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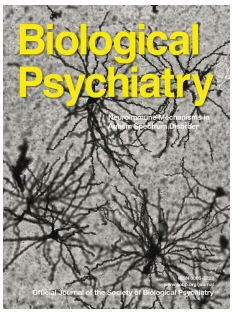

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Allostatic interoceptive overload in frontotemporal dementia

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Short title: Allostatic interoceptive overload in FTD

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Abstract

Background: The predictive coding theory of allostatic interoceptive load states that brain networks mediating autonomic regulation and interoceptive-exteroceptive balance regulate the internal milieu to anticipate future needs and environmental demands. These functions seems to be distinctly compromised in behavioral variant frontotemporal dementia (bvFTD), including alterations of the allostatic-interoceptive network (AIN). Here we hypothesize that bvFTD is typified by an allostatic interoceptive overload. **Methods:** We assessed the resting-state heart evoked potential (rsHEP) modulation as well as its behavioral and multimodal neuroimaging correlates in bvFTD patients relative to healthy controls (HCs) and Alzheimer's disease (AD) patients (N=94). We measured (i) the EEG resting-state heart evoked potential (rsHEP, prompted by visceral inputs and modulated by internal body sensing), (ii) associations between rsHEP and its neural generators (source location), (iii) cognitive disturbances (cognitive state, executive functions, emotion recognition), (iv) brain atrophy, and (v) rsfMRI functional connectivity (AIN vs. control networks). **Results:** Relative to HCs and AD patients, bvFTD patients presented more negative rsHEP amplitudes with sources in critical hubs of the AIN (insula, amygdala, somatosensory cortex, hippocampus, anterior cingulate cortex). This exacerbated rsHEP modulation selectively predicted the patients' cognitive profile (including cognitive decline, executive dysfunction, and emotional impairments). Also, the increased rsHEP modulation in bvFTD was associated with decreased brain volume and connectivity of the AIN. Machine learning results confirmed the AIN specificity in predicting the bvFTD group. **Conclusions:** Altogether, these results suggest that bvFTD may be characterized by an allostatic-interoceptive overload manifested in ongoing electrophysiological markers, brain atrophy, functional networks, and cognition.

Background

Predictive coding theories propose that the brain continuously updates an internal model of the world to anticipate the organism's future states and its responses to external demands(1-3). This process of continuous adjustment to anticipate environmental demands is known as allostasis: the cost of maintaining allostasis is known as *allostatic load*(4). Within this framework, the allostatic-interoceptive load(1, 2, 5-7) refers to internal body states (e.g., moment-to-moment visceral signals) that modulates the response to environmental demands. Allostatic-interoceptive load has been empirically linked to changes in bodily autonomic regulation(2, 8, 9). An allostatic-interoceptive network (AIN) has been identified in the human brain(2). The AIN involves the intersection of two large-scale intrinsic networks, the salience network (SN: bilateral ventral and dorsal anterior insula, anterior cingulate cortex, ventral striatum, thalamus, amygdala, hypothalamus, and brainstem) and the default mode network (DMN: bilateral angular gyrus, precuneus, hippocampus, and medial prefrontal cortices)(2). The AIN-specific connections of each network involve the dorsal mid to posterior insula (primary interoceptive cortex), limbic nodes, motor and pre-motor cortices (visceromotor control), and other fronto-temporo-parietal connections(2). Thus, the predictive coding theory of allostatic-interoceptive load(2, 8) proposed that visceral signals regulate the responses to external stimuli within the AIN(2).

Allostatic-interoceptive overload involves an imbalance between aberrant interoceptive signals and the responses to environmental demands (4). This imbalance of brain-body communication has been associated with pathophysiology (including autonomic outflow, abnormal stress responses, cognitive dysfunction, and behavioral disturbances(4, 10)). The heartbeat-evoked potential (HEP), a brain response triggered by visceral signals and modulated internal body sensing(11), can be considered a marker of allostatic-interoceptive load. Across cognitive domains, the moment-to-moment body internal states tracked with the HEP modulate the brain and cognitive responses to external stimuli(12-17). Source analyses of the HEP (12, 18) and its neuroimaging correlates(19,

20) are concordant with the allostatic-interoceptive brain regions as described above. Although the HEP has been traditionally used in heartbeat detection tasks, recent reports have shown HEP modulation in resting-state conditions (rsHEP) and during non-cardiac monitoring studies(12, 21). In particular, increased rsHEP has been associated with the hypervigilance to interoceptive signals linked to allostatic overload(21, 22).

Thus, according to the predictive coding framework, allostatic-interoceptive overload can be (a) indexed by increased rsHEP modulations, (b) associated with specific, relevant cognitive dysfunctions, and (c) linked to brain anatomy and connectivity of the AIN. Here, we tested these three predictions in the behavioral variant frontotemporal dementia (bvFTD). This is the most prevalent form of frontotemporal lobar degeneration, characterized by early personality changes, behavioral inappropriateness, and fronto-temporo-insular neurodegeneration(23, 24). Several sources of evidence suggest that bvFTD may be associated with an allostatic-interoceptive overload, which we describe below.

First, body autonomic dysregulation is pervasive in bvFTD(25, 26), including impaired skin conductance(27), cardiac vagal tone(28), heart rate, resting, and total energy expenditure(29). Atrophy and dysfunction in the left frontoinsula in bvFTD are deleterious for parasympathetic activity(28). Although autonomic imbalance and dysregulated behaviors involve increased rsHEP modulation in other conditions(22, 30-34), this has not been tested in bvFTD. However, interoceptive impairments, and their brain correlates, have been identified in bvFTD(35, 36). Moreover, these interoceptive impairments in bvFTD have been associated with deficits in recognizing others' emotions (13). Thus, previous research suggests that rsHEP should be impaired in bvFTD and that this impairment will be linked to specific deficits in cognitive-emotional responses to stimuli.

