | (right) |
|                                  | -22 | -4  | -16 | (left)   |
| Caudate                          | 14  | 10  | 16  | (right) |
| Putamen                          | -12 | 18  | -8  | (left)   |

14
Putamen
16 1 -4 (right)
16 -30 8 (right)
Thalamus
14 1 -4 (left)
16 -30 8 (right)
Supplementary motor area
4 10 52 (right) 32
* Superior Temporal Gyrus
58 -38 16 (right) 22
* Inferior Temporal Gyrus
38 -6 -54 (right) 20
* Fusiform Gyrus
-45 -10 -40 (left) 37
* Supramarginal Gyrus
-64 -26 32 (left) 40
* Precuneus
-15 -53 68 (left) 5

Table S12. Voxels with maximum difference activation between HC and AD

| Cortical region                          | MNI coordinates | BA |
|-----------------------------------------|-----------------|----|
| Gyrus Rectus                            | 6 38 -28        | 11 |
| Inferior Frontal Gyrus (pars orbitalis) | -3 20 -20       | 46 |
| Middle Frontal Gyrus (orbital part)     | 47 40 12        | 45 |
| Orbitofrontal Cortex                    | -33 58 -8       | 11 |
| Anterior Cingulate Gyrus                | 2 30 24         | 32 |
| Inferior Frontal Gyrus (pars triangularis) | -6 28 28     |    |
| Inferior Frontal Gyrus (pars opercularis) | -45 47 8       | 44 |
| Insula                                  | 29 15 -16       | 13 |
| Rolandic Operculum                      | -33 17 -16      |    |
| Amigdala                                | 39 -24 20       | 48 |
| Hippocampus (HPC)                       | -41 -22 20      |    |
| ParaHippocampal Gyrus (PGH)             | 25 2 -20        |    |
| Caudate                                 | -29 2 -20       |    |
| Putamen                                 | 12 17 8         |    |
| Pallidum                                | -13 17 8        |    |
| Thalamus                                | 27 -6 8         |    |
| Superior Temporal Gyrus                 | -27 0 -4        |    |
|                                        | 28 -5 -4        |    |
|                                        | -19 -5 -4       |    |
|                                        | 6 -10 4         |    |
|                                        | -14 -10 4       |    |
|                                        | 60 -23 8        |    |
### Table S13. Voxels with maximum difference activation between AD and bvFTD

| Cortical region                      | MNI coordinates | BA |
|--------------------------------------|-----------------|----|
| **Anterior Pre-frontal cortex**      | x   y   z        |    |
| 5                                   | 58  4            | 4  (left) 10 |
| -4                                  | 56  0            | 4  (left) 10 |
| 3                                   | 51  8            | 8  (right) 32 |
| -4                                  | 46  8            | 8  (left) 32 |
| 27                                  | 61  -4           | -4 (right) 11 |
| -6                                  | 61  -6           | -6 (left) 11 |
| 23                                  | 61  8            | 8  (right) 11 |
| -31                                 | 60  -4           | -4 (left) 11 |
| **Middle Temporal Gyrus**            | x   y   z        |    |
| 66                                  | -38  8           | 8  (right) 21 |
| -63                                 | -50  12          | 12 (left) 21 |
| **Inferior Temporal Gyrus**          | x   y   z        |    |
| 64                                  | -38  -20         | -20 (right) 37 |
| -53                                 | -54  -20         | -20 (left) 37 |
| **Fusiform Gyrus**                   | x   y   z        |    |
| 38                                  | -72  -16         | -16 (right) 37 |
| -38                                 | -80  -16         | -16 (left) 37 |
| **Inferior Occipital Gyrus**         | x   y   z        |    |
| 29                                  | -89  16          | 16 (right) 18 |
| -39                                 | -89  -12         | -12 (left) 18 |
| **Ligual Gyrus**                     | x   y   z        |    |
| 7                                   | -77  0           | 0  (right) 18 |
| -8                                  | -76  0           | 0  (left) 18 |

Note: Areas at which activation in bvTD patients was increased in comparison with that of healthy controls or AD are denoted with an asterisk (*).

