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Link between hippocampus' raised local and eased global intrinsic connectivity in AD

Lorenzo Pasquini[a,b], Martin Scherr[b,c], Masoud Tahmasian[a,b,d], Chun Meng[a], Nicholas E. Myers[b,e], Marion Ortner[f], Mark Mühlau[b,g], Alexander Kurz[f], Hans Förstl[f], Claus Zimmer[a], Timo Grimmer[f], Afra M. Wohlschläger[a,b], Valentin Riedl[a,b,d], Christian Sorg[a,b,f,*]

[a]*Department of Neuroradiology, Technische Universität München, Munich, Germany*
[b]*TUM-Neuroimaging Center, Technische Universität München, Munich, Germany*
[c]*Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University Salzburg, Salzburg, Austria*
[d]*Department of Nuclear Medicine, Technische Universität München, Munich, Germany*
[e]*Department of Experimental Psychology, Oxford University, Oxford, United Kingdom*
[f]*Department of Psychiatry, Technische Universität München, Munich, Germany*
[g]*Department of Neurology of Klinikum rechts der Isar, Technische Universität München, Munich, Germany*

Abstract

Background: The hippocampus (HP) is part of the default mode network (DMN), and both are key targets of Alzheimer's disease (AD). Because of widespread network degeneration, it has been suggested that increasing HP disconnection from the DMN may lead to progressive disinhibition of intra-HP synchronized activity.

Methods: To analyze HP local (i.e., within HP) and global (i.e., within DMN) intrinsic functional connectivity (local/global intrinsic functional connectivity [iFC]), healthy controls and patients with mild cognitive impairment and AD dementia were assessed by spatial high and normal resolution resting-state functional magnetic resonance imaging.

Results: Although patients' parietal local-iFC was reduced and positively correlated with reduced global-iFC within the DMN, HP local connectivity was progressively increased and negatively correlated with HP decreased global connectivity. Increased intra-HP connectivity was associated with impaired memory.

Conclusion: Our result demonstrates a link between increased local and reduced global hippocampal connectivity in AD. Increased intra-HP synchrony may contribute to distinct symptoms such as memory impairment or more speculatively epileptic seizure.

Keywords: Alzheimer's disease; Mild cognitive impairment; Default mode network; Hippocampus; Intrinsic functional connectivity; Synchrony; High-resolution resting-state fMRI; Independent component analysis

1. Introduction

The medial temporal lobes (MTL), including the hippocampus (HP), are key targets of Alzheimer's disease (AD) [1,2]. Beyond atrophy, aberrant local activity and global connectivity have been observed in the HP [3], but their relationship is poorly understood.

Global connectivity changes, i.e., aberrant HP connectivity with extra-MTL regions, target mainly the default mode network (DMN). The DMN is characterized by intrinsic functional connectivity (iFC; synchronized ongoing activity) among prefrontal, parietal, and temporal midline structures, including the HP [4,5]. The DMN is affected by amyloid-plaque deposition in prodromal stages of AD [6,7] and appears to show selective deficits in both neuronal activity and iFC in AD dementia and mild cognitive impairment (MCI; a high-risk state for AD) [8–12]. Particularly, iFC of the HP to the parietal DMN is

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*Corresponding author. Tel.: +49-89-4140-4665.
E-mail address: c.sorg@lrz.tum.de

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already strongly disrupted in very early AD [9,10,13–15]. Paradoxically, local HP activity during memory tasks is consistently increased in individuals at-risk for AD such as MCI or cognitively normal Apolipoprotein E (*APOE*) ε4 carriers [3,16–19]. In patients with AD-dementia, HP activity is decreased, creating an inverse U-shaped function of memory-related HP activity. Contrary to the idea that HP hyperactivity in MCI is beneficial, a recent study found antiepileptics to suppress HP hyperactivity during memory performance in MCI and to reduce memory deficits [20]. This result suggests that HP hyperactivity contributes to HP-dependent memory deficits, rather than compensating for them. Furthermore, HP hyperactivity seems to be linked to overall disrupted network health, supporting the idea of a large-scale pattern of neurodegeneration reflective of AD-pathology [20,21].

