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Heart Evoked Brain Synchronization Predicts Progression to Alzheimer's Disease

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Abstract

A promising question in neuroscience is enlightening the interaction between heart and brain electrophysiological activities and its relationship with the cognitive status. Our aim here is to study the Heart-Brain Interplay (HBI) and assess whether HBI alterations can be biomarkers for Alzheimer's disease progression. To this end, we recorded resting state Magnetoencephalography (MEG) for healthy controls and two groups of Mild Cognitive Impairment (MCI) patients without cardiovascular alteration symptoms: stable and progressive to Alzheimer's disease. Our results demonstrated that MCI patients showed alterations in the HBI that can be summarized as follows: (i) heart evoked responses were interrupted in MCI and this lack of interaction correlate with cognitive performance; (ii) the influence of the heart activity onto brain networks fluctuates along cardiac cycle, being less responsive the MCI networks, and (iii) including HBI-MEG signatures in a machine learning procedure to predict AD progression outperform the results obtained using standard resting state MEG signatures. Our results highlight the role of heart in cognitive neuroscience by showing that basal brain networks are interrelated with the cardiac dynamics and propose the use of heart reference as a biomarker. The ignorance of the cardiac dynamic could be resulting in wastage of relevant information otherwise critical to understand disease as dementia.

Keywords: Heart-brain connection; Resting state connectivity; Heart evoked brain response (HER); Heart evoked brain connectivity (HEC); Progression to alzheimer disease; Mild cognitive impairment

Introduction

The study of the Heart-Brain Interplay (HBI) would deeply change our conception of cognition and will edify a most comprehensive understanding of diseases so far considered purely brain-originated. This is the case of Alzheimer Disease (AD). On one hand, previous studies in dementia have related heart and brain stating a high comorbidity between AD and Cardiovascular Diseases (CVD) [1]. These deleterious processes usually share most of the vascular risk factors which that, when accumulated during adulthood, substantially increase the risk of dementia [2]. This fact has been reported reversely as well, since it is well described that cardiovascular health improves cognitive performance and reduces the risk of cognitive impairment and brain network malfunctioning [3-5].

The HBI approach assumes that the heart modulates the brain activity. Therefore, heart-associated signals can be used to obtain time-locked brain electrophysiological activity, which has largely better signal to noise ratio in comparison to standard non-reference resting state brain activity. To analyze the HBI we took two different approaches. First, Heart Evoked brain Response (HER), which has been detected in different neocortical areas such as the insula, the anterior cingulate cortex, the amygdala and the somatosensory cortex [6-11]. Second, we propose a novel approach named Heart Evoked brain Connectivity (HEC) estimated by means of computing the time-frequency brain functional connectivity, with wavelet coherence, referenced to the heart pulse to be compared with the non-reference functional connectivity.

These two sets of the HBI measurements, HER and HEC, could be applied to disentangle whether HBI associated neurophysiological signatures can distinguish between healthy and pathological aging. Previous studies have demonstrated alterations in the organization of the Default Mode Network (DMN) in patients in the process of AD. However, it has not yet been elucidated the origin of these network alterations. A potential hypothesis is the hyperexcitability of the cortical neurons due to the toxicity of the amyloid plaques over the inhibitory terminals [12]. This loss of the excitation/inhibition balance lead to a less flexible state of the oscillatory activity and a tendency to hypersynchronize neurophysiological signals at different frequency bands [13]. Furthermore, these electrophysiological signatures have been linked with an increased risk of conversion to AD [13,14]. A relevant unanswered question is what triggers this hypersynchrony. Here we explore heart associated signals as one potential source for causing such network anomalies. No previous studies have explored the HBI in patients in the process of AD and how these interactions modulate brain activity and cognitive performance. Therefore, two main hypotheses will be tested:

- The first hypothesis states that HER obtained at the sources level, will show differences between Mild Cognitive Impairment (MCI) patients (early stage of the AD continuum) and age matched healthy elders. We expect that these differences will emerge in the MCI patients as an interruption of the brain network organization, being associated with patient's cognitive performance.

- The second hypothesis affirms that the use of HBI-MEG (Magnetencephalography) signatures will enhance the prediction of progression of AD.

