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Modifications in resting state functional anticorrelation between Default Mode Network and Dorsal Attention Network: comparison among young adults, healthy elders and Mild Cognitive Impairment patients

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Abstract

Resting state brain activity incorporates different components, including the Default Mode Network and the Dorsal Attention Network, also known as task-negative network and task-positive network respectively. These two networks typically show an anticorrelated activity during both spontaneous oscillations and task execution. However modifications of this anticorrelated activity pattern with age and pathology are still unclear. The present study aimed to investigate differences in resting state Default Mode Network-Dorsal Attention Network functional anticorrelation among young adults, healthy elders and Mild Cognitive Impairment patients.

We retrospectively enrolled in this study 27 healthy young adults (age range: 25–35 y.o.; mean age: 28,5), 26 healthy elders (age range: 61–72 y.o.; mean age: 65,1) and 17 MCI patients (age range 64–87 y.o.; mean age: 73,6). Mild Cognitive Impairment patients were selected following Petersen criteria. All participants underwent neuropsychological evaluation and resting state functional Magnetic Resonance Imaging.

Spontaneous anticorrelated activity between Default Mode Network and Dorsal Attention Network was observed in each group. This anticorrelation was significantly decreased with age in most Default Mode Network-Dorsal Attention Network connections ($p<0.001$, False Discovery Rate corrected). Moreover, the anticorrelation between the posterior cingulate cortex node of the Default Mode Network and the right inferior parietal sulcus node of the Dorsal Attention Network was significantly decreased when comparing Mild Cognitive Impairment with normal elders ($p<0.001$, False Discovery Rate corrected). The functional connectivity changes in patients were not related to significant differences in grey matter content.

Our results suggest that a reduced anticorrelated activity between Default Mode Network and Dorsal Attention Network is part of the normal aging process and that Mild Cognitive Impairment status is associated with more evident inter-networks functional connectivity changes.

Keywords: Aging; Default Mode Network; Dorsal Attention Network; Mild Cognitive Impairment; Resting State Functional Anticorrelations.

1. Introduction

During the last decades the remarkable improvements in life expectancy have considerably changed the demographic structure of the modern society, increasing the number of older adults, patients with initial cognitive decline (Mild Cognitive Impairment, MCI), patients with Alzheimer Dementia (AD) and other types of dementia (Reitz et al. 2011). Many studies have investigated the neuropathological bases of AD but less attention has been paid to understand brain changes that occur during lifespan, starting from youthfulness, passing through physiological aging and ending with pathological conditions, such as MCI and AD (Price et al. 2009; Braak et al. 2011; Wang et al. 2012). The neuro-biological bases of physiological brain aging is still unclear and its understanding could shed light on age-related neurodegenerative diseases.

Advanced neuroimaging techniques, in association with neuropsychological evaluation, may provide a fundamental tool for differentiating between brain changes due to physiological aging and abnormal changes possibly underlying neurodegenerative pathologies such as AD. In particular, functional MRI (fMRI) has been extensively used to detect changes in brain function due to physiological aging (Brier et al. 2013; Ferreira and Busatto, 2013; Gröschel et al. 2013) and functional changes possibly related to pre-symptomatic clinical stages (Fleisher et al. 2009; Greene and Killiany, 2010; Esposito et al. 2013). FMRI can be performed during the execution of an experimental paradigm involving specific tasks, or to study spontaneous oscillations of brain activity while the subject is at rest (resting-state fMRI, rs-fMRI; Raichle et al. 2001; Damoiseaux et al. 2006; Buckner 2008). Since it does not require any task, rs-fMRI is particularly attractive for protocols on patients, children and elders, increasing participant's compliance and reducing intersubject variability due to task performance. Indeed, in recent years a growing number of studies showed that rs-fMRI may provide a sensitive and valuable tool for the study of normal and pathological aging (Li et al. 2014; Gardini et al. 2014; Vecchio et al. 2015). More specifically, rs-fMRI studies revealed that the brain is organized into specialized networks constituted by regions that show a coherent fluctuation of spontaneous activity (Deco et al. 2011; Hansen et al. 2014).

To date several resting state networks (RSNs) have been identified, such as the Default Mode Network (DMN), the Salience Network (SN); the Fronto Parietal Control (FPC) network, the primary Sensory Motor Network (SMN), the Exastrastriate Visual System (ESV), and the Dorsal Attention Network (DAN) (Van den Heuvel et al. 2009; Van den Heuvel and Hulshoff Pol, 2010; Liang et al. 2015).

The DMN has been the most studied network and consists of the following main regions: Medial Frontal Gyrus (MedFG), Posterior Cingulate Cortex (PCC), bilateral Angular Gyrus (AG) and the Hippocampus (Hp). The DMN is also referred to as the task-negative network because these regions are typically deactivated during execution of attention demanding tasks (Mevel et al. 2013; Passow et al. 2015).

The DAN has received much attention as well, and includes the following main regions: Inferior Parietal Sulcus (IPS); Frontal Eye Field (FEF); Anterior Cingulate Cortex (ACC) and bilateral Middle Temporal Gyrus (MidTempG). The DAN is also referred to as the task-positive network because its main regions are commonly activated in tasks demanding attention and mental control (Corbetta and Shulman, 2002; Fox et al. 2005).

Interestingly, the DMN and the DAN showed a pattern of anticorrelated activity in both task and resting state studies. This behaviour suggested that the brain is intrinsically organized into anticorrelated networks (Fransson 2005).

The strong anticorrelated and competitive relationship between DAN and DMN during resting state impacts on behaviour and cognitive functions (Uddin et al. 2009; Gopinath et al. 2015) and may represent a cerebral mechanism that switches the focus between internal channels (supported by DMN) and external, attention demanding events (supported by DAN; Kelly et al. 2008).

Studies conducted on children during the first years of life have shown that a negative correlation between DMN and DAN is not present at birth, but appears during the first year and strengthens during the second year of life (Wang et al. 2012; Gao et al. 2013; Barber et al. 2013).

In adults, resting state anticorrelations between DMN and DAN are more robust and these intrinsic anticorrelations support the development of executive functions and working memory from childhood to adulthood (Andrews-Hanna et al. 2007; Chai et al. 2014; Keller et al. 2015). Furthermore, decreased coactivations within DMN and anticorrelations between DMN and DAN, were observed in a recent study comparing healthy elders and young subjects (Wu et al. 2011). The authors hypothesize that the reduced anticorrelations may be considered a neuronal substrates of aging brain supporting cognitive decline.

In this study we examined developmental changes in resting state anticorrelation between DMN and DAN, testing the hypothesis that functional anticorrelation between these two systems decrease with age and is further impaired in MCI patients.