In line with such network degeneration, it has been suggested that global HP disconnection may disinhibit local HP activity arising from trisynaptic intra-HP loops [13,22]. This model implies that beyond memory-related activity, the synchrony of ongoing intra-HP activity might be increased in MCI. Such an increase may depend on correspondingly decreased global iFC of the HP within the DMN, and it might grow with progressive disease severity due to progressive HP disconnection. Furthermore, increased intra-HP synchrony might reflect memory deficits in patients. Recently, Das and colleagues reported initial evidence for this hypothesis [13]. They found that local iFC between the HP and adjacent entorhinal cortex increased in MCI (see also [23]). Simultaneously, the overall MTL intrinsic connectivity within the DMN was reduced. However, it was not shown whether local and global connectivity changes are related to each other, whether any of the observed changes had functional consequences for memory, and, importantly, which trajectory of changes takes place beyond MCI.

In this study, we tested these more specific predictions of the HP disconnection hypothesis. We assessed healthy controls (HC) and patients with MCI and AD dementia with resting-state functional magnetic resonance imaging (rs-fMRI) indicating blood-oxygenation-level-dependent signals (BOLD). Independent component analysis (ICA) of fMRI data was used to identify statistically independent spatial patterns of coherent activity in a data-driven, spatially unbiased way. Individual spatial z-maps, which reflect patterns of coactivity, were used as surrogate for iFC and constitute the study's main outcome measure [9,24]. To increase spatial resolution of z-maps and to test for anatomical specificity of potential local iFC increases, additional spatial high-resolution rs-fMRI was applied focused on the HP and retrosplenial parietal cortex. Following previous results, we expected to delineate four regional subsystems within the DMN via local iFC patterns (from here on referred to as "DMN subsystems"), namely the anterior HP (aHP), posterior HP (pHP), precuneus (PrC), and posterior cingulate cortex (PCC) [23,25,26]. We defined local-iFC as iFC-maps derived from the partial-brain high-resolution scan, reflecting only connectivity within the DMN regions covered by its limited field-of-view (FoV). Global-iFC, in contrast, was defined by iFC-maps derived from the whole-brain scans, therefore reflecting connectivity to the rest of the cortex as well. Maps of local- and global-iFC were cross-validated for different methodological approaches, compared across groups, and correlated among each other and with memory scores.

2. Materials and methods

2.1. Subjects

Twenty-two HC (16 females, aged 56–85 years), 22 patients with MCI (11 females, aged 48–80 years) and 21 patients with AD dementia (13 females, aged 57–83 years) participated in this study (Table 1). All subjects provided informed consent in accordance with the Human Research Committee guidelines of the Klinikum rechts der Isar, Technische Universität München. Patients were recruited from the Memory Clinic of the Department of Psychiatry and HC by word-of-mouth advertising. Examination of every participant included medical history, neurological examination, informant interview (Clinical Dementia Rating, CDR) [27], neuropsychological assessment (Consortium to Establish a Registry for AD [CERAD] battery) [27], structural MRI, and blood tests (for patients only). Patients with

Table 1
Demographic and neuropsychological data

	AD (n = 21)	MCI (n = 22)	HC (n = 22)	*F*	*P* value
Age (y)	72.3 (8.6)	65.3 (8.7)	66.3 (9.0)	7.00	.16
Education (years of school)	9.3 (1.6)	9.9 (1.7)	10.1 (1.7)	0.94	.40
% Female	61.9	50.0	72.7	–	.31
CERAD					
Verbal fluency	10.9 (4.9)	15.7 (5.6)	23.3 (1.7)	31.33	.001
Boston naming test	11.4 (3.7)	14.0 (1.1)	14.9 (0.3)	11.15	.001
Word list learning	10.6 (3.0)	16.3 (3.4)	24.2 (2.1)	87.82	.001
Constructional praxis	8.4 (1.9)	9.9 (1.2)	10.8 (0.6)	12.36	.001
World list delayed recall	1.9 (1.6)	4.0 (2.6)	9.1 (1.2)	56.10	.001
World list recognition	7.7 (1.7)	8.0 (1.6)	9.9 (0.3)	9.07	.001

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls; group comparisons: analysis of variance for all measures except gender (Kruskal-Wallis test); CERAD, Consortium to Establish a Registry for Alzheimer's Disease.