Hippocampal volume and functional connectivity transitions of the early stage of Alzheimer's disease: a Spiking Neural Network-based study.

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Introduction

Acting as a dynamical relaying center between different cortical areas, the hippocampus is known to significantly contribute in shaping the functional connectivity (FC) profile of the cortex [Gollo et al., 2011]. Many works in the field are being addressed to understand how the hippocampus has an impact on other cortical areas, both during motor action and at rest, but also from single areas to larger sub-networks, such as the *Default Mode Network* (DMN), a resting state network, more strongly active during idling states than during task performance [Raichle et al., 2001]. On one hand, some studies have reported a progressive decrease of hippocampal volume during the time course of early-stage Alzheimer's Disease (AD), which has been attributed to the loss of neurons and the deterioration of the related connections [Schuff et al., 2009]. On the other hand, the DMN appears to be functionally impaired in AD and even in earlier stages, as in Mild Cognitive Impairment (MCI).

In light of this, the present work aims at understanding the mechanistic underpinnings of FC transitions that take place during MCI. Specifically, we wanted to unveil whether the transitions of the DMN FC observed in this early phase of the AD can be attributed to the deterioration of the hippocampus as a dynamical relaying center between cortical areas. To this purpose, we investigated the resting-state interactions between the hippocampus and the remaining areas of the DMN (identified in our work by 13 areas in total, reported in Fig. 1). Both functional and structural connectivity (SC) profiles have been extracted from n = 9 healthy controls (HC), based on magnetoencephalography (MEG) and magnetic resonance imaging (MRI) data. We generated spiking-neuron based personalized models of the DMN of these subjects, including the hippocampal relay network (HRN, i.e. the star-like network composed of the hippocampal complex and its projections to the 12 remaining areas of the DMN). We generated two different versions of the HRN: HRN_{HC} (the 'healthy version', sized with data from healthy participants) and HRN_{MCI} (the 'degraded version', based on volumetric data from a group of MCI participants). Then, we have simulated 30s of MEG resting state activity and calculated the DMN FC profiles of each virtual subject under the two conditions (i.e., using the HRN_{HC} first, and then the HRN_{MCI}). We compared the FC transitions caused by the degradation of the HRN in the model, with those that have emerged from a previous comparative study (HC vs. MCI) carried out in our laboratory with real subjects [Garces et al., 2014]. Differences among the two conditions were evaluated in the alpha band, where the reference study had reported significant results.

Simulation results show that the structural modification of the HRN is able to predict up to 78% of the FC variations on the whole DMN, found in the reference study.

Our findings suggest that the misadjustment of the hippocampus could be playing a pivotal role on the disruption of the FC at the initial stages of the disease.

ROI name	ROI abbreviation	ROI n.	Color
Precuneus	PCUN	1(*l*), 2(*r*)	
Isthmus/posterior cingulate	IPC	3(*l*), 4(*r*)	
Inferior parietal g.	IP	5(*l*), 6(*r*)	
Superior frontal g.	SF	7(*l*), 8(*r*)	
Middle temporal g.	MT	9(*l*), 10(*r*)	
Anterior cingulate	AC	11(*l*),12(*r*)	
Hippocampal complex	HPC	13	

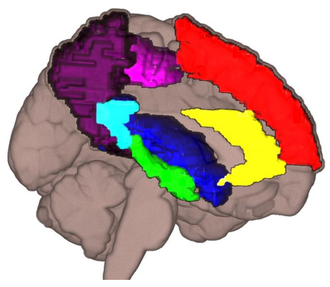

Figure 1: Regions of interest (ROIs) that have been considered in the DMN model (left) and related colour-coded representation (right).

FC and SC extraction

FC and SC profiles have been extracted from the 9 HC (five right-handed; four males; mean age: 28.4, S.D.: 2.5), as described in [Garces et al., 2016].

Five-minute eyes closed resting-state MEG recordings were acquired using an Elekta Vectorview system with 306 sensors (102 magnetometers and 204 planar gradiometers), while patient's MRI data has been acquired using a 3T General Electric MR scanner. Source reconstruction was performed with *linearly constrained minimum variance* beamformer [Van Veen et al., 1997]. 14 ROIs (Fig.1) were defined in the individual's T1 volume, using Freesurfer software and its cortical parcellation [Desikan et al., 2006], to compute FC and SC from MEG and diffusion weighted imaging (DWI).