Second, the bvFTD's socio-cognitive dysfunctions may be linked to interoceptive dysregulation. Patients with bvFTD typically exhibit impairments in the cognitive state (CS; defined as the individual performance across core general functions, such as attentional, memory, and visuospatial domains), executive functions (EFs), and facial emotion recognition (FER)(37). Although not yet linked to allostatic-interoceptive overload in bvFTD, these socio-cognitive processes are plausibly impacted by such overload(38). Moreover, theoretical accounts (24) and metanalytic evidence(39) suggest that cognitive processes usually impaired in bvFTD (social cognition, emotion recognition, and interoception) are interlinked. Patients with bvFTD have poorer responses to external demands (disinhibition, disruptive or inappropriate behaviors; for a review: (40)) and exacerbated reactions in social settings (i.e., increased experience of envy and Schadenfreude(41); violation of social norms(42)). These socio-cognitive inappropriate responses in bvFTD have been theoretically – but not empirically) – linked to allostatic-interoceptive overload(24, 43-46). Beyond these antecedents, the specific association of increased rsHEP and socio-cognitive dysfunctions in bvFTD has not been directly tested yet.

Third, most of the allostatic-interoceptive brain regions are impacted by neurodegeneration in bvFTD(47, 48). Autonomic disruption in bvFTD depends on the integrity of insular networks(49). The core hubs of the AIN(2) comprising specific sub-hubs of the SN and DMN(2) are impaired in bvFTD(50-55). The SN has been associated with interoceptive deficits (35, 36) and impairments on interoceptive priming of recognition of other's emotion(13) in bvFTD. However, although the brain atrophy and connectivity impairment in bvFTD seems to overlap with the AIN, no previous work has examine the potential aberrant rsHEP activity and its specific association with the AIN.

The extant work described above indicates a hypothetical allostatic-interoceptive overload in bvFTD, which remains to be tested empirically. To assess this, we measured rsHEP modulation and its socio-cognitive and multimodal neuroimaging correlates in bvFTD patients relative to healthy

controls (HCs) and Alzheimer's disease (AD) patients. AD patients were included as a control neurodegenerative disease to test the selectivity of the hypothesized impairments in bvFTD. We hypothesized that the rsHEP in bvFTD would be (a) selectively increased, (b) associated with socio-cognitive dysfunctions, and (c) linked explicitly to atrophy and connectivity of the AIN. Our hypothesis leads to three sets of specific predictions. First, we anticipated a selective exacerbated rsHEP (increased amplitude modulation with sources in allostatic-interoceptive regions) in bvFTD compared to HCs and AD groups. Second, even though both AD and bvFTD commonly present cognitive, executive function, and emotion recognition deficits, we predicted specific associations of rsHEP overload and impairments in these measures only in bvFTD. Finally, we anticipated that the rsHEP modulation in bvFTD would be selectively related deficits in multimodal neuroimaging signatures (atrophy of allostatic-interoceptive regions and reduced connectivity of AIN in comparison with other control brain networks).

Methods

Participants

The study comprised 94 participants: 19 bvFTD patients, 33 AD patients, and 42 HCs. This sample size reached an adequate statistical power (0.96) to address our predictions (Supplementary material 1). Patients were diagnosed by expert neurologists following current criteria for probable bvFTD(62), and NINCDS-ADRDA clinical criteria(63, 64) for AD. Recruitment and diagnosis were conducted in clinical centers by a multidisciplinary team as part of an ongoing multicentric protocol(61, 65). Diagnoses were supported by extensive examinations(14, 23, 66, 67), in line with the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat) standardized protocol(68, 69). Importantly, the CS, EF, and FER tasks were not considered as diagnostic criteria. BvFTD patients were in the mild stage of the disease and presented ventromedial compromise, associated with executive impairments(70-73). No patient reported a history of other neurological disorders, psychiatric

conditions, primary language deficits, or substance abuse. All participants provided written informed consent pursuant to the Declaration of Helsinki. The study was approved by the Ethics Committees of the involved institutions. Demographic features of participants and their neuropsychological assessment are provided in Table 1.

Experimental protocol

Figure 1A describes the experimental protocol

Neuropsychological assessment

Cognitive state (CS), Executive function (EF) and Facial emotion recognition (FER) assessment are detailed in Supplemental material 8.

hdEEG methods

Acquisition and signal preprocessing

We obtained hdEEG signals during a ten-minute resting-state protocol detailed in supplementary section 3. To examine the HEP, we segmented the continuous EEG signal into epochs from -300 to 800 ms around the R-wave peak and baseline-corrected relative to -300 ms time window preceding the heartbeat(15, 17, 41, 74-76). Noisy epochs were rejected using the criteria of trials that exceeded a threshold of 2.5 SD from the mean probability distribution calculated from all trials and then measuring probability distribution kurtosis(77). The percentage of final trials was similar across groups (Supplementary material 3). Low drifts were removed by linear trend corrections(78). Trials were averaged across subjects for group comparisons.

Spatiotemporal clustering

The significance of differences in HEP modulation between groups was tested using a cluster-corrected permutation test(79), implemented in the Fieldtrip toolbox(80). The *t*-values that

exceeded a threshold of $P < .05$ (two-tailed) were clustered based on spatiotemporal adjacency. Each resulting cluster was assigned cluster-level statistics corresponding to the sum of the *t*-values of the samples belonging to that cluster. A minimum of 10 neighboring electrodes was required to pass this threshold and form a robust cluster(81). We assessed the significance of a spatiotemporal cluster identified above. This procedure was repeated 5000 times, with recombination and randomized resampling of the subject-wise averages before each repetition using the Monte Carlo method(82). Se full details in Supplementary section 3.

Source localization

Whole-brain activation maps were estimated for each subject, for each of the 564 scalp voltage distributions comprising the time window defined for rsHEP analysis (-300 to 800 ms around the R-wave of the heartbeat). As in spatiotemporal clustering analyses HEP for scalp data, we calculated normalized z-scores for bvFTD and AD comparison using the parameters (mean and *SD*) derived from the respective control group. Activation maps were obtained using the Bayesian model approach (BMA) of the EEG inverse problem(83) implemented in a Source Localizer(84). BMA addresses the problem of model uncertainty that arises when particular data (EEG scalp distribution in this case) is explained by different models –primary current densities (PCD) inside the brain. In this case, a set of models is defined based on anatomical constraints, each model consisting in a particular combination of anatomical compartments to which the generation of the PCD is restricted. BMA allows for the accurate estimation of deep EEG sources, and results in PCD maps with lower localization error and higher resolution than those obtained with traditional source analysis methods(83, 85). See full detains in Supplementary section 3.