2. Materials and Methods

2.1 Study population

All procedures were conducted following Helsinki Declaration principles and the study was approved by the Institutional and Ethics Committee of the University "G. d'Annunzio" of Chieti-Pescara (clinical trial registration number: 1711). All participants gave written informed consent to join the study. We retrospectively enrolled in this study 27 healthy young adults (age range: 25–35 y.o.; mean age: 28,5), 26 healthy elders (age range: 61–72 y.o.; mean age: 65,1) and 17 MCI patients (age range 64–87 y.o.; mean age: 73,6; Table 1). All participants had comparable levels of education (8–10 years) and were neurologically examined to exclude visual and motor impairments, major medical conditions, psychiatric or neurological disorders and consumption of psychotropic drugs.

2.2 Neuropsychological assessment

MCI status was assigned according with Petersen criteria (Petersen and Negash, 2008). Cognitive status of elders and MCI patients was evaluated using the following neuropsychological

tests: Mini Mental State Examination (MMSE) to evaluate the global cognitive status (26-30: normal; 25-23: MCI; <22: cognitive impairment); prose memory test (Babcock story) to evaluate prose memory (cut-off : 10,4; immediate recall: 5,33; delayed recall: 5,07) and the Frontal Assessment Battery (FAB) to screen for global executive functions (14-18: normal; <13: cognitive impairment; Table 1). Young group was evaluated by means of Millon Test and Trail Making Test (Table 1).

2.3 Resting State fMRI acquisition

Functional and structural fMRI imaging was performed with a Philips Achieva 3T Scanner (Philips Medical Systems, Best, The Netherlands) using a whole-body radiofrequency coil for signal excitation and an eight-channel head coil for signal reception. Subjects and patients were asked to relax while fixating a white dot in the centre of a grey-background screen, projected via an LCD projector and viewed via a mirror placed above the subject's head. Foam padding was employed to minimize involuntary head movement. Resting state fMRI data were collected in four runs lasting four minutes each. The small pauses between runs were used to check that patients and subjects didn't fall asleep. Blood Oxygen Level Dependent data were acquired by means of T2*-weighted echo planar imaging (EPI) sequences with the following parameters: TE 35 ms, matrix size 64x64, FOV 256 mm, in-plane voxel size 4x4 mm, Sensitivity Encoding (SENSE) factor 1.8 anterior-posterior, flip angle 75°, slice thickness 4mm and no gap. Functional volumes consisted of 30 trans-axial slices, acquired with a volume TR of 1700 ms (145 volumes per run). A high resolution structural volume was acquired at the end of the session via a 3D fast field echo T1-weighted sequence (sagittal, matrix 256 x 256, FOV 256 mm, slice thickness 1 mm, no gap, in-plane voxel size 1 mm x 1 mm, flip angle 12°, TR 9.7 ms and TE 4 ms).

3. Statistical Analysis

3.1 Analysis on demographic variables and neuropsychological scores

A one-way ANOVA was performed on Young, Elderly and MCI subjects for the dependent variable Age, revealing significant differences across the three groups ($F(2,67)=790,28$; $p<0,001$). The Duncan's post-hoc test revealed significant differences for between-groups comparisons ($p<0,0001$). In a similar ANOVA, the education level measured in years revealed no significant differences across groups ($F(2,67) =2,29$; $p=0,11$). To assess between groups differences for the dichotomous variable Sex, a series of χ^2 tests with Yates correction were performed. No significant differences were observed between Elderly and MCI ($\chi^2 =0,7$; $p<0,99$ Yates corrected), between Elderly and Young ($\chi^2 =0,49$; $p<0,68$ Yates corrected), and between MCI and Young ($\chi^2 =0,86$; $p<0,53$ Yates corrected). To assess between-group differences of neuropsychological scores, a one way MANOVA was performed, considering the group of participants (MCI vs Elderly) as the independent variable and neuropsychological scores (Immediate Recall (IR), Delayed Recall (DR), MMSE, FAB) as dependent variables. A significant between group overall difference was observed in this MANOVA (λ $(4,34)=0,22$; $F(4,33)=29,23$, $p<0,0001$). The Levene's test showed non-homogeneous variances for IR and DR ($p<0,001$ and $p<0,0001$ respectively). Thus, a Mann Whitney's non parametric Test was preferred to assess significant differences for IR ($U=61,5$, $p<0,001$) and DR ($U=95$, $p<0,05$). For MMSE and FAB scores, a one-way MANOVA was calculated (λ =,28255, $F(2, 38)=48,244$, p=,00000). The univariate test showed significant results for MMSE ($p<0,001$) and FAB ($p<0,001$). Finally, a one way MANCOVA was performed to assess the effect of age on the testing results, showing no significant effect for the age as covariate (λ $=0,98$; $F(4,33)=0,14$; $P=0,98$).

3.2 fMRI data preprocessing

Resting state fMRI data were analysed using AFNI (http://afni.nimh.nih.gov/afni). The first 4 volumes of each functional run were discarded to allow T1 equilibration of the MR signal. Initial pre-processing included despiking, slice scan time correction and motion correction. Motion

correction was performed using a rigid body registration of EPI images to a reference image represented by the fifth volume of the first run. The root mean square (RMS) of the six realignment parameters (three translations and three rotations) was considered, in order to inspect for runs affected by excessive movement. One run for one young subjects, one run for two elders and one run for one MCI patient exceeded a root mean square (RMS) movement of 1.5 mm and were discarded from further analysis. Furthermore, the root mean square values of the differentiated BOLD timeseries (DVARS) (Power et al., 2012) were derived as a summary statistics of motion, compared across groups and used as covariates in a control analysis to rule out potential effects of movement on the connectivity results.

Additional pre-processing was performed removing from the EPI time series the six motion regressors and two nuisance regressors obtained extracting the EPI average time course within the cerebrospinal fluid (CSF) and white matter (WM) masks. These masks were obtained from the structural scans segmentation using AFNI's "3dSeg". Note that the debated global signal regression was not performed in this study. Although this pre-processing step has been often used in resting state functional connectivity analysis (Weissenbacher et al. 2009), recent evidence showed that it biases inter-voxel, creating artificial anti-correlations (Murphy et al. 2009; Chai et al. 2012).

To prepare the data for functional connectivity analysis, spatial normalization into the Talairach space, spatial smoothing with an isotropic gaussian kernel (full width at half maximum = 6 mm), scaling to a common mean and temporal band-pass filtering ($0.01 < f < 0.1$ Hz) were performed. Finally, the four runs of each subject were concatenated resulting in voxel time courses with 564 time points (423 for the few subjects that contributed with three runs). The realignment to a common reference image and the scaling to a common mean performed in the previous preprocessing steps prevented discontinuities in the concatenated timeseries.