### 8. bvFTD specific associations of rsHEP and multiple socio-cognitive measures

#### Cognitive state (CS)

The Montreal Cognitive Assessment (MoCA)(58) tracks CS decline in patients with neurodegenerative diseases(59-61). It evaluates attention, concentration, EFs, memory, language,
visorconstructional and visuospatial skills, conceptual thinking, calculations, and orientation. Its maximum score is 30, with higher scores indicating better performance.

Executive function (EF)
The INECO Frontal Screening (IFS) battery\(^{(62)}\) is sensitive and specific to detect frontal-executive dysfunction in patients with neurodegenerative diseases\(^{(62-65)}\). It includes eight subtests that tap three EFs: response inhibition and set shifting, working memory, and abstraction capacity. Its maximum score is 30, with higher scores indicating better performance.

Facial emotion recognition (FER)
We used a standard FER task in which participants must identify emotional expressions depicted in a series of photographs\(^{(66)}\). Stimuli comprise 35 faces selected from the larger emotion face set developed by Ekman\(^{(67)}\). Participants are instructed to associate each facial expression with one of six possible emotion labels (happiness, surprise, sadness, fear, disgust, anger) or a neutral expression. A score (max. 15) was calculated from the percentage of correct responses.

We compared the rsHEP and cognitive associations in tandems (bvFTD and HCs; and then AD and controls). First, for each subject, we calculated the rsHEP modulation as the area under the curve (AUC) based on the significant spatiotemporal cluster discriminating bvFTD patients from HCs (Figure 1B). Similarly, for AD and HCs, we considered the largest spatiotemporal cluster discriminating AD patients from HCs. Thus, larger rsHEP negative modulations were indexed by more negative AUC values. Each AUC was calculated via MATLAB’s trapz function. The MMLR model included CS, EF, and FER scores (dependent variables); and the interaction between the rsHEP modulation (AUC) and group (dummy variable: bvFTD-HCs) as predictors. The same MMLR was conducted for AD patients and HCs. The significance level was defined as \(P = .05\). By performing a MMLR model with an overall \(F\)-test first, the following univariate \(F\)-tests were protected against an inflation of the overall error rate\(^{(68)}\). In this sense we only inspected the univariate test when multivariate analysis yielded significant effects. All the analyses were performed with the lme4 library on R (version 3.5.2). To control for sample sizes differences across groups, we repeated all analyses on subsamples of AD and HCs as detailed above.

We evaluated to which extent the rsHEP in bvFTD was related to cognitive deficits at individual basis. To this end, we ran a MMLR between the three neuropsychological variables (CS, EF, FER) and the rsHEP modulations. We expected that the rsHEP would explain the socio-cognitive deficits only in bvFTD. In the bvFTD-HC model, results revealed significant multivariate effects for the interaction term between rsHEP modulation (AUC of rsHEP) and Group \([F(3,43) = 3.40, P = .025, \eta^2 = 0.19]\). The rsHEP modulation significantly predicted the three neuropsychological scores in bvFTD patients \([CS: F(3,45) = 4.76, P = .005; EF: F(3,45) = 8.30, P < .001, FER: F(3,45) = 10.43, P < .001]\) for full results see Table S14, Figure 3A] but not in HCs. The larger negative rsHEP modulation, the higher the deficit of bvFTD patients in multimodal behavioral performance including CS, EF and FER.

In the AD-HC MMLR model, although we found a significant multivariate main effect of Group \([F(3,49) = 35.81, P < .001, \eta^2 = 0.68]\), no significant interaction between rsHEP modulation and Group \([F(3,49) = .76, P = .51, \eta^2 = 0.04]\). Results showed that AD patients were outperformed in the three neuropsychological tests by HCs, independently of the rsHEP modulation \([CS: F(3,51) = 28.40, P < .001; EF: F(3,51) = 41.22, P < .001, FER: F(3,45) = 12.92, P < .001]\) for full results, see Table S14, Figure 3B]. Our results indicate that while behavioral performance in AD patients and HCs was not directly related to rsHEP amplitude, negative rsHEP modulation was associated with neuropsychological deficits in bvFTD at individual basis.
Table s14: Multivariate multiple regressions