Therefore, based on the clinical evidences linking cognition and cardiovascular health in elderly individuals, we expect that an HBI-based approach will uncover more reliable brain integrity markers than those obtained by assessing the spontaneous oscillations observed in resting state [1]. The expected outperformance will be tested by means of employing a machine learning methodology over standard resting state brain synchronization and HEC in a longitudinal dataset including stable and progressive MCI.

Materials and Methods

Sample and disease characterization

We enrolled 53 patients diagnosed with amnestic-Mild Cognitive Impairment (MCI) according to the National Institute on Aging-Alzheimer Association (NIA-AA) criteria [15]. They also showed significant hippocampal atrophy, which was evaluated by an experienced radiologist. Additionally, we carried out a clinical 3-year follow-up of the MCI subjects with the aim to determine if they either remained as MCIs or fulfilled the criteria for probable Alzheimer's disease according to the NIA-AA [16]. Based on their clinical outcome, MCI participants were split into two subgroups for the prediction analysis: the stable MCI group (sMCI; n=26), and the progressive MCI group (pMCI; n=27). A sample of 26 age-matched healthy control individuals was also selected with the same gender distribution and educational level of the MCI patients. Control and MCI patients differed in the Mini-mental State (MMSE) examination score (Table 1). All participants were in good health and had neither history of psychiatric, other neurological disorders nor cardiac disease history. The local Ethics Committee approved the investigation.

Cognitive performance tests							
Group	**Age**	**Education**	**MMSE**	**PF**	**SF**	**TMTt**	**TMTa**
Control	72.8±4.2	3.5 ±1.2	29.5 ±0.6	14.8 ±4.9	16.4 ±3.9	72.2 ±14.5	21.6 ±3.5
sMCI	71.3±5.4	2.9 ±1.3	27.7 ±2.1	10.9 ±5.1	13.5 ±4.4	86.2 ±7.4	19.8 ±6.1
pMCI	72.3±3.2	3.3±1.9	25.7±2.4	9.2 ±43.3	10.9 ±2.6	82.1 ±4.5	17.9 ±7.8
Stat-p	0.032	0.035	0.001	0.003	0.001	0.004	0.002

Note: Education: 1 (basic) to 5 (high professional); MMSE, mini-mental state; PF, phonetic fluency; SF, semantic fluency; TMTt and TMTa, trail making test time and accuracy (respectively, measured in seconds), and corrected statistics. sMCI: stable MCI; pMCI: progressive MCI

Table 1: Socio-demographic and cognitive test table.

MEG acquisition

Three-minute MEG resting-state recordings were acquired using an Elekta Vectorview system with 306 sensors, inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany). To determine the head position inside the MEG helmet, we digitalized the head with a Fastrack Polhemus, and four coils attached to the forehead and mastoids. Signals were sampled at 1 kHz with an online filter of bandwidth 0.1–300 Hz. Maxfilter software (version 2.2, Elekta Neuromag) was used to remove external noise with the Temporal extension of the Signal Space Separation (tsss) method with movement compensation [17]. The number of trials per subject is given by the number of heart pulses, being statistically similar in controls and patients (664 trials for controls and 587 for MCIs).