Prediction of behavior with rsHEP

To evaluate the relations between neurovisceral markers of allostatic load (rsHEP) and cognitive deficits in bvFTD, we ran a multivariate multiple linear regression (MMLR(86)) considering

rsHEP modulations as predictor and the three neuropsychological variables (CS, EF, FER) as outcomes. See supplementary data 8 for full procedure.

Neuroimaging methods

Data acquisition

MRI/fMRI acquisition and pre-processing steps are reported following OHBM recommendations(87, 88) (Figure 1A). We acquired three-dimensional volumetric and ten-minute-long resting-state MRI sequences. As in the case of hdEEG recordings, participants were instructed not to think about anything in particular while remaining still, awake, and with eyes closed(17, 89). For details, see Supplementary material 4

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

Our assessed whether rsHEP modulation correlates with the volume and cortical thickness of key allostatic-interoceptive regions. We processed all T1 images via SBM on the FreeSurfer software suite (v 6.0 https://surfer.nmr.mgh.harvard.edu/). See supplementary section 4 for details.

Preprocessing of fMRI data for rsFC analysis

Images were then preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF V2.3)(90) as detailed in supplementary section 4.

Analysis of rsFC fMRI data

We evaluated associations between the rsHEP modulations and FC patterns. We implemented a seed analysis to examine associations between the HEP modulation and FC of the AIN(1) (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. See supplementary section 4 for details on analysis.

Results

hdEEG results

rsHEP modulations

The rsHEP comparisons between bvFTD patients and HCs revealed a significant cluster over right centro-temporal regions in a window of 290-600 ms post R-peak period (*t*-sum= -6141.61, cluster-level $P = .004$, $d = .78$ corrected for multiple comparisons in space and time, Figure 1C1 left panel), with its maximum *t*-value at 400 ms. Specifically, bvFTD patients presented a larger negative amplitude compared to HCs, indexing greater rsHEP modulation. The results were not biased by the difference in sample size across groups (Supplementary material 6). No significant clusters were observed between AD patients and HCs (*t*-sum = -2481.15 cluster-level $P = .08$, Figure 1C1 right panel).

To control for potential confounding differences between bvFTD and AD patients, we compared their respective normalized (Z-scored) mean rsHEP modulations in the cluster differentiating bvFTD patients from HCs. The difference was higher for bvFTD than for AD patients between 190 and 310 ms ($P < .05$, FDR-corrected, $d = .50$, Figure 1C2). Overall, the results shown that the rsHEP is increased in bvFTD patients relative to both control groups (HCs and AD).

Source space of rsHEP

The source localization analyses of rsHEP in bvFTD patients revealed statistically significant activation in most of the AIN hubs (crucially, the insula, the anterior cingulate cortex, and the amygdala) –permutation test, mean vs. 0 contrast, $P < .05$ FDR-corrected (Supplementary material

7.1). In the same line, HCs and AD patients also presented a distributed brain activation within the AIN–permutation test, mean vs. 0 contrast, $P < .05$ FDR-corrected (Supplementary material 7.2 and 7.3, respectively).

Compared to HCs, bvFTD patients showed significantly lower activation in relevant interoceptive hubs, including the insula, the anterior cingulate cortex, the opercular region, and the thalamus – permutation test, HCs > bvFTD patients contrast, $P < .05$, FDR-corrected. The compromise of these primary nodes was accompanied by hyperactivation of temporal regions of the AIN – permutation test, HCs < bvFTD patients contrast, $P < .05$, FDR-corrected (Figure 2A, Supplementary material 7.4). The aforementioned regions included the inferior temporal gyrus/superior temporal sulcus (ITG/STS), supramarginal, and fusiform cortices, which are relevant for visuomotor control, sensory integration, and stress regulation. In contrast, AD patients showed lower activation in frontal and temporal cortices –permutation test, HCs > AD patients contrast, $P < .05$, FDR-corrected (Figure 2B, Supplementary material 7.5), and presented no exacerbated activity –permutation test, HCs < AD patients contrast, all *P*-values > .05, FDR-corrected. Regarding the AD and bvFTD comparisons, bvFTD patients had lower activation in superior frontal medial gyrus and anterior cingulum; –permutation test, AD > bvFTD patients contrast, $P < .05$, FDR-corrected; Figure 2C, Supplementary material 7.6), and also hyperactivation in the inferior and medial temporal areas, as well as in inferior lingual and occipital cortices –permutation test, bvFTD > AD patients contrast, all *P*-values > .05, FDR-corrected (Figure 2C, Supplementary material 7.6). Thus, the rsHEP source space results indicate a combination of reduced (insula, anterior cingulate cortex, opercular region, and thalamus) and overactive (inferior temporal gyrus/superior temporal sulcus, supramarginal, and fusiform cortices) regions of the AIN only in bvFTD patients. Importantly, these results were not biased by the difference in sample size across groups (Supplementary material 7.7).

BvFTD specific associations of rsHEP and multiple socio-cognitive measures

We evaluated the extent to which rsHEP in bvFTD was related to cognitive deficits by running a multivariate multiple linear regression (MMLR(61)) considering rsHEP modulations as the predictor variable and the three neuropsychological measures (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. We expected that the rsHEP would explain the socio-cognitive deficits only in bvFTD. The rsHEP modulation significantly predicted the three neuropsychological scores in bvFTD patients as evidenced by the significant interaction between rsHEP and bvFTD group[CS:β =0.04, P = .05; EF: β =0.06, P = .01, FER: β =0.06, P = .01, for full results see Table 2, Figure 2A] but not in AD patients or HCs. The larger the negative rsHEP modulation, the higher the deficit of bvFTD patients in multimodal behavioral performance, including CS, EF, and FER. The larger the negative rsHEP modulation, the higher the deficit of bvFTD patients in multimodal behavioral performance, including CS, EF, and FER. Importantly, additional MMLR analysis with bvFTD and AD groups separately showed the same results (Supplementary material 8) and were not biased by the difference in sample size across groups (Supplementary material 8.1). Furthermore, given the importance of these results, we have conducted multiple checks to assess their robustness (see Supplementary material 8.2). In particular, we replicated the previous result with alternative bootstrapping methods and confirmed that low sample sizes and the potential non-linear data do not explain these significant results.

