Hippocampus-Cortical Structural Networks in the Progression of Cognitive Impairment: A Source-Based Morphometry Analysis in Alzheimer's Disease continuum

Laura Serra[1,2], Matteo Mancini[2,3], Sabrina Bonarota[2], Carlotta Di Domenico[2,4], Giulia Caruso[2], Martina Rizzuti[1,5], Francesco Di Lorenzo[6], Lucia Mencarelli[6], Giacomo Koch[6,7], Marco Bozzali[8], Carlo Caltagirone[9], Federico Giove[2,3], Francesca Gelfo[1,5].

1)Department of Human Sciences, Università degli Studi Guglielmo Marconi, Rome, Italy; 2) Neuroimaging Laboratory, Fondazione Santa Lucia IRCCS, Rome, Italy; 3) Museo Storico della Fisica e Centro Studi e Ricerche Enrico Fermi, Rome, Italy; 4) Department of Psychology, Sapienza University of Rome, Rome, Italy; 5) Laboratory of Experimental and Behavioral Neurophysiology, Fondazione Santa Lucia IRCCS, Rome, Italy; 6) Experimental Neuropsychophysiology Laboratory, Fondazione Santa Lucia IRCCS, Roma, Italy; 7) Department of Neuroscience and Rehabilitation University of Ferrara, Ferrara, Italy; 8) Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy; 9) Scientific Direction, Fondazione Santa Lucia IRCCS, Rome, Italy.

INTRODUCTION

Neural plasticity and memory mechanisms in humans undergo progressive alterations during pathological aging (1). Cognitive functions that rely on the medial temporal lobe and prefrontal cortex, such as learning, memory and executive function, are particularly vulnerable to the neurodegenerative processes (2). Alterations in the connections between hippocampus and cortices play a central role in the progression of the cognitive decline observed during different AD stages (3,4). We aimed to identify specific patterns of structural covariance between hippocampus and associative cortices that characterize different stages of cognitive decline and, secondly, to determine their relationship with memory test performance.

METHODS

46 SCD, 59 aMCI, 59 AD, and 49 HS underwent neuropsychological assessment including measures for **verbal episodic memory:**

RAVLT-IR, RAVLT-DR, RAVLT-HIT RATES, RAVLT FA,SHORT STORY-IR, SHORT STORY DR

Participants underwent a 3T-MRI scan to acquire T1-weighted images (MAGNETOM Prisma MRI scanner, Siemens Healthcare, Erlangen, Germany). Images were processed to extract structural networks (2) by using the **Source-based morphometry (SBM)** a data-driven linear multivariate approach for decomposing structural brain imaging data into commonly covarying imaging components and subject-specific loading parameters (2). The goal of SBM is to estimate maximally spatially independent sources (whole-brain spatial maps) that covary among subjects and to compute potential individual subject or group differences based on the degree of expression of these sources. SBM utilizes the combined techniques of VBM preprocessing (spatial normalization, segmentation, and intensity correction) and independent component analysis (ICA) to extract maximally spatially independent sources and then uses statistical measures to identify sources of interest (3). SBM was computed by using the software GIFT.

ANOVA models were used to compare different groups and **Pearson's coefficient** was used to assess correlations between structural networks and memory in each group separately

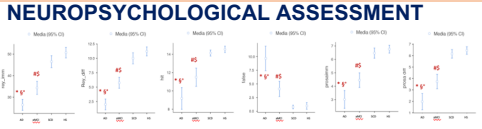
RESULTS

	AD	aMCI	SCD	HS
N	59	59	46	49
Age mean(SD)	73.3(6.6)*°	72.3(8.2)#§	68.2(7.3)	64.6(8.1)
Education mean(SD)	10(4.4)*°§	12.8(4.5)	13(3.4)	14.3(3.9)
Sex F/M	39/20	32/27	28/18	31/18
MMSE mean(SD)	22.4(3.3)*°§	27.2(2.1)#§	29.6(0.7)	29.5(0.8)

*AD vs HS p<0.05 °AD vs SCD p<0.05 §AD vs aMCI p<0.05

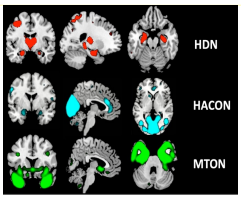
#aMCI vs HS p<0.05 $aMCI vs SCD p<0.05

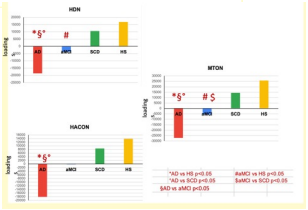
NEUROPSYCHOLOGICAL ASSESSMENT



MRI RESULTS

Three different networks involving the hippocampus were identified:
1) **hippocampal-diencephalic network (HDN),**
2) **hippocampal-anterior cingulate-occipital network (HACON)**
3) **mesiotemporo-orbitofrontal network (MTON).**





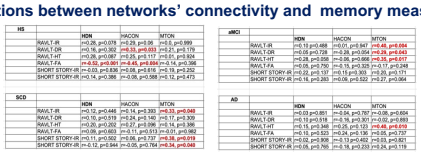
In each network patients showed an inverse pattern of covariance respect to SDC and HS.
Moreover, AD patients showed low connectivity level in each network; aMCI patients showed lower connectivity level than HS in the HDN and than HS and SCD in the MTON.

Inter-network correlations

HS		HDN	HACON	MTON
	HDN		**r=0.42, p=0.003**	**r=0.42, p=0.002**
	HACON			r=0.25, p=0.089
	MTON			
SCD		**HDN**	HACON	MTON
	HDN		**r=0.34, p=0.020**	**r=0.34, p=0.021**
	HACON			r=0.13, p=0.387
	MTON			
aMCI		**HDN**	HACON	MTON
	HDN		**r=0.39, p=0.003**	r=0.24, p=0.071
	HACON			r=0.20, p=0.123
	MTON			
AD		**HDN**	HACON	MTON
	HDN		r=0.07, p=0.569	r=0.24, p=0.064
	HACON			**r=0.208, p=0.028**
	MTON			

HDN, HACON and MTON showed a progressive decrease in their inter-network correlation passing form HS and AD group.

Correlations between networks' connectivity and memory measures



Significant associations between HDN and HACON, in turn, and recall and recognition scores in the HS group were found. The MTON connectivity's measure significantly correlated with memory measures in SCD, aMCI and AD patients.

RESULTS

We showed a peculiar pattern of correlations between network and memory tests across different groups. MNTON shows a positive correlation with several memory measures in the aMCI and SCD groups, suggesting a supporting role in long-term memory in the early stages of cognitive decline. In the AD group the correlation is lower suggesting a possible disconnection within the hippocampal-frontal network that could explain the memory disorder. **Conclusion:** this study underlines the presence of a progressive impairment of structural connections between the hippocampus and other brain structures involved in memory as one moves from healthy to AD.

Reference

1 Burke et al . doi: 10.1038/nrn1809. 2 Gupta et al., doi: 10.1007/s00429-019-01969-8; 3 Saha et al., doi: 10.1002/hbm.26483.; 4 Liang L et al., doi: 10.1002/hbm.26344.