Estimation of the cardiac magnetic activity in the brain

The standard pre-processing of MEG/Electroencephalogram (EEG) data entails the rejection of components originated in external brain sources, such as eyes, muscles or the heart, to obtain a clean signal of the magnetic field of the brain. However, we consider that the cardiac magnetic component arriving at the brain far from being an artefact, influences neuronal activity even in resting state. To estimate such cardiac component, we applied Independent Component Analysis as implemented in Fieldtrip to MEG segments of 4 seconds length [18,19]. We manually selected the components of interest for this study, namely the neuronal and cardiac components for each segment and subject. Those components of neuronal origin were used for the source reconstruction method, avoiding the mixture with influences external to the brain. We individually checked the topography of the cardiac components and the presence of heartbeat and T wave, excluding those subjects with doubtful morphology. With this procedure, we expand MEG as a technique to study the brain activity to the Magneto-Encephalo-Cardiography (MEKG) to explore the brain-heart interaction. ICA has been proved to be a robust method for artifact detection and is nowadays a standard technique used in the preprocessing of M/EEG data. In this study, we estimate the cardiac magnetic dynamics from the raw data by means of ICA (named here MEKG) instead of using a direct Electrocardiogram (EKG). The first advantage of this procedure is to correlate both the brain and heart bio magnetic activities since the standard EKG estimates only the electric component of the heart electromagnetic field. Furthermore, with MEKG we estimate the cardiac magnetic field as arrived at the brain. As pointed by Winston and Rees, the possible distortion of the cardiac electromagnetic field from the heart to the brain is nowadays unknown [20]. In order to validate our procedure, we estimate the correlation between the manually extracted components from ICA and the EKG for a subset of participants (N=10). We obtain a 100% of coincidence in the time location of heart pulses (1000 Hz sampling rate). This issue is essential since we estimate heart evoked brain modulation considering the pulse as a trigger. In addition, ICA algorithm supposes that the propagation delays from the sources to the electrodes are negligible. Respect to the dynamics, the correlation between both time series is, on average, of 87%. We segmented the EKG in trials starting 50 ms before the QRS peaks and lasting until 50 ms before the next QRS peak. We have 664 trials for controls and 587 for MCIs.

MEG source reconstruction and heart evoked brain dynamics

After artifact rejection and the separation of the heart component, the 4 seconds segments of purely neuronal activity were used to estimate the sources in the standard spectral bands. Source locations were defined in the subject's space by using the cortical segmentation produced by Freesurfer with a regular mesh of points with 1 cm spacing, following a AAL atlas. We used a single shell model to solve the forward model and source reconstruction was estimated with Linearly Constrained Minimum Variance Beamformer for each

spectral band [21,22]. Individually, spatial filter's coefficients were computed by averaging the covariance matrix over all trials. Dynamics (time series) per segment and source localization were obtained from these coefficients when applied to individual trials. To avoid mixing MEG sensors with different sensitivities or resorting to scaling, only magnetometers were used for source reconstruction. Note, however, that gradiometer information is indirectly present as both magnetometers and gradiometers were included in the tsss filtering.

Heart-brain interplay

Heart-Brain Interplay (HBI) is assessed with two different approaches:

Heart Evoked brain Response (HER), where the time series of the brain sources are referenced to the heartbeats [23].

Heart Evoked brain Connectivity (HEC) by means of computing the time-frequency brain functional connectivity, with wavelet coherence, referenced to the heart pulse [24,25].

HEC is defined to estimate the pairwise brain connectivity referenced to the heart as well as to estimate the direct heart-brain synchronization. In order to study the dynamics of the HBI, four successive time windows of 100 ms length starting in the heart pulse are defined. Basal reference where the cardiac wave decay and therefore brain activity is free from electrical heart contractions is defined in the interval (400,600) ms after the heart pulse [7,26]. The HEC comparison between controls and MCI participants is done by means of the topological measurements as degree, number of connections per node (brain area) [27].

Statistical analysis and machine learning classification

We used nonparametric Mann–Whitney tests to check for differences between controls and MCIs in HER and connectivity. Further, we corrected by multiple comparisons by using a nonparametric permutation approach, as follows [28]. First, the original values were 5000 times randomly assigned to the original groups (controls and MCIs) and a Mann–Whitney test was performed for each randomization. Then, the U-value of the original dataset was compared to the ones obtained with the randomized data. The final p-value was defined as the proportion of permutations with U-values higher than the one of the original data. In all the correlations, we estimated the normalized Pearson correlation coefficient. We established a threshold of abs(R>0.5) in order to avoid statistical correlation with a small slope for its risky interpretation. Statistical p-values is thresholed to p<0.01 for all correlations showed in this work.

Additionally, we used a multivariate machine learning algorithm, support vector machine (SVM), to classify stable and progressive MCI [29]. The training phase (where the classifier was trained using group-labeled data) learns from the wavelet coherence between brain sources and heart dynamics from both sMCI and pMCI, and the accuracy is estimated from the testing phase with unseen data to be classified. A linear kernel was used to represent the data, reduce computational cost and improve classification accuracy (i.e., the overall rate of correct classification). An enhanced recursive feature procedure was implemented to ensure that discrimination accuracy was not due to overfitting and to select the best predictive features (brain areas) [30]. Finally, we used leave-one-out cross-validation to test classification accuracy and whether the results were independent of the initial training data [31].