Neuroimaging results

Associations between brain structure and rsHEP modulation

We assessed whether the rsHEP modulation was related to the volume and cortical thickness of AIN regions. For bvFTD patients, this modulation was positively correlated with the volume, and

cortical thickness of the bilateral insula, the right amygdala, and the bilateral anterior cingulate –P < .05, whole-brain FDR-corrected (Figure 4B, Supplementary material 8.1). In the same vein, the HC group showed significant positive associations (P < .05, whole-brain FDR-corrected) between rsHEP modulation and the volume and cortical thickness of the bilateral insula and the left amygdala (Figure 4A, Supplementary material 9.2), among other regions (right superior and middle temporal gyrus). Finally, the rsHEP modulation of the AD group correlated with the structure of the disease-atrophied regions, such as the middle temporal gyrus, the left supramarginal gyrus, and middle frontal gyrus (Figure 3C, Supplementary material 9.3). Thus, rsHEP modulations, particularly in bvFTD patients (and HCs) were related with anatomical integrity of key AIN regions. Importantly, these results were not biased by the difference in sample size across groups (Supplementary material 9.4).

Association of rsHEP with functional connectivity of AIN and control networks

We first ran seed analyses to compare the AIN between patients and HCs, and then examined associations between the rsHEP and the AIN as well as five control networks (SN, EN, DMN, VN, and MN). Compared to HCs, bvFTD patients exhibited lower mean connectivity across specific AIN hubs (bilateral insula and amygdala, and the right anterior cingulate cortex) (P < .05, FDR-corrected). This pattern seemed distinctive of bvFTD, since the AD group did not show significant AIN hypoconnectivity compared with HCs (P > .05, FDR-corrected). Furthermore, for the bvFTD group, seed analysis revealed a significant positive association between connectivity of the AIN and the rsHEP modulation: the larger the rsHEP modulation, the lower the connectivity of the AIN (r = .44, P-FDR = .01) (Figure 5A). Conversely, the rsHEP modulation of both AD patients and HCs exhibited no significant associations with connectivity of the AIN –all P-values > .05, FDR-corrected (Figure 5A). Finally, the specificity of the rsHEP-AIN association in bvFTD was confirmed by non-significant associations between rsHEP modulation and control networks across groups (including the SN, EN, DMN, VN, and MN; all P-values > .05, FDR-corrected;

Figure 5C). These results were not biased by the difference in sample size across groups (Supplementary material 10.1). Furthermore, we computed Bayes factors quantifying evidence for or against the presence of correlation between the AIN connectivity and the rsHEP (Supplementary material 10.2)

Machine learning approach to multimodal allostatic interoceptive features in bvFTD

Our hypothesis suggests a multimodal (HEP sources, atrophy, and functional connectivity) allostatic-interoceptive overload impairment in bvFTD. In order to asses if these allostatic-interoceptive contributions were specific for the bvFTD group, we ran a machine learning algorithm with the rsHEP sources, the functional connectivity, and the volumetric data, as features to classify across the three groups. In short, for bvFTD discrimination – versus HCs and AD – the classificatory relevance was highest for the allostatic interoceptive features (see Supplementary material 11.0).

Discussion

This work examined the hypothesis of bvFTD selectively presenting an increased rsHEP modulation linked to specific socio-cognitive disfunctions, atrophy and connectivity of the AIN. Altogether, our findings suggest that disparate physiopathological processes and behavioral impairments constituting hallmarks of bvFTD could be better understood under a predictive coding framework of allostatic-interoceptive overload.

The rsHEP modulation was exacerbated in bvFTD patients, but not in AD patients or HCs. Such an effect was observed over right fronto-centro-temporal topographies, within the expected time window (200 ms – 800 ms). Increased rsHEP amplitude has been linked to different autonomic markers, including higher cortisol levels(91), pain perception(92), myocardial functional response to stress(93), depression(44), and overload response in autonomic dysfunction(41). A similar

rsHEP modulation has been observed in other disorders with maladaptive responses to environmental demands(57, 94-96). As in other populations (hypertensive patients(19) and patients with borderline personality disorder(47, 50)), the increased trait-like rsHEP in bvFTD patients was consistent with the opposite pattern (more positive HEP amplitude) reported during active interoceptive-emotional tasks(17, 61, 75). These results can be understood in the twofold model of neurovisceral integration(22, 58, 59). In this model, neurovisceral responses at resting (increased rsHEP) can be interpreted as basal interoceptive hyperactivation driven by allostatic-interoceptive overload. The reduced autonomic responsiveness during task (decreased HEP) can be understood as a lack of regulation triggered by exacerbated baseline modulations. These results suggest that a trait-like basal allostatic interoceptive overload is accompanied by impaired neurovisceral responsiveness to external demands(22, 58-60). Further combined assessment of resting state and active task HEP modulations would confirm this interpretation.

Right lateralization is consistent with previous HEP results(35, 57, 99), autonomic dysregulation(41), convergence of interoceptive and emotion processing(16), core emotional deficits in bvFTD(100), and AIN lateralization(1). In this sense, the scalp topography, time windows, amplitude modulation, and delimited results to bvFTD, together with previous evidence, suggest that the rsHEP can index allostatic interoceptive load(2-5).

Source-space analyses linked rsHEP modulations to AIN regions (insula, anterior cingulate cortex, amygdala, hippocampus, supramarginal gyrus, superior temporal gyrus) in bvFTD patients and HCs, consistent with other source-location studies(20, 62, 63) and neuroanatomical models(2). These results, then, support the hypothesis of an allostatic-interoceptive overload in bvFTD. Compared with HCs, bvFTD patients exhibited a hypoactivation of key interoceptive nodes (insula, anterior cingulate cortex, opercular region), consistent with interoceptive impairment of

perception and control(35, 56, 57), along with hyperactivated areas linked to allostatic-interoceptive load in healthy aging (superior temporal pole, supramarginal gyrus)(64).

Furthermore, compared to AD, bvFTD had lower activation in interoceptive frontal areas. Conversely, hyperactivation in inferior and medial temporal areas, as well as in inferior lingual, fusiform and occipital cortices was observed in bvFTD. These regions are involved in allostatic visceral integration (somatosensory areas) and temporal regions the AIN(1, 104). Of particular relevance to our hypothesis, this pattern was specific for bvFTD.