3.3 Functional connectivity analysis

First, a seed-based resting state connectivity map was created for each subject calculating

the Pearson correlation coefficient (r-value) between the PCC time series and the time series at each voxel. The PCC time series was derived averaging the time courses of voxels inside a sphere with 6 mm radius (Table 2). Individual correlation maps were converted using the z-Fisher transformation (z=atanh (r), where r is the correlation coefficient) to approach a normal distribution before calculating the random effect group analysis. A one-sample t-test was performed on the z-Fisher maps to obtain group statistical functional connectivity maps, separately for Young, Elderly and MCI patients. These group statistical maps were thresholded at $p<0.05$ corrected for multiple comparisons using False Discovery Rate (FDR). A number of spherical nodes (6 mm of radius) for DMN and DAN were defined using independent coordinates from the literature (Greicius et al. 2003; Fox et al. 2005; De Luca et al. 2006; Dosenbach et al. 2007; see Table 2) in order to avoid circularity problems in the analysis (Kriegeskorte et al. 2009). Then, connectivity matrices were obtained considering the defined set of nodes by calculating the Pearson r-value between the time series of each node pair. After r to z-Fisher transformation, the matrices were compared across groups in order to reveal significant differences in connectivity strength (the significance threshold was set at $p<0.05$, corrected for multiple comparisons using FDR). The connectivity matrices approach allowed a more thorough investigation of connectivity changes with respect to voxel-wise contrasts of connectivity maps that are necessarily limited to connections with the seed (the PCC).

3.4 Voxel Based Morphometry

Between groups differences in grey matter (GM) volume in the considered set of nodes were investigated using an optimised Voxel Based Morphometry (VBM) protocol as implemented in FSL (Good et al. 2001; Smith et al. 2004; Douaud et al. 2007; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). First, structural images were segmented and the extracted GM portion was registered to MNI-152 standard space using non-linear registration. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template. Second, all native GM images were subsequently non-linearly registered to

this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, to reveal significant between groups differences, a general linear model was applied using permutation-based non-parametric testing, correcting for multiple comparisons across the considered spatial mask. The average GM value in each node was also extracted to be used in the following analysis. In addition, whole brain GM maps were obtained and compared across groups.

3.5 Analysis of covariance of imaging data and neuropsychological scores

To assess the effect of cognitive impairment on the functional connectivity and VBM data, two separate Multivariate Analysis of Covariance (MANCOVAs) were carried out considering the group as the independent variable, the imaging data as dependent variables and the MMSE score as a continuous predictor. Furthermore, to assess the effect of GM content on the functional connectivity data, a MANCOVA was carried out considering the group as the independent variable, the connectivity value as the dependent variable and the GM values in the relevant nodes as a continuous predictor. To assess the normality of distribution of the dependent variable and the continuous predictors the Kolmogorov-Smirnoff's test was carried out, whereas Levene's test was performed to assess the homogeneity of variances. To assess the effect of continuous predictors on each dependent variable a series of one-way ANCOVAs of follow up was carried out. Finally, to assess the effect of performance in the immediate and delayed recall tests on the observed functional connectivity differences, a one-way MANCOVA was performed taking into account the functional connectivity results as the dependent variable, the group (MCI vs Elderly) as the independent variable and the DR and IR scores as covariates.

4. Results

4.1 Functional connectivity analysis

For each group a positive correlation with the PCC time course was observed in the AG, MedFG and Hp regions, according to the well known topography of DMN (Figure 1).

Furthermore, for each group, a negative correlation with the PCC time course was observed in the IPS, FEF, ACC and MidTempG. These regions overlap with well known DAN nodes, according to previously reported patterns of anti-correlated activity between DMN and DAN (Figure 1). This anticorrelation was reduced in elderly and MCI patients with respect to young. Specifically, when investigating the connectivity pattern between the considered nodes, the comparison of connectivity matrices between groups revealed a significant reduction of anticorrelation in elderly with respect to young for the following connections: right AG-left FEF and right AG-left IPS ($p<0.001$, FDR corrected; Figure 2,3). Anticorrelation was significantly decreased in MCI patients with respect to young in the following connections: right AG-right IPS, right AG-left IPS, left AG-left IPS, left AG-right IPS, PCC-right IPS, PCC-left IPS PCC-dorsal ACC (dACC) and MedFG-left IPS ($p<0.001$, FDR corrected; Figure 2,3). Moreover a significant reduction of DMN-DAN anticorrelation was observed between PCC-right IPS when comparing healthy elderly with MCI ($p<0.001$, FDR corrected; Figure 2,3). The analysis of motion parameters revealed no significant differences in DVARS values across groups (Elderly vs MCI: $p=0.87$, Elderly vs Young: $p=0.09$, MCI vs Young: $p = 0.44$; unpaired t-tests). Furthermore, the connectivity comparisons across groups were re-run using DVARS values as covariates. In this control analysis the connection left IPS – PCC showed an increased but still significant p-value ($p<0.03$, FDR corrected) when comparing MCI patients with young subjects, while all the other results remained highly significant ($p<0.001$, FDR corrected).

The VBM analysis within the considered nodes revealed a significant reduction of GM volume in elderly and MCI compared to young adults ($p<0.05$, corrected for multiple comparisons using Threshold-Free Cluster Enhancement). No significant differences in GM content were observed in our set of nodes when comparing MCI patients with healthy elders. Whole-brain VBM

analysis also showed widespread significant GM reduction in elderly and MCI compared to young adults, whereas no significant differences were observed when comparing MCI with elderly (Figure 4). At a more liberal threshold ($p<0.05$ uncorrected), a reduced GM was observed in MCI with respect to healthy elders in bilateral hippocampus, precuneus and anterior cingulate (Figure 5).

No significant effect of the MMSE (λ =0.94; F(9,58)=0.43; p=0.912) and VBM (λ values between 0.94-0.78; F(9,46) values between 0.23-1.39; p values between 0.98-0,22) continuous predictors on the functional connectivity results was observed. Furthermore no significant effect of MMSE on the VBM results was observed (λ =0.80; F(13,54)=1.005; p=0.459). Finally, no significant effect of the DR (λ =0.82; F(7,33)=1.07; p=0.40) and IR (λ =0.87; F(7,33)=0.65; p=0.70) predictors on the functional connectivity results was observed.