Results

Heart evoked brain response disruption in MCI

Our results show that the Heart-Evoked Response (HER) is lower in MCI participants than in controls (p<0.001, corrected) in three areas of the left hemisphere: the frontal orbital cortex, the frontal pole and the left caudate, in a time window 200 ms after the QRS peak, corresponding to the T wave (Figure 1).

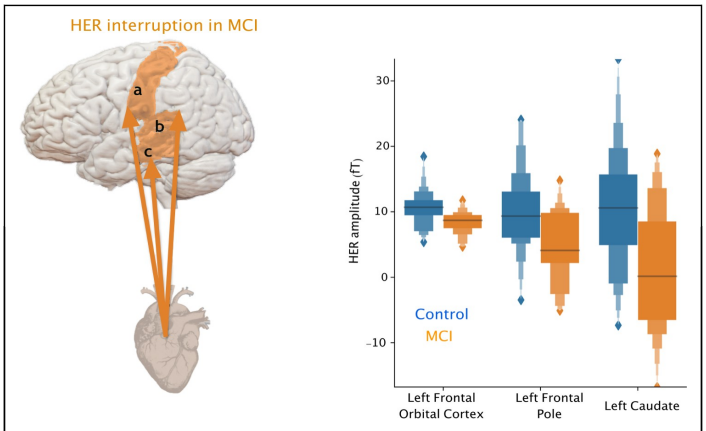


Figure 1: Heart evoked neuronal response alteration in MCI. Brain areas where heart modulation of brain activity is interrupted in MCI patients labelled as a) left frontal pole, b)Left insular cortex, and c) Left frontal orbital cortex, and the scatter diagram of averages. Average of HER (and standard deviation) in MCI and controls in the corresponding areas.

The possible relationship between HER and the degree of cognitive impairment as assessed by the MMSE score is studied. The MMSE performance correlated with the HER (Figure 2) in the left supracalcarine (r2=0.28) and precuneus cortices (r2=0.21) in the QRS peak, and in the left superior parietal lobe (r2=0.31) and posterior paracingulate gyrus (r2=0.09) 200 ms after the QRS peak. The decline of the MMSE is correlated with lower HER showing that a reduction of heart evoked brain response co-occurs with a cognitive deficit.

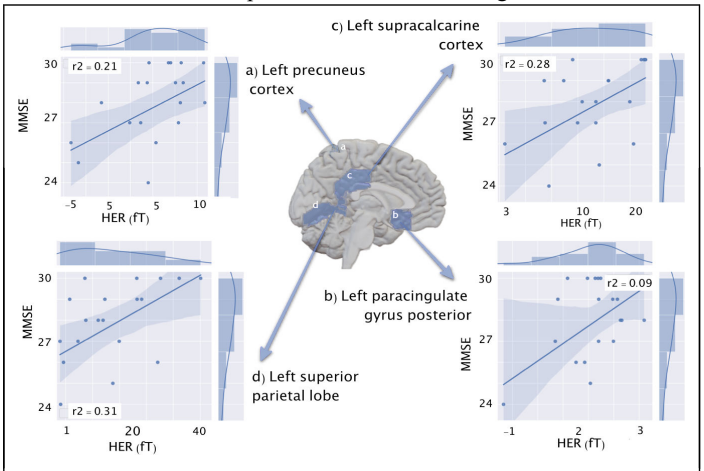
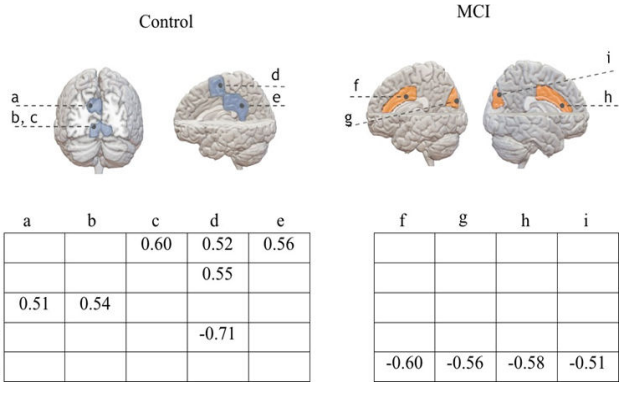