Although socio-cognitive alterations are affected in multiple neurodegenerative diseases(105, 106), CS, EFs, and FER are canonically impaired in bvFTD (23, 107, 108). Particularly, current meta-analytic evidence(109, 110) points to executive dysfunctions as core symptoms of bvFTD(111). More importantly, these impairments were selectively associated with enhanced rsHEP amplitudes only in bvFTD patients. These deficits compromise bvFTD patients' everyday behavior and functionality, increasing the maladaptive responses to environmental demands(107, 108, 112, 113). These impairments could be the result of many different factors(114) including atrophy of different brain areas (115), impairment of other related cognitive processes(116), or different physiopathology mechanisms (such as stroke(117), vascular(118), neurodegeneration(119), metabolic disbalance (120), or neurotransmitter dysregulation(121)). However, we found converging evidence that exacerbated rsHEP increased modulation systematically predicted cognitive, executive, and emotional dysfunctions only in bvFTD. This association was not found in HCs or AD patients. These cognitive functions in healthy populations and conditions other than bvFTD seem to be supported and modulated by allostatic-interoceptive load (1, 16), and impaired by allostatic overload(9, 18-22). In sum, these results suggest that allostatic-interoceptive overload in bvFTD is associated with the patients' socio-cognitive impairments.

In bvFTD patients and HCs, anatomical correlates of rsHEP confirmed its grounding in the AIN(insula, anterior cingulate, with more right-lateralized involvement in bvFTD). Particularly, the exacerbated rsHEP was related with increased AIN atrophy, critically compromised in bvFTD(122), and affected by allostatic-interoceptive load in healthy aging(103) and other disorders(123, 124). This is in concordance with previous studies showing that bvFTD patients have increased resting energy expenditure (a symptom of allostatic-interoceptive overload) compared to control and AD groups, associated with volume reductions in structures that are known to be involved in autonomic regulation(125).

Functional connectivity analyses confirmed a selective association between rsHEP modulation and impaired right AIN in bvFTD. First, bvFTD (but no AD) patients showed lower AIN connectivity compared to HCs. Second, the more negative the rsHEP in bvFTD patients, the lower the AIN connectivity. Third, the specificity of AIN involvement in rsHEP increased responses in bvFTD was confirmed by null associations between rsHEP and AIN connectivity in HCs and AD participants as well as non-significant associations with other functional networks (SN, EN, DMN, VN, MN). Typically, bvFTD presents altered connectivity of the SN(126-128) but also the DMN(32), both partially involved with the AIN(1, 28). Crucially, the SN has been associated with tracking of moment-to-moment body states(127), and implicated in the interaction between interoceptive awareness tracked by HEP and emotion recognition tasks(61, 86). Additionally, some hubs of the DMN are involved in allostatic-interoceptive load (1, 129). However, previous results of the SN and the DMN in bvFTD are controversial, with reduced (128) or increased(28) DMN connectivity as well as SN abnormalities that seem absent in familial bvFTD(32) or unspecific to bvFTD given their presence in AD(130). Present results provide novel support for a more extended and specific AIN disruption in bvFTD, selectively associated with ongoing exacerbated rsHEP.

The absence of association between the SN or the DMN with rsHEP modulations in bvFTD patients, suggests that the exacerbated rsHEP is specifically associated with reduced connectivity of certain hubs of the AIN in bvFTD; and unrelated with other impairments in SN or DMN dysfunctions. In this sense, the AIN is involved in in a wide range of cognitive, executive, and emotional phenomena that can be explained by their reliance on allostatic-interoceptive load(1). To the best of our knowledge, this is the first study evidencing that the moment-to-moment cortical processing of body signals in bvFTD is selectively and specifically associated with the connectivity of the AIN.

Traditionally, distinctions between neurological and psychiatric diseases have been overestimated(112, 131, 132). Currently, bvFTD provides a model combining neurological and psychiatric approaches. The allostatic and interoceptive frameworks have been widely applied in psychiatry, but their use in neurology is more scarce and the transnosological implications are unexplored. BvFTD patients have been systematically characterized by a wide range of behavioral and personality changes, often hindering timely diagnosis and treatment(133). Allostatic-interoceptive overload have been more thoroughly assessed in psychiatric conditions(134, 135). Connecting allostatic-interoceptive overload and interoceptive dysregulation with large-scale behavioral dysfunction can help to reduce the schism between psychiatry and neurology(112), while bringing more convergent clinical and biomarker insights(6, 136). Thus, our work sets the basis for future studies applying an allostatic interoceptive dimensional and transnosological framework across different brain diseases.

In this work, we show that exacerbated rsHEP in bvFTD are associated with different neuroanatomical markers of allostatic-interoceptive overload, including source space, anatomy, and specific AIN connectivity. These deficits also selectively explain the socio-

cognitive impairments in bvFTD. However, our work features some limitations that future work could address. First, it would be desirable to connect the rsHEP alterations in bvFTD with independent measures of allostasis and interoception, which have already reported in bvFTD separately. For instance, allostatic dysregulation via energy expenditure has been reported in bvFTD(125) and we have previously shown interoceptive deficits in bvFTD(17, 75). Thus, future studies may use the rsHEP alterations in bvFTD to test their impact in independent measures of allostasis and interoceptive performance, and also evaluate their specificity of such disturbances in bvFTD relative to AD. Second, diagnoses were based on standardized clinical assessments, in the absence of neuropathological confirmation. However, we have followed international standards(23, 62, 137) and multimodal studies with the current clinical criteria(17, 62, 67, 138). Third, the patient samples had moderate sizes. Although other studies reported replicable findings with similar or smaller groups(17, 139, 140), our approach should be tested using larger samples. Also, this caveat is counteracted by stringent control of clinical variables, systematic diagnostic procedures, and harmonized assessments. Similarly, the convergent cognitive, electrophysiological, neuroanatomical, and functional connectivity results, with moderate to large effect sizes, further attest to the robustness of the sample. Further longitudinal studies should evaluate the primary or secondary nature of allostatic-interoceptive overload in the neurodegenerative and clinical profile of bvFTD patients.