5. Discussion

The aim of this study was to explore and compare the patterns of resting state functional anticorrelation between DMN and DAN among the three following groups: young adults, healthy elders and MCI patients. The functional anticorrelation between the two networks was significantly reduced in elders and in MCI patients with respect to young adults. When comparing elders with respect to young, a significant reduction of functional anticorrelation in the right AG-left FEF and right AG-left IPS connections was observed; DMN-DAN anticorrelation was also significantly decreased in MCI group with respect to young for the right AG-right IPS, right AG-left IPS, left AG-left IPS, left AG-right IPS, PCC-right IPS, PCC-left IPS PCC-dorsal ACC and MedFG-left IPS connections. Finally, a significant reduction of DMN-DAN anticorrelation was observed for the PCC-right IPS connection when comparing healthy elders with MCI.

A significant reduction of GM was also observed in the considered nodes of DAN and DMN when comparing elders and MCI patients with young subjects, whereas no significant GM changes were observed in DMN and DAN nodes when comparing elders with MCI group.

Furthermore, no statistically significant correlation was observed between functional connectivity values and GM levels and when comparing neuroimaging data with MMSE, DR and IR. DMN is also referred to as the task negative network because it shows consistently higher activation during rest condition than during cognitive tasks (Kottlow et al. 2015; Lin et al. 2015). In the current interpretation of brain networks, it is considered to be involved in monitoring internal and external environment, supporting memory and self-related functions (Spreng et al. 2009; Deco et al. 2011; Fox et al. 2015). In contrast, the DAN is also referred to the task positive network because it increases its activity during attention-demanding tasks, featuring a typical pattern of anticorrelated activity with DMN (Lei et al. 2014; Vossel et al. 2014; Alnæs et al. 2015). This functional anticorrelation has been repeatedly observed not only during attentional/cognitive paradigms, but also in spontaneous fluctuations of brain activity during resting state. The pattern of anticorrelated activity between DMN and DAN indicates that these networks are temporally modulated in opposite directions (Fox et al. 2006), supporting at the same time complex functions, for example redirecting attention from internal to external-oriented events (DAN; Chai et al. 2014).

Several studies tried to relate within-network connectivity changes to aging or pathology, mostly considering the DMN (Ouchi and Kikuchi, 2012). For example, a reduced DMN connectivity was observed with normal aging and in pre-clinical stages of dementia (Song et al. 2014). Modifications of DMN have also been related to impairment of executive functions and working memory capacity in normal elders and MCI (Ouchi et al. 2012). In particular, age-related reduction of functional connectivity between anterior and posterior DMN components, e.g. between Medial Prefrontal Cortex (MPFC) and PCC, correlated with cognitive impairment (Vidal-Piñeiro et al. 2014). While the posterior nodes of the DMN (PCC/Precuneus) seem to be associated with episodic memory retrieval (Lou et al. 2004; Ferreira and Busatto, 2013), the anterior nodes seem to support self referential mental processes (Gilbert et al. 2006) and perception and judgment of other people (Mitchell et al. 2006). However these results remain still controversial, with other studies

showing age-related increase of functional connectivity within fronto-parietal cortical regions of DMN (Filippini et al. 2012; Mowinckel et al. 2012).

In this regard, functional anticorrelation between brain regions or networks could be a more sensitive and robust marker of functional impairment than within-network functional correlation. Indeed, it has been pointed out that functional anticorrelation between networks is an important aspect of intrinsic brain functional organization and its impairment may negatively impact on cognitive functions during aging, possibly explaining attentional lapses and working memory deficits (Kelly et al. 2008; Wu et al. 2011).

In our study a significant decrease of functional anticorrelation between the right AG, and the left FEF and IPS nodes of the DAN was observed when comparing elders with young subjects.

The AG within the Supramarginal Gyrus (SG) and IPS constitutes the so called Inferior Parietal Cortex (IPC), whose dysfunction has been reported in MCI and AD patients (Liang et al. 2012) and may predict the conversion to dementia (Schroeter et al. 2009). AG is a key parietal posterior node within the DMN, supporting language and semantic processing, as well as spatial attention and memory functions (Trelle 2014) and the reduction of its activity in MCI patients has been related to the impairment of memory functions (Wendelken 2015).

Within DAN, both IPS and FEF contain areas with retinotopically organized maps of contralateral space (Silver and Kastner, 2009), supporting visual working memory (Jerde et al. 2012) and spatial orienting of attention (Vossel et al. 2014). Moreover, left FEF is strongly activated during attentional tasks with strong connections with the visual cortex in both humans and monkeys (Corbetta and Shulman, 2002) and its involvement with attention control was also demonstrated in Transcranial Magnetic Stimulation-EEG studies (Sauseng et al. 2011). A significant functional disconnection between IPS and DAN frontal regions was also observed in MCI and related to attention deficits (Liang et al. 2011).

The failure of anticorrelation between right AG and left FEF and IPS in elders with respect to young adults, may explain the concurrent memory disorder and attention deficit in the former.

As suggested by Fransson and colleagues (2006), the pattern of anticorrelated activity may represent a "division of labour" between networks supporting opposite functions such as attention and memory. While a certain reduction of functional anticorrelation between the two systems could characterize physiological aging, we hypothesize that when this reduction reaches a significant level overcoming possible compensatory mechanisms, it may negatively affect cognitive functions.

In our study comparing MCI with young subjects, we observed a significant reduction of functional anticorrelation between PCC, bilateral AG, MedFG nodes of the DMN and bilateral IPS and dACC, nodes of the DAN. Moreover a significant reduction of anticorrelation between PCC and right IPS was observed in MCI compared with healthy elders. PCC is part of the posteromedial cortex of DMN and is known to support internally directed cognition, autobiographical memory and future planning (Leech and Sharp, 2014) but also attention, regulating the internal and external focus of thoughts. It has strong functional and anatomical connections with other brain regions, such as the medial temporal lobes, ventro medial PFC (vmPFC) and ACC (Greicius et al. 2009). The PCC is a key area involved in aging processes and AD, showing amyloid deposition and reduction of metabolism, especially in APOE E4 patients (Filippini et al. 2009). This area seems to be involved in several other diseases as well (Buckner and Krienen, 2013; Crone at al. 2015). The impairment of PCC functioning may be an early biomarker of AD showing a failure of deactivation during task performance (Sambataro et al. 2010; Ishibashi et al. 2015) or a reduction of functional connectivity during resting state (Weiler et al. 2014).

The dACC is a critical region involved in attention regulation and cognitive control processes (Niendam et al. 2012; Petersen and Posner, 2012; Clarke and Johnstone, 2013). This area is involved in two different subsystems: a dorsal fronto-parietal system that mediates the top-down attentional regulation, and a ventral system involved in detecting unattended or unexpected stimuli and in attentional shift (Bae et al. 2006; Alexopoulos et al. 2012).