Figure 2: Heart evoked neuronal response and cognitive status in MCI. Correlation between HER with cognitive status as measured by MMSE in MCI patients. Areas labelled as: a) left precuneus cortex, b) left paracingulate gyrus posterior, c) left supracalcarine cortex, and d) left superior parietal lobe.

The correlation between HER and cognitive performance, assessed with several neuropsychological test (see Figure legend), is studied in both MCIs and controls. Pearson correlation coefficients R (at the p-corrected<0.01 statistical significance) are estimated and only considered those following a threshold of abs (R>0.5). Results show that HER is correlated with cognitive status in several areas belonging to the DMN (Figure 3) as follow: In controls, immediate recall performance correlate with the HER in left frontal pole (R=0.51), and left paracingulate gyrus posterior (R=0.54); phonetic fluency outcome correlated with HER in right superior parietal lobe (R=0.60), right cuneal cortex (R=0.52), and right precuneus (R=0.56); semantic fluency correlates with HER in right cuneal cortex (R=0.55) and trail making test time negatively correlates with HER in right cuneal cortex (R=-0.71). Regarding MCI participants, trail making test accuracy (measured in seconds) correlates with HER in right supramarginal gyrus (R=-0.60), Right Parietal Operculum cortex (R=-0.56), Left Supramarginal gyrus (R=-0.58) and Left Parietal Operculum cortex (R=-0.51). These results show that the lower HER and the reduced cognitive response in both populations.



	a	b	c	d	e	f	g	h	i
PF			0.60	0.52	0.56				
SF				0.55					
IR	0.51	0.54							
TMTt				-0.71					
TMTa						-0.60	-0.56	-0.58	-0.51

Figure 3: Heart evoked neuronal response and cognitive performance. Areas in the DMN presenting a significant correlation between HER and the cognitive test in control subjects (green areas) and MCI patients (red areas). Labels for brain areas: a) left parietal operculum cortex, b) left and c) right superior parietal lobe, d) right cuneal cortex, e) right precuneus, f) right supramarginal gyrus, g) right parietal operculum cortex, h) left supramarginal gyrus and i) left parietal operculum cortex (symmetrical areas not shown). Labels for cognitive tests: pf, phonetic fluency; sf, semantic fluency; ir, immediate recall; tmtt and tmta, trail making test time and accuracy (measured in seconds).

Heart evoked brain networks

To know whether resting state brain networks are influenced by cardiac cycle is, per se, an important topic in neuroscience. On the other hand, variability of spontaneous fluctuations observed in resting state is a phenomenon that could be hindering its application as biomarker in clinical research. We test the hypothesis that HEC, brain coherence referenced to the heart pulse, is a more relevant biomarker than non-reference resting state networks to study MCI. To end this, we estimated the time-frequency brain functional connectivity using heart pulse as a reference (called HEC) and without reference (called the standard procedure in resting state functional connectivity), and then, we compared the degree (number of connections per node) of MCI and control networks in HEC along the cardiac cycle (4 successive time windows of 100 ms length starting in the heart pulse are defined) and the standard resting state network in the standard spectral bands: Theta (4-8Hz), Alpha (8-12 Hz), Beta (20-30 Hz) and Gamma (30-50 Hz).