Conclusions

Multiple disparate deficits in bvFTD, including behavioral maladaptation(23), cognitive impairments (in CS, EFs, FER, and interoception)(17), autonomic disbalance(11), electrophysiological atypicalities (HEP), and atrophy and altered connectivity of fronto-insular-temporal hubs(17, 61) could be better integrated into an allostatic-interoceptive overload framework. In such account, the interoceptive signals are parameterized to anticipate changing needs, evaluate priorities, and prepare the organism to satisfy those priorities before leading to

errors(141, 142). Physiological and behavioral adaptation to environmental demands relies on the integration of body state signals with socioemotional stimuli(61), situational context(12, 13), and self-protection(143) processes which are impaired in bvFTD. A novel predictive coding framework based on multimodal markers may provide fruitful insights on the physiological and behavioral underpinnings of the disease.

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Figure Legends

Figure 1. Experimental design and hdEEG results. A) Experimental design. Participants completed a neuropsychological assessment evaluating cognitive state (CS), executive functions (EFs), and facial emotion recognition (FER). The protocol involved a 10-minute resting-state session while hdEEG signals were recorded, and a resting-state MRI and fMRI session. **B)** Data

941 analyses. First the rsHEP from the hdEEG signal, and its socio-cognitive (CS, EF, and FER) and
942 multimodal neuroimaging correlates (source localization, SBM and FC-fMRI analyses), were
943 calculated. **C)** rsHEP results. **C1.** rsHEP modulations during resting-state. Left: HC (green line) vs.
944 bvFTD (violet line). Right: HC (green line) vs. AD (pink line). Gray shaded boxes show statistically
945 significant differences at P = .05 cluster corrected (from 290 to 600 ms). Scalp topographies show
946 the significant electrodes of the cluster and the differences in amplitude (microvolts) between rsHEP
947 at 400 ms. **C2.** Subtraction of the mean rsHEP modulations between bvFTD and HC (violet line),
948 and AD and HC (pink line) in the cluster significant electrodes. Gray shaded boxes show statistically
949 significant differences at P = .05 FDR-corrected (between 190 and 310 ms). Scalp topographies
950 show the differences in amplitude (microvolts) at 250 ms and the electrodes used for the analysis.
951 AD: Alzheimer's disease; bvFTD: behavioral variant of frontotemporal dementia; HC: healthy
952 controls; CS: cognitive state; EF; executive functions; FER: facial emotion recognition; SBM:
953 surface based morphometry; FC: functional connectivity; MMLR; multivariate multiple regression;
954 AIN: allostatic-interoceptive network; rsHEP: resting state heart evoked potential.
955
956 **Figure 2. Source localization results.** Activation maps were obtained using the Bayesian model
957 approach (BMA (83)) of the EEG inverse problem (implemented in Neuronic Source Localizer(83,
958 84)). **A.** Subtraction of the mean activation maps between HC and bvFTD. **B.** Subtraction of the
959 mean activation maps between HC and AD. BMA images were visualized using the software
960 Neuronic Tomography Viewer and segmented with the AAL atlas (144). **C.** Subtraction of the mean
961 activation maps between AD (Z-scored) and bvFTD (Z-scored). AD: Alzheimer's disease; bvFTD:
962 behavioral variant of frontotemporal dementia; HC: healthy controls; INS: insula; AMY: amygdala;
963 HPC: hippocampus; BG: basal ganglia; THAL: thalamus; ITG: inferior temporal gyrus; STS:
964 superior temporal sulcus.
965
966

Figure 3. Multivariate multiple linear regression models. A) Association between rsHEP modulation and neuropsychological performance for bvFTD and HC. Significant interactions ($P < .05$) between rsHEP modulation and group were found for the CS (right), the EF (middle) and the FER (left) scores, evidencing that only in bvFTD, the larger negative rsHEP modulation (more negative values) the increased multimodal behavioral impairment. **B)** Association between rsHEP modulation and neuropsychological performance for AD and HC. AD patients were outperformed in the three neuropsychological tests by HC, independently of the rsHEP modulation. For estimates and statistical details see Table 2. bvFTD: behavioral variant of frontotemporal dementia; HC: healthy controls; AD: Alzheimer's disease; CS: cognitive state; EFs: executive functions; FER: facial emotion recognition; rsHEP: resting state heart evoked potential.

Figure 4. Associations between rsHEP modulation and whole-brain structure. A) BvFTD group showed significant correlations of rsHEP modulation on core allostatic-interoceptive regions (the anterior cingulate, and the bilateral insula, inferior temporal). **B)** HC group analyses revealed significant associations between rsHEP modulation and the cortical structure of allostatic-interoceptive regions ($P < .05$, FDR-corrected). **C)** AD group exhibited positive association of rsHEP modulations with the cortical structure of the left middle temporal gyrus, the right rostral middle frontal gyrus, and the left supramarginal gyrus. Cortical structure was obtained via surface-based morphometry. Results are presented using Desikan-Killiany cortical atlas (145). For structural association details, see Supplementary material 8. A: anterior; LH: left hemisphere; P: posterior; RH: right hemisphere. SF; superior frontal; ISTC: Isthmus cingulate; ENT: entorhinal; PREC: precentral; INS: insula; PSTS: postcentral; ST: superior temporal gyrus; MT: middle temporal gyrus; SMAR: supramarginal gyrus; RMF: rostral middle frontal; PARC: paracentral lobule; RAC: rostral anterior cingulate; CMF: caudal middle frontal; IT: inferior temporal gyrus.

Figure 5. The rsHEP modulation and functional connectivity of AIN and control networks. Seed analyses over different networks (FDR-corrected) were performed to test the IAN impairments in bvFTD and associations between rsHEP modulation and the FC of each network. **A)** FC differences between bvFTD and HC. BvFTD patients exhibited lower mean connectivity across bilateral insula and amygdala, and the right anterior cingulate cortex. ($P < .05$, FDR corrected). **B)** rsHEP-AIN associations. Only bvFTD showed significant positive correlation ($r = .44$, P-FDR = .01). **B)** AIN-connectivity topography. Lateral and sagittal views of intrinsic connectivity discovery maps depicting all voxels whose time course is correlated with the AIN seeds (right dorsal middle insula, right anterior midcingulate, and the right dorsal amygdala). **C)** Seeds and correlation matrices. Left: seed analysis and correlation matrix of the AIN matrix for all groups. Right; control networks (SN, EN, MN, VN, DMN) and correlation matrix across groups. Bold font indicates statistical significance. bvFTD: behavioral-variant frontotemporal dementia; HC: healthy controls; AD: Alzheimer's disease; AIN: allostatic-interoceptive network; SN: salience network; EN: executive network; DMN: default mode network; VN: visual network; MN: motor network.