Considering the *amplitude envelope correlation* (AEC) index [Brookes et al 2011], we computed the AEC values among the ROIs and then generated the alpha-band FC matrix considering the first 12 regions only, to evaluate the repercussion of HRN degradation on the FC of the remaining areas of the DMN.

Regarding the SC, considering the DWI obtained from the MRI sequences an SC value has been computed for each couple of regions *(i,j)* of the DMN, as the average of the sum of the streamlines seeded in one region *i* that ended in region *j*, and the streamlines seeded in *j* that ended in region *i*.

Synthesis and tuning of the SNN model

To model spontaneous activity, we generated a spiking neural network (SNN) for each participant, where:

- local node dynamics have been obtained considering groups of leaky integrate and fire with latency (LIFL) neurons [Susi et al, 2018]. The hippocampus complex has been modeled with two nodes operating prevalently in a burst regime (as in [Gollo et al. 2011]),. The remaining 12 nodes are represented by identical groups of spiking neurons (see [Nakagawa et al., 2014]), operating in a regular spiking regime [Gollo et al, 2011]. Each node of the network is modeled with n = 100 neurons for a total of 1400 neurons. E/I ratio has been set to 0.8 for all the modeled areas revealed by experimental observations [Izhikevich et al. 2004] and p_{rew} = 0.5 in order to obtain small-world properties.
- edges have been generated on the basis of the connectograms of the 9 subjects. The inter-areal weight W has been initially set to 0.055, as in [Susi et al, 2019]. For the characteristic lengths of the subnetwork, we considered those of the 66-parcellated template in *The Virtual Brain* repository [Sanz Leon et al., 2013; Hagmann et al., 2008]. Connections among neurons of the same area are characterized by negligible conduction delays. Conduction velocity has been set to 5 m/s on the basis of best-matching values reported in literature [Nakagawa et al, 2014].

An external excitatory background input has been predisposed consisting of spike trains representing the noisy fluctuations observed in vivo, with amplitude chosen in such a way that an isolated neuron of the 12 nodes of the cortex displays predominant spiking activity in the alpha band, whereas hippocampal activity is characterized by slow theta oscillations (frequency range from 6.5–7.5 Hz) and an interspike frequency of 35–45 Hz. Being W the free parameter of the system, it has been varied for each SNN, without altering significantly the power spectrum previously set, to achieve the best matching with the real subject. The matching has been evaluated in terms of Pearson's *r* (as in [Nakagawa et al, 2014]) between the vectorized triangular part of the FC matrices, excluding the HPC. Three participants have been discarded (s.1, 8, 9) because their models have not been able to fit the corresponding real brain networks accurately (r<0.4). We simulated 30s of activity for each virtual participant and summed up all synaptic pulses, as in Nakagawa et al. (2014), to extract a source-space MEG comparable signal . The whole process is summarized in Fig.2.

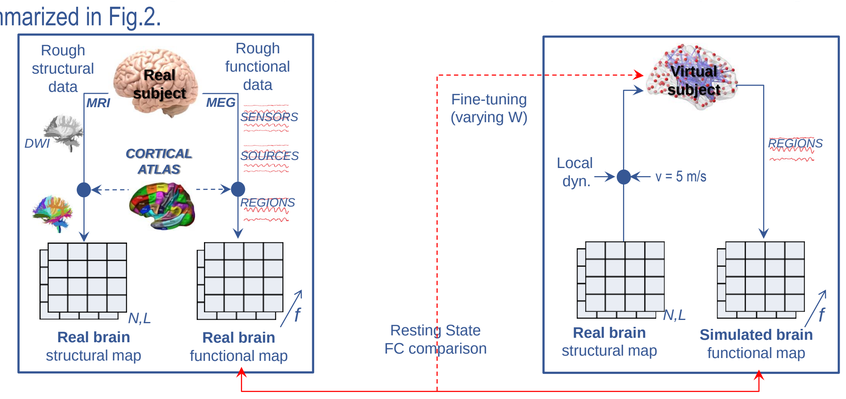

Figure 2 : FC and SC extraction, model synthesis and tuning of the SNN associated to the virtual subject.