The topological comparison of HEC in controls and MCI networks is done by the number of connections statistically different in both population networks, i.e., the count of the statistical pairwise comparison of the networks |D|. This measure provides an estimation of the number of pathological links (present or absent) in the MCI networks along the cardiac cycle (for HEC) or in average (for non-reference networks). Figure 4A shows the bar diagrams with |D|, the number of pathological links, along the cardiac cycle and |D| for non-reference networks, in dashed line. We observe that the highest difference occurs in the heartbeat window and 200 ms later (two first bars), especially in the Alpha and Beta bands in favor of MCI subjects. There is accumulated evidence that resting state brain activity in MCI subjects is hypersynchronized in these bands [13,32,33]. Regionally, HEC differences between controls and MCIs in the alpha band in the heartbeat window included a range of brain areas bilaterally. Namely, they were the temporal and occipital fusiform cortex, the temporal lobe, the insular cortex, the intracalcarine cortex, the precuneus and the frontal orbital cortex in the left hemisphere, and the frontal pole, medial and operculum cortex in the right one. In the second time window (200 ms after the heartbeat), the areas affected were frontal poles, right occipital fusiform gyrus, left insular cortex and left intracalcarine cortex. Although we observed a hypersynchronization in alpha and beta bands in MCIs, the connection between left insular cortex and left frontal operculum cortex was missed in MCIs until 250 ms in both bands.

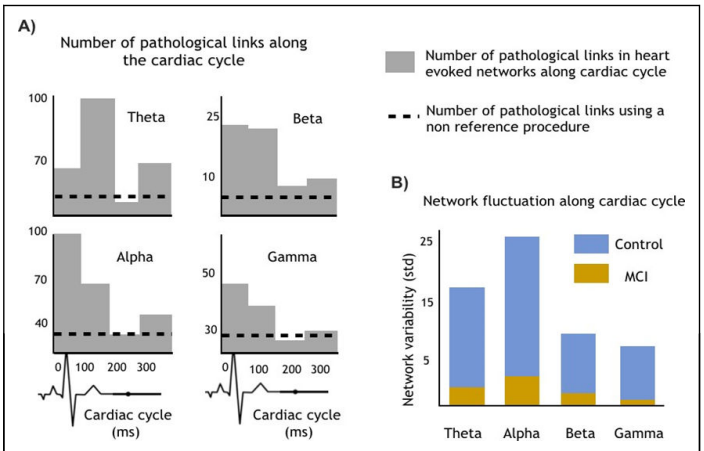


Figure 4: Heart modulation of brain network along cardiac cycle. (A) Number of pathological links (the count of the statistical pairwise comparison of the networks) in spectral bands in 4-time windows of 100 ms length after the heartbeat. Dashed line represents the number of pathological links without considering the cardiac events (i.e., brain activity not locked to heartbeats or non-reference resting state standard procedure). (B) Time variability of networks as a measure of the response of brain connectivity to heart beat for controls (blue bars) and MCI (yellow bars), and estimated as the standard deviation of the degree of the networks in the four consecutive time windows of the cardiac cycle in the typical spectral bands.

As we can see, the topological difference between both populations varies with time along cardiac cycle, being the period (0-200 ms) the

most discriminative of MCI and control networks. The fluctuation (time variability) of degree (grand average of the standard deviation of degree in the four-time windows) in both MCI and Controls networks in different spectral bands is summarized in Figure 4B. These results show that HEC of the control group varies with cardiac cycle, indicating that networks are responsive to the cardiac events by showing a wide pattern of rhythms. Conversely, the dynamic of the HEC in the MCI group was stiffer, changing less in all frequency bands than that of the control one. It indicates that HEC in MCI are less responsive to the cardiac events, showing an aberrant (practically constant) pattern of networks.

In order to test whether the results could be reproduced by using brain activity not locked to heartbeats (ignoring cardiac dynamics) we designed a surrogate procedure obtained by randomizing the temporal dependence of the cardiac pulse, by running the same analysis but randomly sampling the HEC at intervals mimicking heartbeats (the standard procedure in resting state studies). This comparison was repeated 10.000 times in order to estimate the rate of coincidences. The results of our simulations show that HEC are different from resting state networks with less than 1/1000 coincidences (0.0007% of cases). Resting state is a non-reference condition where the beginning of the segments selected for analysis is typically chosen randomly. Clearly, such strategy results in a wastage of relevant information (dashed line in Figure 4A), as compared to selecting the segments using the heartbeat as a trigger (bars diagram in Figure 4A). In summary, heart-evoked functional connectivity differences between controls and MCI varies during the cardiac cycle, showing a greater modulation of pre-beat network topology in controls than in MCI subjects.