Table 1. Demographic and neuropsychological data.

	bvFTD *N* = 19	**HC** *N* = 42	**AD** *N* = 33	**Statistics (all groups)**	**Post-hoc comparisons** Groups	*P-value*
Demographic data						
Sex (F:M)	5:14	22:9	18:11	$\chi^2 = 10.64$ $P = .006$[a]	HC-bvFTD HC-AD bvFTD-AD	.008[b] .31[b] .16[b]
Years of age	68.57 (1.92)	69.87 (1.50)	74.65 (1.55)	$F = 2.13$ $P = .08$[a]	HC-bvFTD HC-AD bvFTD-AD	.85[c] .07[c] .04[c]
Years of education	14.57 (0.91)	13.64 (0.71)	11.20 (0.74)	$F = 3.30$ $P = .01$[a]	HC-bvFTD HC-AD bvFTD-AD	.70[c] .06[c] .03[c]
Neuropsychological assessment						
Cognitive state (MoCA)	22.22 (0.92)	25.66 (0.75)	16.48 (0.72)	$F = 16.12$ $P < .001$[a]	HC-bvFTD HC-AD bvFTD-AD	.01[c] < .001[c] <.001[c]
Executive functions (IFS)	19.66 (0.90)	23.45 (0.78)	14.43 (0.71)	$F = 36.99$ $P < .001$[a]	HC-bvFTD HC-AD bvFTD-AD	.01[c] < .001[c] <.001[c]
Facial emotion recognition	10.16 (2.63)	12.35 (1.80)	9.78 (2.83)	$F = 8.74$ $P < .001$[a]	HC-bvFTD HC-AD bvFTD-AD	.009[c] < .001[c] 0.86

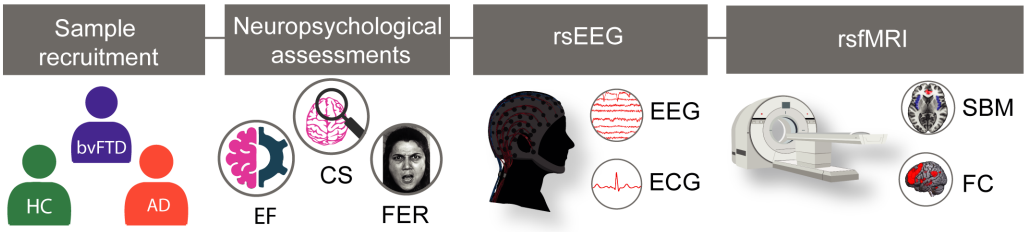
Data presented as mean (*SD*), with the exception of sex.
bvFTD: behavioral variant frontotemporal dementia; HC: healthy controls; AD: Alzheimer's disease.
MoCA: Montreal Cognitive Assessment
IFS: Ineco Frontal Screening
[a] *P*-values calculated via independent measures ANOVA.
[b] *P*-values calculated via chi-squared test ($\chi 2$).
[c] *P*-values calculated via Tukey HSD test.

Table 2: Multivariate multiple regressions
BvFTD and AD relative to HC

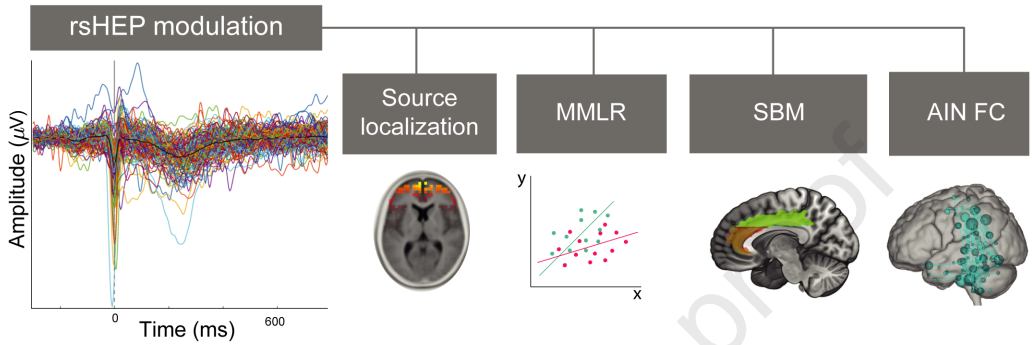
	CS					EF					FER				
	β	SE	*CI* (95%)	*P*	R^2	β	SE	*CI* (95%)	*P*	R^2	β	SE	*CI* (95%)	*P*	R^2
bvFTD	-1.65	1.60	-4.9 – 1.5	0.3	0.5	-1.10	1.50	-0.48 – 0.19	0.5	0.6	-1.35	0.66	-2.7 – -0.04	.04	.38
AD	**-9.81**	**1.21**	**-12 – -7.4**	**<0.001**		**-9.57**	**1.11**	**-12 – -7.3**	**<.001**		**-2.31**	**0.50**	**-3.3 - -1.3**	**<0.001**	
rsHEP	-0.02	0.01	-0.05 – 0.01	0.2		-0.01	0.01	-0.04 – 0.01	0.4		**-0.01**	**0.06**	**-0.02 – 0.00**	**.04**	
rsHEP*bvFTD	**0.04**	**0.02**	**0.01 – 0.1**	**0.05**		**0.06**	**0.02**	**0.01 – 0.1**	**0.013**		**0.03**	**0.01**	**0.01 – 0.05**	**.012**	
rsHEP*AD	0.01	0.02	-0.03 – 0.05	0.6		0.01	0.02	-0.02 – 0.04	0.6		0.01	0.01	-0.01 – 0.02	0.22	

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.