| Predictors | CS β | SE | CI (95%) | P | R² | EF β | SE | CI (95%) | P | R² | FER β | SE | CI (95%) | P | R² |
|------------|------|----|---------|----|-----|-------|----|---------|----|-----|------|----|---------|----|-----|
| Group      | -0.20| 0.18| -0.56 – 0.17 | 0.27 | 0.24| -0.14| 0.17| -0.48 – 0.19 | 0.39 | 0.35| -0.35| 0.16| -0.67 – 0.02 | 0.03 | 0.41|
| HEP        | 0.07 | 0.15| -0.24 – 0.39 | 0.63 | 0.23| 0.14| -0.05 – 0.52 | 0.11 | 0.02| 0.14| -0.25 – 0.30 | 0.15 |
| HEP*Group  | 0.33 | 0.15| 0.01 – 0.065 | 0.046| 0.42| 0.14| 0.12 – 0.71 | 0.006| 0.38| 0.14| 0.10 – 0.66 | 0.009|

To evaluate the relations between neurovisceral markers of allostatic load (rsHEP) and cognitive deficits in bvFTD, we ran a multivariate multiple linear regression (MMLR(69)) considering rsHEP modulations as predictor and the three neuropsychological variables (CS, EF, FER) as outcomes. We compared the rsHEP and cognitive associations in the three groups (bvFTD, AD, and HCs). The MMLR model included CS, EF, and FER scores (dependent variables); and the interaction between the rsHEP modulation (AUC) and group (dummy variable: bvFTD-HCs-AD) as predictors. All the analyses were performed with the lme4 library on R (version 3.5.2). The significance level was defined as P = .05. We first performed an overall F-test on the MMLR model, and only inspected the univariate test if the multivariate model was significant.

Table S15. Multivariate multiple regressions with AD and HC subsamples.

| BvFTD relative to HC | CS β | SE | P | R² | EF β | SE | CI (95%) | P | R² | FER β | SE | CI (95%) | P | R² |
|----------------------|------|----|----|-----|-------|----|---------|----|-----|------|----|---------|----|-----|
| bvFTD                | -1.5 | 1.62| 0.4 | 0.3 | -0.72 | 0.01| 0.6 | 0.3 | -1.18 | 0.38 | 0.1 | .4 |
| rsHEP                | -0.02| 0.01| 0.1 | 0.01| 0.01 | 0.3 | -0.01 | 0.007 | 0.08 |
| rsHEP*bvFTD          | 0.05 | 0.02| 0.04| 0.06| 0.02 | 0.012| 0.02 | 0.01 | .02 |

| BvFTD and AD relative to HC | CS β | SE | P | R² | EF β | SE | CI (95%) | P | R² | FER β | SE | CI (95%) | P | R² |
|----------------------------|------|----|----|-----|-------|----|---------|----|-----|------|----|---------|----|-----|
| bvFTD                      | -1.5 | 1.60| 0.4 | 0.6 | -0.72 | 1.45| 0.61| 0.6 | -1.19 | 0.73 | 0.11 | .32|
| AD                         | -8.02| 1.35| <0.001| -8.21| 1.27 | <0.001| -1.97 | 0.64 | <0.001|
| rsHEP                      | -0.02| 0.02| 0.13| -0.01| 0.01 | 0.25 | -0.01 | 0.007 | 0.08 |
| rsHEP*bvFTD               | 0.05 | 0.02| 0.03| 0.06| 0.02 | 0.008| 0.03 | 0.01 | .020 |
| rsHEP*AD                  | 0.04 | 0.02| 0.06| 0.03| 0.02 | 0.1 | 0.02 | 0.01 | 0.072|

HC: healthy controls; bvFTD: behavioral variant frontotemporal dementia; AD: Alzheimer’s disease; CS: cognitive state; EF: executive functions; FER: facial emotion recognition; rsHEP: resting state heart evoked potential. Bold lines highlight significant differences.