Heart - Brain interplay predicts progression to AD

We used a multivariate machine learning technique (support vector machine, SVM) to test whether HEC is an accurate predictor of the progression of MCI individuals to AD. For this purpose, we estimated the accuracy of SVM to classify these individuals as sMCI or pMCI using HEC and compared it with that obtained using brain connectivity without reference to heart dynamics. We used a recursive feature elimination algorithm to choose the most relevant time interval, spectral band and the strength (average of the weight of functional connectivity) of brain areas in both the HEC and solely brain synchronization. The subset of brain areas performing better was later used in the classification. In this way, we not only prevented overfitting but also ensured that the number of features used for classification was the same in both cases. Selected features are: time interval (200-400 ms) after the heartbeat (T wave) in beta band and the following areas: right middle temporal gyrus, right frontal orbital cortex, right frontal operculum cortex, right supracalcarine cortex, right occipital fusiform gyrus, right intracalcarine cortex, right frontal medial cortex, left intracalcarine cortex, left precuneous cortex, and left frontal orbital cortex. In all these regions, the heart-evoked brain synchronization-strength-was higher for the sMCI group than in pMCI ($p<0.001$, corrected). Notably, the total classification accuracy was greater when we used the HEC values (86.7% of accuracy) as compared to the situation when we classified the subjects using the brain-brain interaction only (74.5%). Regarding the classification accuracy according to subgroups of MCI patients, we found a heart-brain classification accuracy of 93.5% and 80% for stable and progressive MCI, correspondingly. Whereas that the classification accuracy was the 60% and 72% for stable and progressive MCI, correspondingly when just considering the brain networks. Figure 5 shows prediction in classification accuracy for the progressive group when the brain-heart interaction is taken into account as compared to when only information from the brain-brain interaction is used.

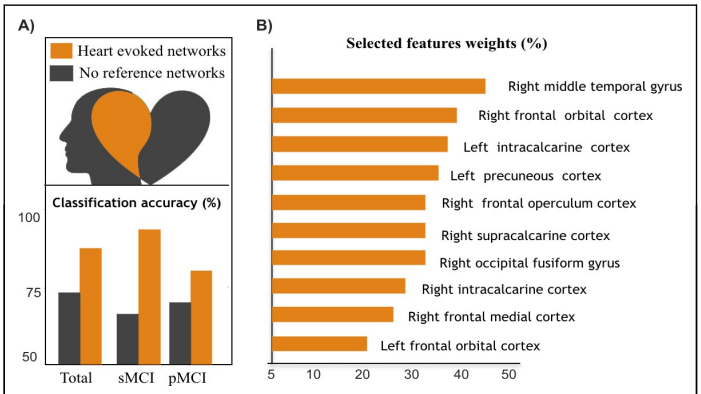


Figure 5: Heart evoked connectivity as a biomarker for Alzheimer disease. Classification accuracy (%) for stable and progressive MCI groups for the beta band in a time window (200, 400 ms) after the heartbeat and the corresponding classifiers brain areas where the heart adulation has a role as a biomarker for progression to AD (as selected by a recursive feature selection).

Discussion

We showed, in this work, that heart-evoked responses correlated with cognitive performance and dementia status in different brain regions including those belonging to the DMN. The heart and brain dynamics interact not only in response to the heartbeat but along the cardiac cycle. Considering the heartbeat as a temporal trigger to study resting state, unveil interesting phenomena in brain dynamics. For example, this continuous connection would be one of the factors responsible for the richness of rhythms observed in brain activity and the aberrant brain network found in pathology (Figure 4B).

Our results show, for the first time, that considering both heart and brain dynamics simultaneously enriches the study when compared with the cerebral activity alone. As shown in Figure 4A (dashed lines) results are not reproduced using brain data not locked to heartbeats (activity randomly sampled at intervals mimicking heart pulses) and the average of resting state intervals supposes no additional information. Additionally, based on machine learning results we show that the prediction to progression to AD is higher from the heart-brain interaction than from brain synchronization (Figure 5). It strongly suggests the need to rethink the role of the heart in cognitive neuroscience.