Several neuroimaging studies identified changes of functional connectivity within resting state networks in MCI condition. In a recent work, Liang and colleagues (2014), investigated the

patterns of functional connectivity within different resting state networks in a population of amnesic MCI patients, showing a significant modification of functional connectivity that correlated with disease severity as measured by neuropsychological examinations. The authors found increased anterior-posterior connectivity within DMN, in line with previous resting state studies reporting increased PCC functional connectivity with the frontal regions of DMN (Qi et al. 2010) in amnestic MCI patients that may be interpreted as a failure of deactivation of DMN in this population during cognitive tasks (Celone et al. 2006; Petrella et al. 2007). They thus postulated that the increased anterior-posterior connectivity within DMN may compensate the decreased anterior-posterior connectivity within task positive networks (FPC and DAN) observed in amnestic MCI patients, suggesting that these patients tend to recruit more attention and executive control resources to support episodic memory processes.

Some studies suggest that elders may counteract cognitive impairment through a plastic cerebral mechanism of reorganization called "posterior-anterior shift in aging" (PASA), consisting in the progressive increase of brain prefrontal regions engagement (Davis et al. 2008; Fjell et al. 2014; McCarthy et al. 2014). This result seems to be in contrast with the frontal lobe theory of aging, which suggests that many of age-related changes in cognition are due to the vulnerability of frontal lobes to cerebral changes (neurochemical and structural) that occur with age (Dirnberger et al. 2010; Behrman-Lay et al. 2014). Recent studies also reported that the functional integrity of task positive networks and DMN may be strictly related, impacting on behavioural performance (Bonnelle et al. 2012; Wen et al. 2013).

In our study we focused the attention on the modifications of DMN-DAN anticorrelations rather than exploring within network functional connectivity changes. The most intriguing result is that DMN and DAN anticorrelation is reduced with age and further reduced in MCI patients

Interestingly, a significant decrease of functional anticorrelation between MedFG and left IPS was observed in our data when comparing MCI with young adults. Frontal cortex includes key brain areas that support memory processes (Qi et al. 2010). Modifications of its functioning was

also observed in several studies conducted on populations of MCI and AD patients, explained as a compensatory mechanism to counteract aging processes (Grady et al. 2003; Wang et al. 2006). For example, Bai and colleagues (2009) found an increased functional connectivity within frontal areas of the DMN in MCI patients interpreted as a compensatory mechanism for cognitive functions decline in other brain regions (Grady et al. 2003). We hypothesize that abnormalities observed between network connectivity during resting state may reflect cognitive impairment.

Regarding VBM results, it is well known that intracellular deposition of amyloid-beta protein occurs together with structural changes in AD patients but also in the preclinical stages of dementia (Savva et al. 2009). Brain atrophy characterizes normal aging, AD and MCI status, with a specific pattern, more pronounced in those patients with initial cognitive decline but with higher risk of conversion to dementia (Good et al. 2001; Chetelat et al. 2005; Risacher et al. 2009). These structural modifications particularly involve temporal brain regions such as Hp (Baron et al. 2001). Moreover many studies have reported that brain structural modifications observed in elders involve posterior DMN regions (Supekar et al. 2010; Segall et al. 2012) extending to prefrontal cerebral cortex (Li et al. 2013). Posterior midline atrophy is usually related to pathological aging and correlates with memory impairment (Buckner et al. 2009) even if it also characterizes elders with low risk to convert to AD (Fjell et al. 2009). In our data the GM reduction in MCI with respect to healthy elders did not reach statistical significance, probably because of the sample size or the high scores of MMSE of our patients. However, since the main focus of this work is on functional connectivity, our main concern was to rule out potential influences of increased atrophy on functional results.

In this regard, no significant correlation between functional connectivity and GM values was observed in our data, suggesting that the changes of anticorrelation between DMN and DAN areas are not the result of increased atrophy in the same regions. This is in line with other studies demonstrating that changes of functional connectivity remain significant after correction for GM volumes (Damoiseaux et al. 2008).

Some limitations should be acknowledged for this study. First a more accurate neuropsychological evaluation exploring different cognitive domains may help to explain neuroimaging results. In particular, we did not observe a statistically significant effect of the neuropsychological scores on the reduction of DAN-DMN anticorrelation in MCI compared with healthy elders. However, this negative result may depend on the partial availability of the immediate and delayed recall scores in our patients and on the overall sample size as well. Increasing the sample size and improving the neuropsychological evaluation in future studies would allow to better address the relationship between variation in anticorrelation and cognitive performance, enhancing the significance of the present results. Second, increasing the patient sample could also help to reveal more subtle structural differences.

Furthermore, it still remains unclear whether the observed decrease of functional anticorrelation may be a cerebral plastic reorganization to maintain cognitive functions (Wen et al. 2013) or instead a neural excitotoxicity representing an impending neuronal failure.

6. Conclusion

In conclusion, our results suggest that reduced resting state anticorrelations between DAN and DMN characterizes normal aging and is more pronounced in MCI patients. The variations in anticorrelations between the task positive and task negative networks may serve as an indicator of cognitive functioning and could be helpful in understanding cognition decline in aging. Future studies including a clinical and neuroimaging follow-up could add significant information, possibly allowing the identification of markers indexing the conversion of MCI to AD.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional and Ethics Committee of the University "G. d'Annunzio" of Chieti-Pescara (clinical trial registration number: 1711). All participants gave written informed consent to join the study.

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Captions to figures

Figure 1: Seed based connectivity maps (seed: PCC) obtained from the random effects group analyses showing the DMN and the anticorrelated DAN for the three groups. The statistical maps were thresholded at $p<0.05$ (corrected for multiple comparisons using FDR) and superimposed on a partially inflated Talairach template.

Figure 2: Between groups comparisons (t-tests) of connectivity matrices derived from the considered set of nodes. In the ring graphical form of connectivity matrices the colored lines represent the functional connection between two nodes and the lines colors represent the statistical significance of the connection. In our figure the lines colors represent the t-score of the between-

groups comparison of functional connectivity, with darker blue indicating a more significant reduction of anticorrelation between groups. The shown comparisons were all significant at $p<0.001$ (FDR corrected).

Figure 3: Anticorrelation values (group mean z-Fisher values +- standard errors) for the connections showing significant between group differences, as shown in Figure 2.

Figure 4: Results of the whole brain VBM analysis showing significant GM differences across groups ($p<0.05$, corrected for multiple comparisons using Threshold-Free Cluster Enhancement). Elderly and MCI, compared to young adults, showed significant GM reduction within frontal lobe (superior, middle and inferior gyri), pre-central and post-central cortex, cingulated cortex, precuneus, supramarginal gyrus, angular gyrus, superior parietal lobule, temporal lobe (superior, middle, inferior, lingual, fusiform gyri), hippocampus, thalamus, occipital lobe (calcarine cortex, cuneus), in both hemispheres.