8.1 Socio-cognitive split analysis results

8.2 bvFTD associations of rsHEP and multiple socio-cognitive measures: bootstrapped models
Table S16. Cognitive screening

|                | Estimate | Confidence Interval | Significance |
|----------------|----------|---------------------|--------------|
| rsHEP          | 0.009    | -0.03 - 0.001       |              |
| AD             | 1.44     | -12.34 - 7.162      | ***          |
| bvFTD          | 1.44     | -4.46 - 1.27        |              |
| rsHEP*AD       | 0.01     | -0.024 - 0.05       |              |
| rHEP*bvFTD     | 0.023    | 0.005 - 0.091       | **           |

AD: Alzheimer’s disease; bvFTD: behavioral variant Frontotemporal Disease; rsHEP: resting state Heartbeat evoked potential; *P < .05; **P < .01; ***P < .001

Table S17. Executive functions

|                | Estimate | Confidence Interval | Significance |
|----------------|----------|---------------------|--------------|
| rsHEP          | 0.006    | -0.02 - 0.007       | ***          |
| AD             | 1.55     | -12.52 - 6.65       |              |
| bvFTD          | 1.93     | -4.09 - 3.51        |              |
| rsHEP*AD       | 0.02     | -0.02 - 0.04        |              |
| rHEP*bvFTD     | 0.025    | 0.02 - 0.12         | **           |

AD: Alzheimer’s disease; bvFTD: behavioral variant Frontotemporal Disease; rsHEP: resting state Heartbeat evoked potential; *P<.05; **P<.01; ***P<.001

Table S18. Facial emotion recognition

|                | Estimate | Confidence Interval | Significance |
|----------------|----------|---------------------|--------------|
| rsHEP          | 0.003    | -0.02 - 0.004       | *            |
| AD             | 10.41    | -3.95 - -1.54       | ***          |
| bvFTD          | 0.78     | -2.61 - 0.53        |              |
| rsHEP*AD       | 0.005    | -0.0003 - 0.022     |              |
| rHEP*bvFTD     | 0.013    | 0.004 - 0.056       | *            |

AD: Alzheimer’s disease; bvFTD: behavioral variant Frontotemporal Disease; rsHEP: resting state Heartbeat evoked potential; *P<.05; **P<.01; ***P<.001

9. SBM associations with rsHEP modulations

9.1. SBM results for bvFTD patients

Table S19. Associations between SBM results and rsHEP modulations for bvFTD patients.

| Region         | Hemisphere | r    | P    |
|----------------|------------|------|------|
| Precentral     | Left       | .54  | <.001|
| Caudal middle frontal | Left   | .40  | .001 |
| Entorhinal     | Left       | .16  | .01  |
| Entorhinal     | Left       | .15  | .01  |
| Paracentral    | Right      | .13  | .01  |
### 9.2. SBM results for HCs

**Table S20.** Associations between SBM results and rsHEP modulations for HCs.

| Region                | Hemisphere | $r$  | $P$  |
|-----------------------|------------|------|------|
| Temporal pole         | Right      | .28  | .002 |
| Isthmus cingulate     | Left       | .27  | .003 |
| Middle temporal       | Left       | .20  | .004 |
| Pericalcarine         | Left       | .19  | .006 |
| Hippocampus           | Right      | .15  | .01  |
| Frontal pole          | Left       | .15  | .01  |
| Cuneus                | Left       | .14  | .01  |
| Superior frontal      | Left       | .14  | .01  |
| Insula                | Right      | .13  | .01  |
| Temporal pole         | Left       | .13  | .01  |
| Rostral middle frontal| Right      | .12  | .01  |
| Supramarginal         | Right      | .12  | .01  |
| Amygdala              | Left       | .11  | .02  |
| Frontal pole          | Right      | .11  | .02  |
| Insula                | Left       | .11  | .03  |
| Medial orbitofrontal  | Left       | .11  | .03  |
| Postcentral           | Left       | .11  | .03  |
| Entorhinal            | Left       | .11  | .03  |
| Lingual               | Left       | .11  | .03  |
| Insula                | Right      | .11  | .03  |
| Superior temporal     | Right      | .11  | .04  |
| Pericalcarine         | Right      | .11  | .04  |
| Supramarginal         | Right      | .11  | .04  |
| Temporal pole         | Left       | .11  | .04  |
| Precentral            | Left       | .11  | .04  |
9.3. SBM results for AD patients

Table S21. Associations between SBM results and rsHEP modulations for AD patients.

| Region            | Hemisphere | $r$  | $P$   |
|-------------------|------------|------|-------|
| Temporal pole     | Right      | 0.51 | 0.01  |
| Supramarginal     | Left       | 0.39 | 0.01  |
| Rostral middle frontal | Right | 0.31 | 0.02  |
| Frontal pole      | Right      | 0.29 | 0.03  |
| Temporal pole     | Right      | 0.28 | 0.03  |
| Middle temporal   | Right      | 0.24 | 0.04  |
| Lingual           | Right      | 0.24 | 0.04  |