It is well known, that the visceral status influences stimuli processing requiring, therefore, the integration of sensorial information with autonomic control of the cardiovascular function. A question derived from this assumption is to what extent cardiac and brain malfunctioning appears simultaneously, and whether the former relates to the latter in diseases traditionally considered as a purely cerebral such as dementia [1,34]. Several studies have reported that CVDs such as heart failure, hypertension, atrial fibrillation produce cognitive decline, either transitory or chronic [35-38]. A direct example of the influence of cardiac dynamics on brain activity is cardiac variability. It has been shown that patients in the process of AD showed lower cardiac variability and this lack of flexibility could be ending-up in a more rigid dynamic of the DMN. Consequently,

DMN could show a lower flexibility to desynchronize in the presence of new stimuli, leading to errors in cognitive processing and daily living activities.

Dementia is also characterized by a loss of subjectivity or self-experience, whose relationship with the HER has been probed recently with a MEG study [39]. The influence of cognition in the selfhood and the autonomic system has been proposed although is still a topic that should be studied more [40-42]. Dementia could be a proper platform to study this relation, and the current work is the first to show the reduction of the heart evoked neuronal dynamics and its correlate with cognitive status as measured by MMSE test (Figure 2) in brain areas previously reported with fMRI studies [43]. Therefore, our results support the hypothesis that neuronal response to viscera activity is disrupted in MCI patients essentially in regions associated with the DMN which has been associated with the self-experience integrating the body as a whole [44,45]. This heart-brain disruption can alter the self-experience contributing to cognitive impairment in dementia.

The fact that HER phenomena are improving the classification between pMCI and sMCI is providing a clinical implication of these findings. As indicated by the results from the SVM technique, putting the heart into it improves our ability to distinguish between both groups as compared to using brain synchronization alone. In addition, we found that sMCI individuals showed higher synchronization than pMCIs in all the brain regions being more predictive of progression. One plausible explanation is that sMCI subjects compensate cognitive deficits by increasing the rate of synchronization of their brain networks. Indeed, compensation is a common interpretation for the higher activation/synchronization in MCI subjects as compared to controls. However, such increased activity correlates with close-to-random organization of the MCI network and inversely correlate with performance on cognitive tests [14, 46]. Furthermore, using a computational model, De Haan and colleagues demonstrated that increased activation and synchronization is a trigger of the pathological cascade in this disease [47]. Linked to this last idea, is the other plausible interpretation of sMCI hypersynchronization as a sign of functional network disruption. Hypersynchronization, can be induced by the impaired excitatory/inhibitory balance as indicated in animal models of the disease due to the toxicity of amyloid plaques to inhibitory terminals [12, 48, 49]. The fact that MCI patients showed hypersynchronization (and less variability across the QRS window) as compared to the control group, reinforces this interpretation. However, it is a counterintuitive finding that the sMCI group is the one showing highest hypersynchronisation. We interpret it by arguing that the fast converters, our pMCI group, showed less heart-evoked brain synchronization because they were in a more advanced stage (i.e., closer to Alzheimer disease), thereby presenting a more disconnected network as shown in AD patients [50]. In contrast, sMCI subjects are at an earlier stage and therefore still able to demonstrate a higher response to the heart dynamics. This idea was recently demonstrated by Pusil et al [13]. They did two consecutive MEG scans to sMCI and pMCI. At the second scan sMCI showed increased brain synchronization in comparison to pMCI, when initially they were showing a reverse pattern. This was indicating that pMCI were in a more advanced stage (network breakdown), while sMCI were in a more initial stage showing increased synchrony predicting conversion to AD [14]. It has to be tested in humans, whether the reduction of this brain response by anti-epileptic drugs could improve cognitive status as already demonstrated in animal models [51]. However, an important implication from our research could be how the improvement of cardiac function, increased variability, could improve as well the dynamics of brain activity by reducing the synchronization cycle. In turn, this excessive response will decrease the normal cortical representation of heart's dynamics in MCI patients, which will also produce a loss of subjectivity and self-experience, very common alterations in dementia patients.

Conclusion

Some questions still remain unanswered. How this heart-brain disruption affect the organization of the functional networks during performance of a memory task or how different life-styles (physical exercise, meditation or nutrition) can modulate this disrupted HER activity.

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