FC transitions driven by HRN disruption

From a database of volumetric brain data from 54 HC and 46 MCI subjects, scanned at the laboratory of Cognitive and Computational Neuroscience of CTB (Madrid), we estimated an HC/MCI average ratio of hippocampal volume $\bar{R}$=1.15, reflecting the loss of neurons and the deterioration of the related connections during the early stage of the AD [Schuff et al., 2009]. On this basis, we generated a MCI version of the 9 virtual subjects by proportionally decreasing both number of neurons and connections of the HRN.

We repeated the simulation of 30s of activity for each virtual participant and computed the FC matrices of the virtual MCI subjects. Finally we computed the FC modifications obtained during the HC - MCI transition and compared with those highlighted by the reference study (HC vs. MCI), carried out on real subjects [Garces et al., 2014], which proved to be emblematic of the HC -> MCI transition.

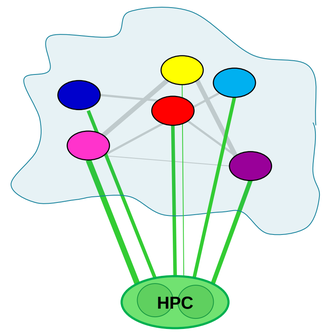

Figure 3: scheme of the DMN. HRN (in green) is composed of HPC and related connections to the remaining ROIs of the DMN.

Conclusion

Simulation results show that the structural modification of the HRN is able to predict a large part of the significant FC variations on the whole DMN found in the reference study for the alpha band (up to 78%, see Table I). Complete results are shown in Fig. 4. Our findings suggest that the misadjustment of the hippocampus as a relaying center between cortical areas could be playing a pivotal role on the disruption of the FC at the initial stage of the disease, when the SC is not yet considerably altered. It could be the hippocampus malfunction that subsequently triggers a plasticity-driven reconfiguration process, causing over time the structural and functional disruptions that characterize most advanced AD stages.

ROI couple	AEC transition (FC_{HC} to FC_{MCI})
***l*PCUN - *l*IP**	↓
***l*PCUN - *r*IP**	↓
***l*PCUN - *l*AC**	↓
***r*PCUN – *l*IP**	↓
***r*PCUN – *r*IP**	↑
***r*PCUN – *l*AC**	↓
***l*IPC – *r*IP**	↑
***r*IPC – *l*AC**	↓
***l*IP – *r*IP**	↓

Table I: Example of FC transitions induced by the deterioration of HRN in the alpha band (subj. 7 of the study). Green (red) arrows indicates a decrease (increase) of FC after the transition. In the reference work (Garces et al., 2014), FC(HC) > FC(MCI) for all the listed ROI couples.

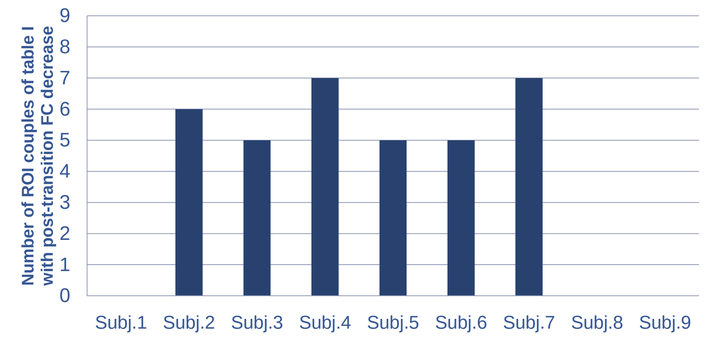

Figure 4: Number of ROI couples, among the significant ROI couples evidenced in the study of Garces et al., (2014) (see Table I), for which the HRN degradation caused a decrease of FC.

Acknowledgements

This work is supported by a project from the Spanish Ministry of Economy and Competitiveness (PSI2009-14415-C03-01), the project Neurocentro (B2017/BMD-3760) funded by the Community of Madrid, and the European Union's Horizon 2020 research and innovation programme under grant agreement No 826421 (project Virtual Brain Cloud).

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