9.4 Split analysis of the associations between brain structure and rsHEP modulation

Table S22. AD subsample

| Region                | Hemisphere | $P$ | $r$ |
|-----------------------|------------|-----|-----|
| Transversetempora     | Left       | 0.019 | 0.4  |
| Temporalpole          | Right      | 0.021 | 0.38 |
| Medialorbitofrontal   | Left       | 0.024 | 0.38 |
| Rostralmiddlefrontal  | Right      | 0.030 | 0.32 |
| Vessel                | Right      | 0.038 | 0.28 |
| Lateralorbitofrontal  | Left       | 0.038 | 0.28 |
| Supramarginal         | Left       | 0.038 | 0.28 |
| Cuneus                | Left       | 0.038 | 0.28 |
| Frontalpole           | Right      | 0.042 | 0.24 |
| Inferiortemporal      | Right      | 0.042 | 0.24 |
| Rostralanteriorcingulate | right | 0.047 | 0.23 |

Table S23. HCs subsample

| Region                | Hemisphere | $P$ value | $R$ score |
|-----------------------|------------|-----------|-----------|
| Amygdala              | Left       | 0.001     | 0.25      |
| Rostralmiddlefrontal  | Right      | 0.005     | 0.17      |
| Postcentral           | Left       | 0.005     | 0.16      |
| Cuneus                | Right      | 0.006     | 0.15      |
| Hippocampus           | Right      | 0.007     | 0.15      |
| Amygdala              | Right      | 0.008     | 0.15      |
| Superiorfrontal       | Left       | 0.011     | 0.12      |
| Pericalcarine         | Right      | 0.015     | 0.12      |
| Frontalpole           | Right      | 0.015     | 0.12      |
| Insula                | Left       | 0.017     | 0.12      |
| Precentral            | Left       | 0.019     | 0.12      |
| Cuneus                | Left       | 0.019     | 0.12      |
| Pericalcarine         | Left       | 0.023     | 0.11      |
10. Functional connectivity supplementary analyses

10.1. Functional connectivity split analysis

Table S24: connectivity matrix results

|         | AIN    | SN     | EN     | DMN    | VN     | MN     |
|---------|--------|--------|--------|--------|--------|--------|
|         | r  | p  |        | r  | p  |        | r  | p  |        |
| bvFTD   | 0.42 | 0.03 | 0.37   | 0.05 | 0.19 | 0.06  | 0.12 | 0.07 | 0.17  | 0.06  | 0.13  | 0.07  |
| HC      | 0.13 | 0.07 | 0.14   | 0.07 | 0.17 | 0.06  | 0.16 | 0.07 | 0.16  | 0.06  | 0.12  | 0.07  |
| AD      | 0.18 | 0.06 | 0.21   | 0.05 | 0.13 | 0.07  | 0.32 | 0.04 | 0.14  | 0.07  | 0.13  | 0.07  |

10.2. Bayes factors’ analyses

We computed Bayes factors in order to grade the decisiveness of the evidence for and against the presence of a correlation (70-74) between AIN connectivity and the rsHEP modulation. The Bayes factor compares the adequacy of two models. Here, the first model is the alternative hypothesis – H1 – that postulates the presence of a correlation between the AIN connectivity and the rsHEP modulation. The second model is the null hypothesis – H0 – representing the absence of correlation between the two measures. We used conventional cut-offs: a Bayes factor >3 was considered as substantial evidence for the H1; conversely, a Bayes factor <0.33 represents moderate evidence in favor of the H0; and anything in between is weak or anecdotal evidence(71). All analyses were performed with the BayesFactor library(75) in R. Only bvFTD patients showed moderate evidence (BFH1 = 8.96) for a positive correlation between AIN rsFC and the rsHEP modulation (see Table S21).