A. Experimental design



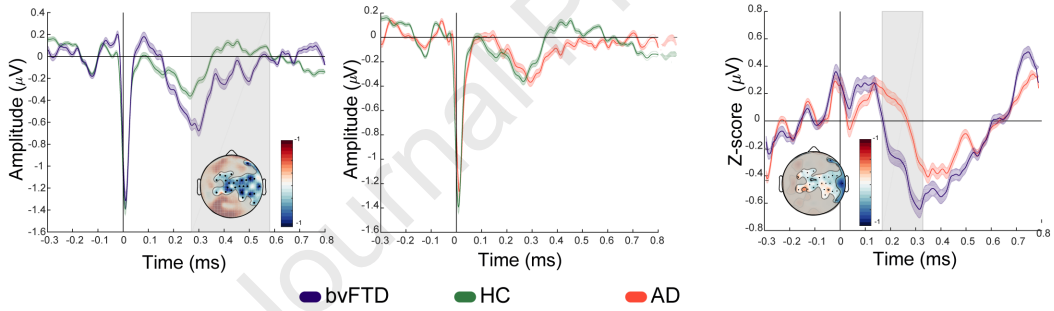
B. Data analyses

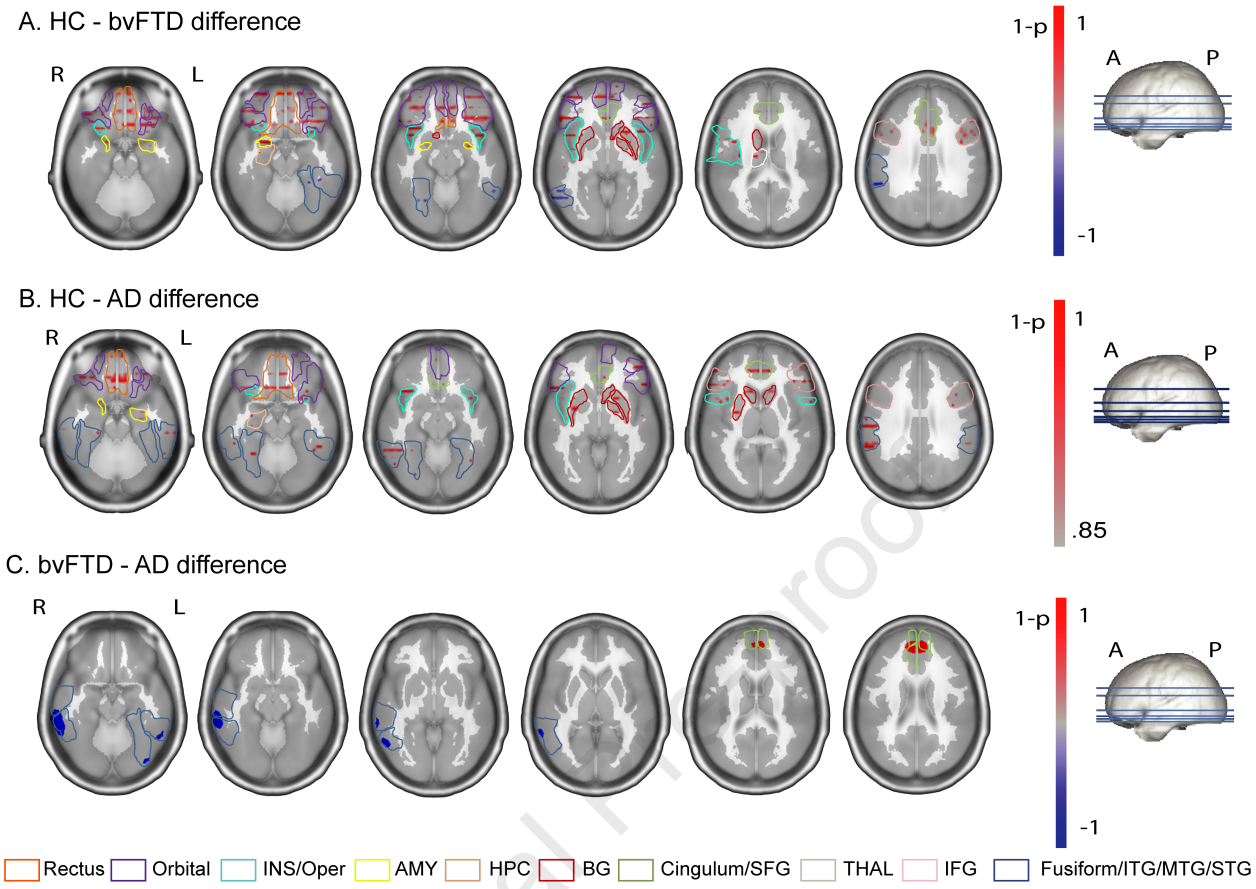


C. rsHEP results

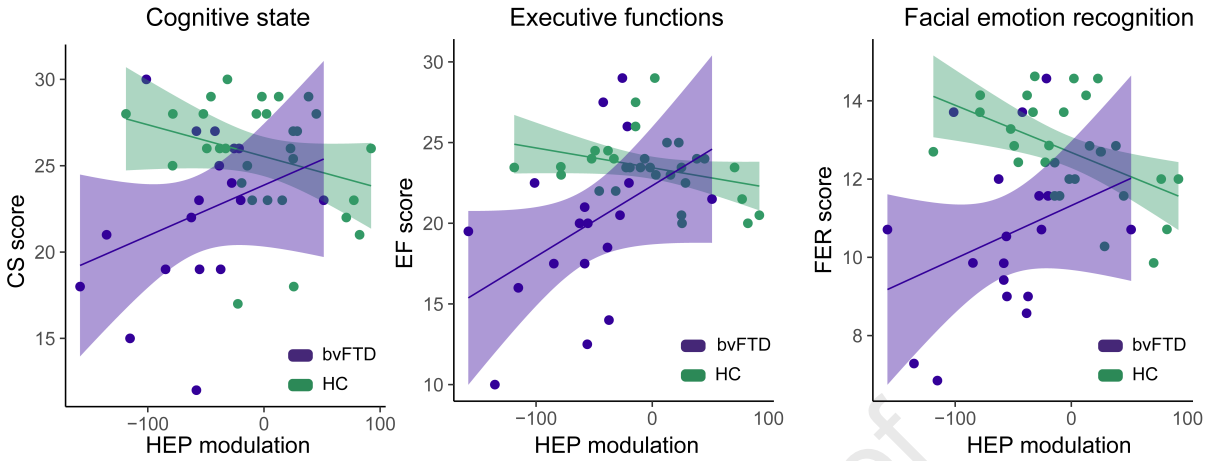
C1. rsHEP modulations

C2. bvFTD-HC vs AD-HC





A. MMLR for bvFTD and HC



B. MMLR for AD and HC