Figure 5: At a more liberal threshold ($p<0.05$ uncorrected), a reduced GM was observed in MCI with respect to healthy elders in bilateral hippocampus, precuneus and anterior cingulate.

Table 1: Demographics and neuropsychological tests scores for healthy elderly, MCI patients and healthy young subjects. Neuropsychological scores are corrected for age and years of education. Some patients did not complete the tests due to their clinical conditions

Table 2: Talairach coordinates of the spherical nodes defined for DMN and DAN.

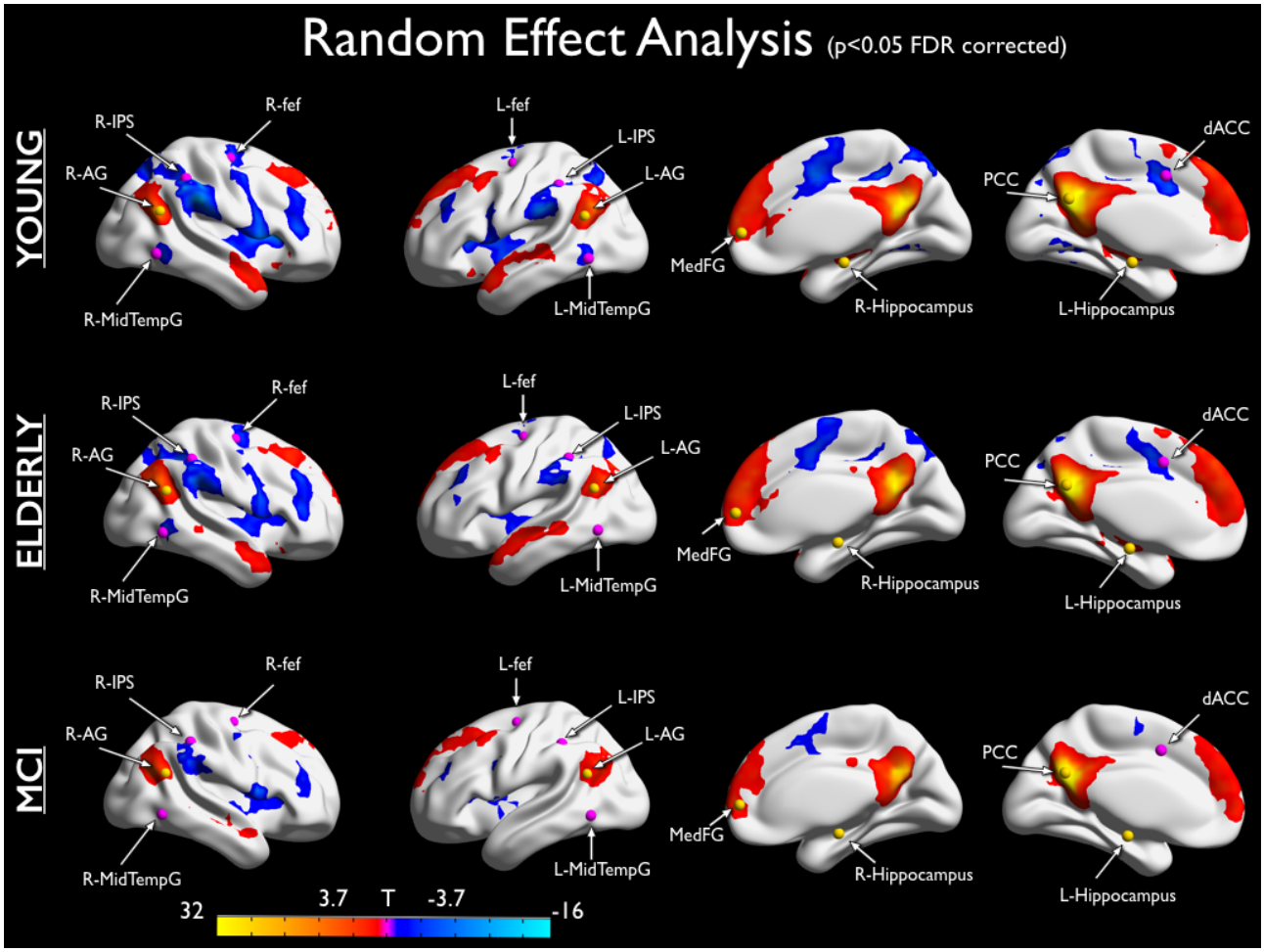
Random Effect Analysis (p<0.05 FDR corrected)
YOUNG
ELDERLY
MCI
R-IPS
R-fef
R-AG
R-MidTempG
L-fef
L-IPS
L-AG
L-MidTempG
MedFG
R-Hippocampus
dACC
PCC
L-Hippocampus
32
3.7
T
-3.7
-16