Table S25. Bayes factors’ results

| Group   | BFH1 | Evidence Categorization       |
|---------|------|--------------------------------|
| bvFTD   | 8.96 | Moderate evidence for H1       |
| HC      | 1.34 | Anecdotal evidence for H0      |
| AD      | 0.52 | Moderate evidence for H0       |
11.0: Machine learning analysis

11.1. Machine learning methods

We used a multimodal machine learning approach to evaluate whether multimodal neuroanatomy of allostatic interoceptive regions, rather than other less specific neuroanatomical regions, would better discriminate bvFTD patients relative to AD and HCs. Following machine-learning analysis guidelines(76), we split the datasets in a ratio of 80% for training, and 20% for testing, using random division, to test for generalizability without employing the testing dataset during the validation phase for out of k-folds predictions. The 80/20 split is the gold-standard for obtaining robust cross-validation results across neuroimaging research(77). We trained the model with all anatomical data: rsHEP sources, volumetric data, and seeds of all rsFC networks. For the training phase in all our analyses, following best practices, we employed a k-fold cross-validation for Bayesian hyper-parameter tuning(78, 79). First, we ran a classifier to discriminate between bvFTD patients from HCs. Then, to test the specificity of potential results from that analysis, we examined the classification accuracy between bvFTD and AD patients. To establish which features were the most relevant for each classification scheme, we employed the feature importance analysis technique, building in our machine learning algorithm(80). We used a GBM classifier library called eXtreme Gradient Boosting (XGBoost)(80), because of its high accuracy and robustness relative to other algorithms, tuning its hyper-parameters by Bayesian Optimization(81, 82). GBMs are based on the gradient boosting technique, in which ensembles of decision trees iteratively attempt to correct the classification errors of their predecessors by minimizing a loss function (i.e., a function representing the difference between the estimated and true values) while pointing in the negative gradient direction(83). The XGBoost classifier provides both parallel computation tree boosting, enabling fast and accurate predictions which have proven successful in several fields(84); and also regularized boosting, helping to reduce overfitting and thus providing more generalizable results. Following guidelines for reporting machine learning results(85), classification accuracy values were accompanied by (i) calculations of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, and (ii) confusion matrices capturing the sensitivity and specificity of each classification.

11.2. Machine learning results

The machine learning classification between bvFTD patients and HCs, based on an XGBoost algorithm including all neuroanatomical measures (HEP source space, brain structure and rsFC networks), achieved the highest accuracy rate with top features indexing allostatic interoceptive regions. The classificatory relevance was highest for the AIN rsFC feature, followed by activity of the medial frontal gyrus. The area under the curve (AUC) of the receiver operating characteristic (ROC) was 0.89 (80% sensitivity, 88% specificity) shown in the confusion matrix (Figure S3A). The classification between AD patients and HCs, achieved less accuracy rate. The classificatory relevance was highest for the DMN rsFC, followed by the activity of the left middle temporal gyrus. The AUC was 0.83 (82% sensitivity, 80% specificity) (Figure S3B). The classification between bvFTD and AD patients achieved an 82% accuracy rate. The classificatory relevance was highest for the AIN rsFC and followed by the activity of the left middle frontal gyrus. The AUC was 0.81 (85% sensitivity, 78% specificity) (Figure S3C).
Figure S5: Machine learning results. (A) bvFTD patients vs controls. ROC curve indicating specificity (true positive rate) and sensitivity (false positive rate), while calculating the area under the curve. Confusion matrix for true label and predicted label accuracy details. Feature importance plot of the most relevant features for the classification. Results show an 87% accuracy rate, an AUC of 0.89, a sensitivity of 80%, and a specificity of 88%, with the functional connectivity of the AIN as the top feature, followed by the activation of the middle frontal gyrus, a key region of the allostatic processes. (B) AD patients vs HCs. Results show an 81% accuracy rate, with an AUC of 0.83, with a sensitivity of 82% and a specificity of 80% specificity. The functional connectivity of the DMN and the activity of the middle temporal gyrus were the top features. (C) bvFTD vs AD patients. Results yielded an 82% accuracy rate, an AUC of 0.81, a sensitivity of 85%, and a specificity of 78%, with the AIN and middle frontal gyrus as the top features. ROC: Receiver operating characteristic, AUC: Area under the curve, bvFTD: behavioral variant of frontotemporal dementia; AD: Alzheimer’s disease; HCs: healthy controls; AIN: allostatic interoceptive network; SN: salience network; DMN: default mode network; EN: executive network.

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