Fig. 1

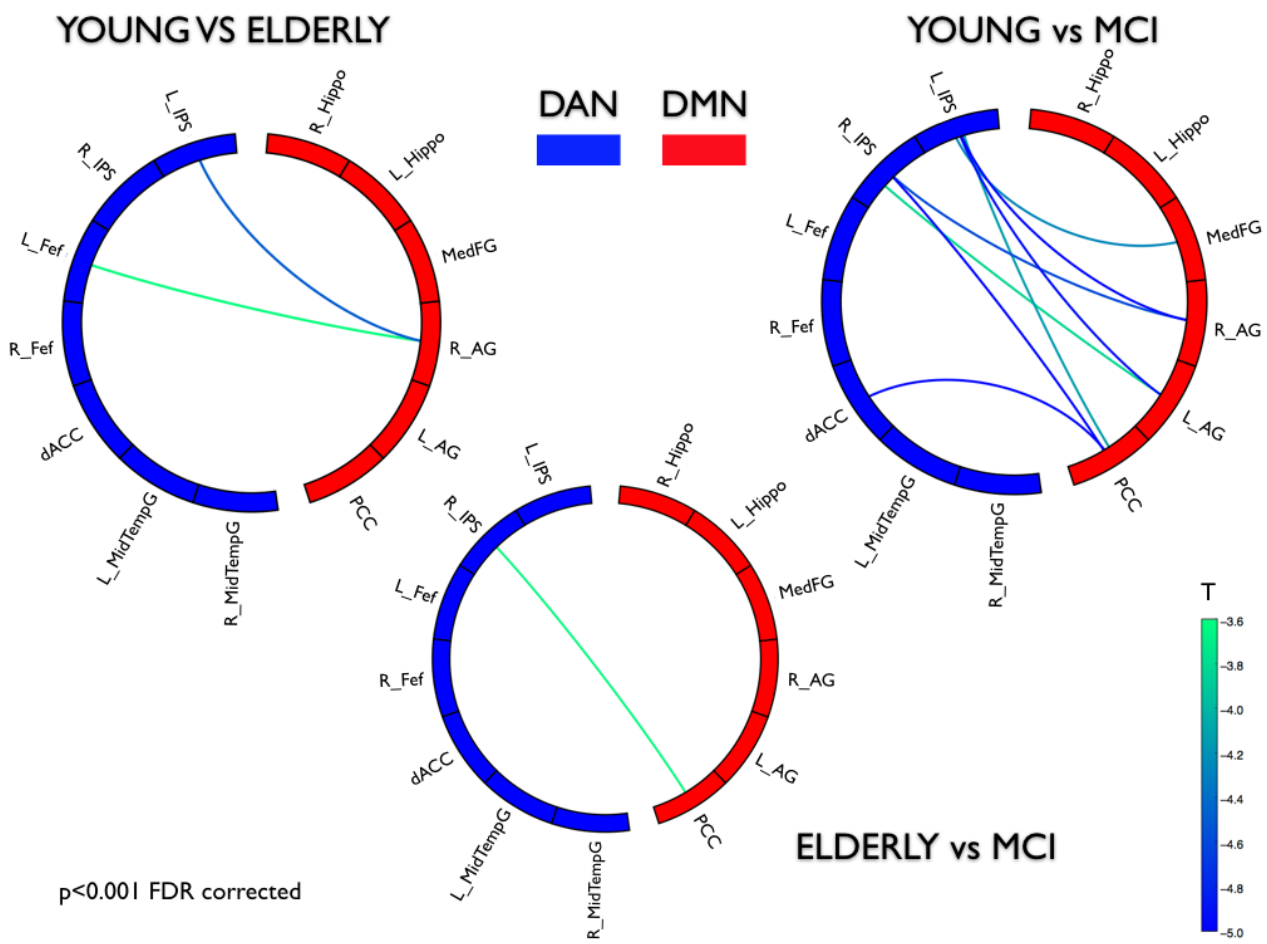
YOUNG VS ELDERLY
DAN
DMN
L_IPS
R_Hippo
R_IPS
L_Hippo
L_Fef
MedFG
R_Fef
R_AG
dACC
L_AG
L_MidTempG
PCC
R_MidTempG
YOUNG vs MCI
L_IPS
R_Hippo
R_IPS
L_Hippo
L_Fef
MedFG
R_Fef
R_AG
dACC
L_AG
L_MidTempG
PCC
R_MidTempG
T
-3.6
-3.8
-4.0
-4.2
-4.4
-4.6
-4.8
-5.0
L_IPS
R_Hippo
R_IPS
L_Hippo
L_Fef
MedFG
R_Fef
R_AG
dACC
L_AG
L_MidTempG
PCC
R_MidTempG
ELDERLY vs MCI
p<0.001 FDR corrected

Fig. 2

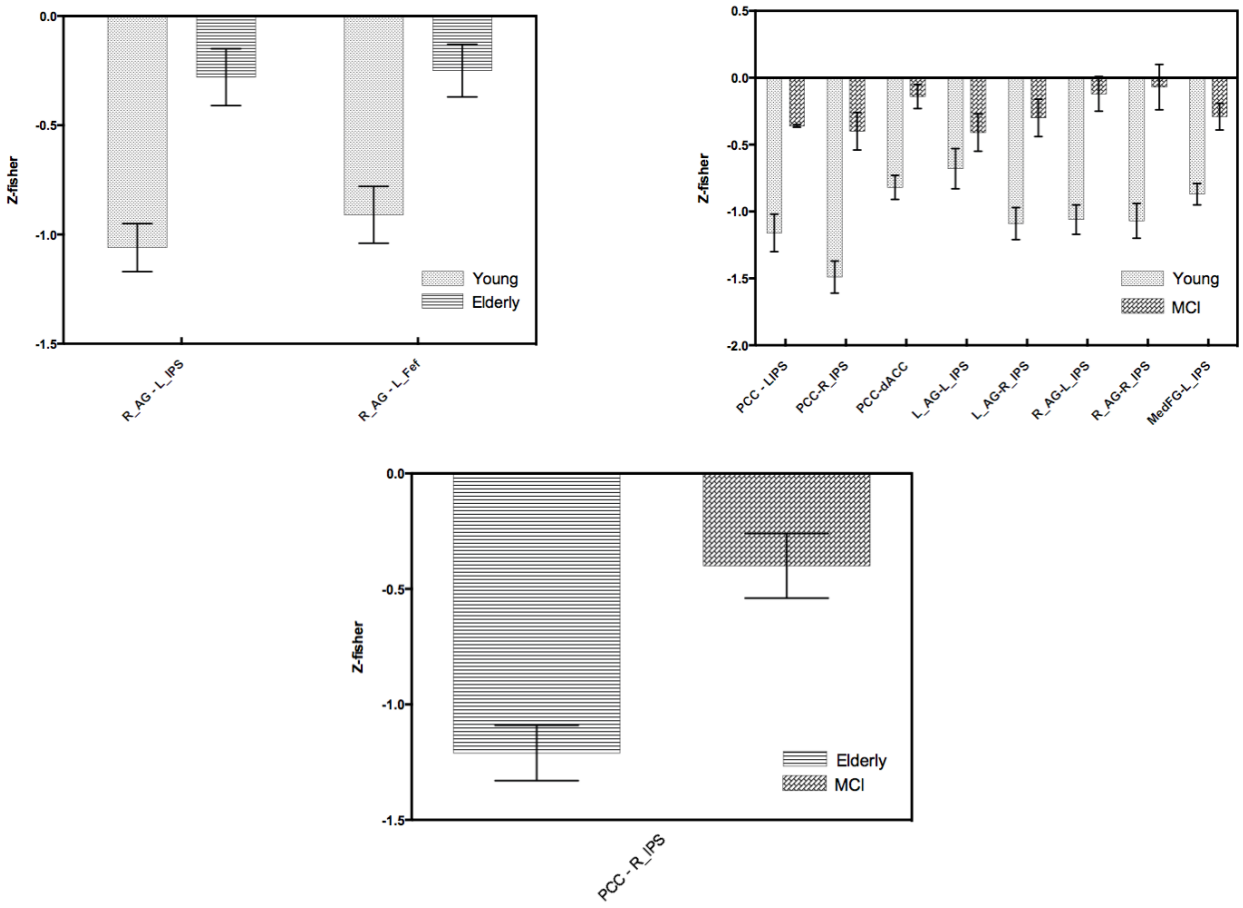
Z-fisher
0.0
-0.5
-1.0
-1.5
Young
Elderly
R_AG - L_IPS
R_AG - L_Fef
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Young
MCI
PCC - LIPS
PCC-R_IPS
PCC-dACC
L_AG-L_IPS
L_AG-R_IPS
R_AG-L_IPS
R_AG-R_IPS
MedFG-L_IPS
Z-fisher
0.0
-0.5
-1.0
-1.5
Elderly
MCI
PCC - R_IPS

Fig. 3

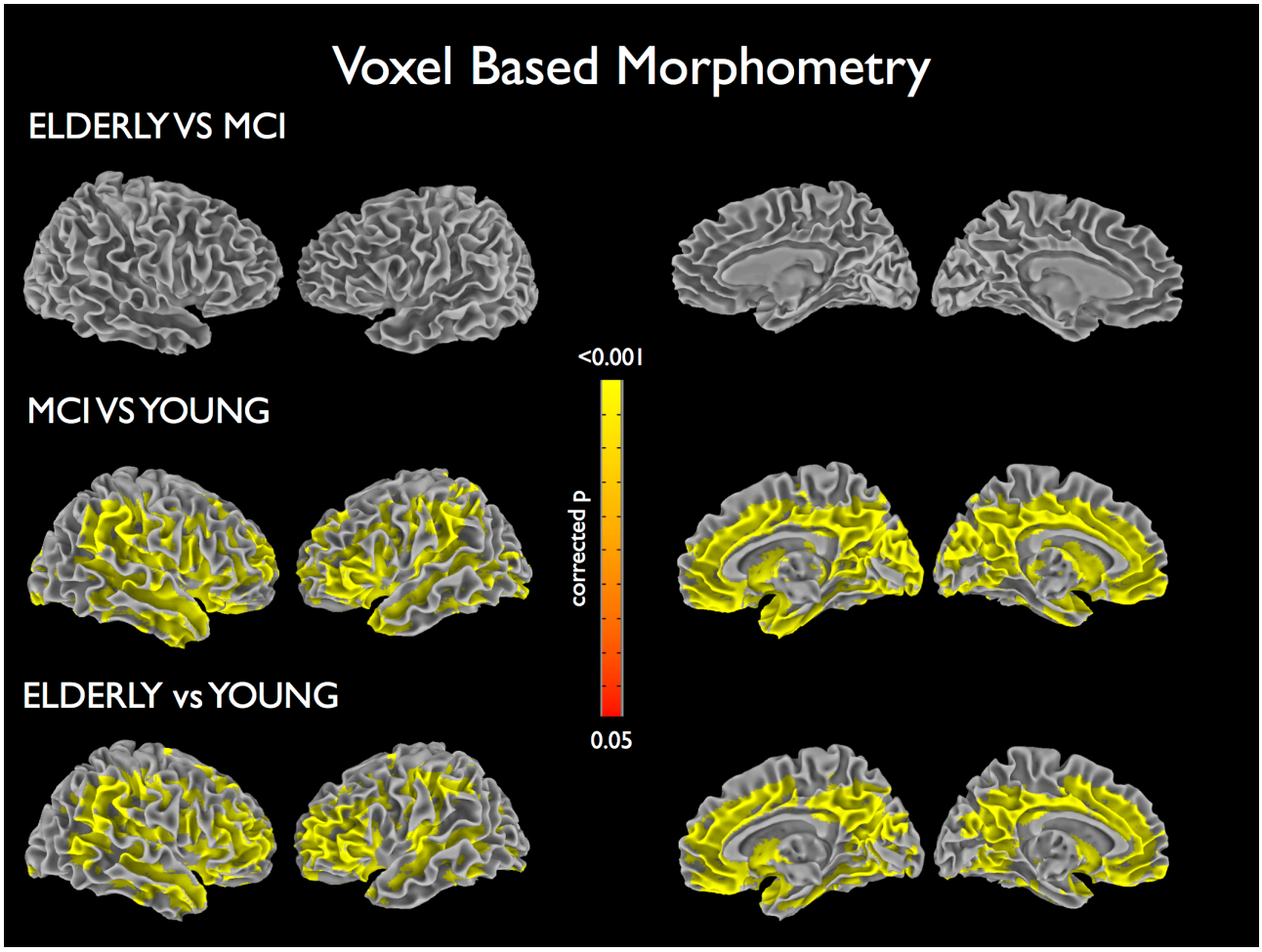
Voxel Based Morphometry
ELDERLY VS MCI
MCI VS YOUNG
ELDERLY vs YOUNG
<0.001
corrected p
0.05

Fig. 4

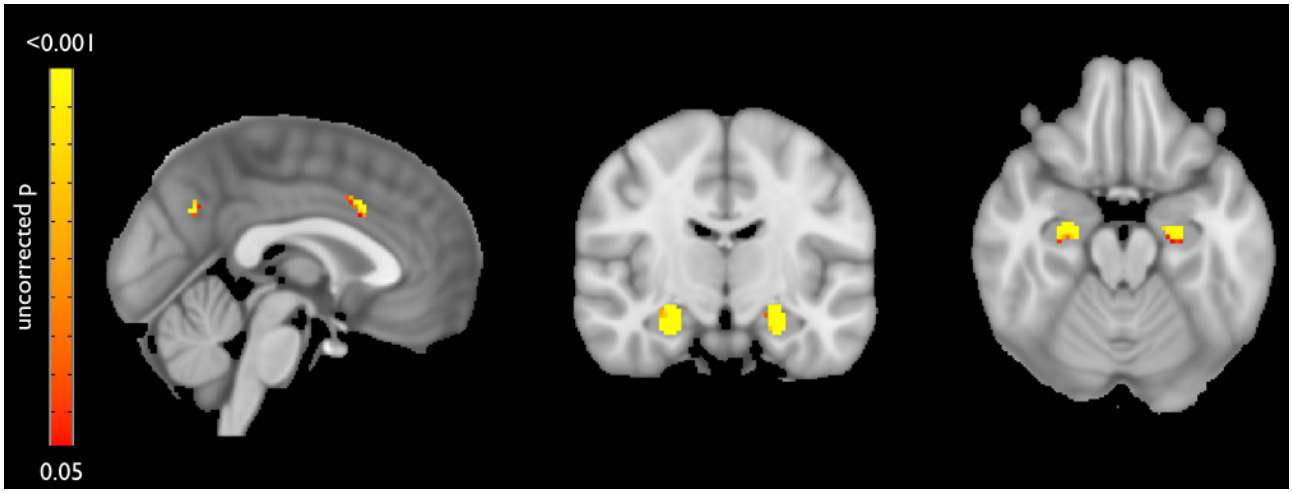
<0.001
uncorrected p
0.05

Fig. 5