Posterior Compensatory Network in Cognitively Intact Elders With Hippocampal Atrophy

Michael J. Valenzuela,[1,2†*] Andrew J.F. Turner,[1] Nicole A. Kochan,[3,4] Wei Wen,[3,4] Chao Suo,[1,5] Harry Hallock,[1] Randy A. McIntosh,[6] Perminder Sachdev,[3,4] and Michael Breakspear[3,7,8,9]

ABSTRACT: **Functional compensation in late life is poorly understood but may be vital to understanding long-term cognitive trajectories. To study this we first established an empirically derived threshold to distinguish hippocampal atrophy in those with Mild Cognitive Impairment (MCI $n = 34$) from those with proficient cognition (PRO $n = 22$), using data from a population-based cohort. Next, to identify compensatory networks we compared cortical activity patterns during a graded spatial working memory (SWM) task in only cognitively proficient individuals, either with (PRO_{ATR}) or without hippocampal atrophy (PRO_{NIL}). Multivariate Partial Least Squares analyses revealed that these groups engaged spatially distinct SWM-related networks. In those with hippocampal atrophy and under conditions of basic-SWM demand, expression of a posterior compensatory network (PCN) comprised calcarine and posterior parietal cortex strongly correlated with superior SWM performance ($r = -0.96$). In these individuals, basic level SWM response times were faster and no less accurate than in those with no hippocampal atrophy. Cognitively proficient older individuals with hippocampal atrophy may, therefore, uniquely engage posterior brain areas when performing simple spatial working memory tasks.** © 2014 Wiley Periodicals, Inc.

KEY WORDS: **compensation; functional MRI; hippocampus; mild cognitive impairment; working memory**

INTRODUCTION

The brain like most organs manifests both functional redundancy and compensatory reserve (Tononi et al., 1999). More than 80% of putamal dopaminergic neurons are lost before Parkinsonian symptoms arise (Dauer and Przedborski, 2003), and there are well documented studies of substantive stroke (Das et al., 2008), tumor (Vernooij et al., 2007), and head injury (Grafman et al., 1988) that nonetheless remain clinically silent. In the context of neurodegeneration, several clinicopathological studies note that burden of Alzheimer's disease (AD) pathology is a poor predictor of neuropsychological deficits (Davis et al., 1999; Price and Morris, 1999; Knopman et al., 2003). For example, a population-based investigation found that 30% of those with moderate or severe AD at death were not demented at their final clinical interview (CFAS-MRC, 2001). Presumably, those older individuals with pathologically significant degenerative disease, but intact cognition, benefit from as yet poorly understood compensatory processes (Stern, 2002; Brayne et al., 2010).

Neuronal network reorganization is one possible mechanism by which compensation may occur in the aged brain (reviewed by Grady, 2012). Functional neuroimaging studies of memory in older individuals have suggested that bilateral prefrontal task-related activity, in contrast to left-sided unilateral activity normally observed in young adults, may be implicated (Reuter-Lorenz et al., 1999, 2000; Cabeza et al., 2002; Grady et al., 2003; Morcom et al., 2003; Cabeza et al., 2004). Alternatively, increased hippocampal activity in those at greater risk for dementia has also been interpreted as part of a compensatory process (Bookheimer et al., 2000; Dickerson et al., 2004; Quiroz et al., 2010). However, it is not clear whether these changes are adaptive or disease-related (Persson et al., 2006; Stevens et al., 2008; Putcha et al., 2011; Bakker et al., 2012), or even simply a physiological age-related process (Buckner, 2004).

Here, we report that older individuals with wholly intact cognition and hippocampal atrophy recruit very different brain networks to successfully mediate spatial working memory (SWM) compared to those with no such atrophy. Unexpectedly, at basic SWM load, those

[1] Regenerative Neuroscience Group, Brain & Mind Research Institute, University of Sydney, Sydney, Australia; [2] School of Medical Sciences, Sydney Medical School, University of Sydney, Sydney, Australia; [3] School of Psychiatry, University of New South Wales (UNSW), Sydney, Australia; [4] Centre for Healthy Brain Ageing, UNSW, Sydney, Australia; [5] Monash University, Melbourne, Australia; [6] Rotman Research Institute, Baycrest, University of Toronto, Toronto, Canada; [7] Division of Mental Health Research, Queensland Institute of Medical Research, Brisbane, Queensland, Australia; [8] The Black Dog Institute, Sydney, New South Wales, Australia; [9] The Royal Brisbane and Woman's Hospital, Brisbane, Queensland, Australia

[†]M.V. is a NHMRC Career Development Fellow (ID 1004156).

Additional Supporting Information may be found in the online version of this article.

Grant sponsor: National Health and Medical Research Council (NHMRC); Grant number: 568969; Grant sponsor: James S. McDonnell Foundation Grant; Grant number: JSMF22002082; Grant sponsor: Australian Rotary Health Research Grant.

*Correspondence to: Michael Valenzuela, Brain & Mind Research Institute, University of Sydney, 94 Mallett St, Camperdown, NSW 2050, Australia. E-mail: michael.valenzuela@sydney.edu.au

Accepted for publication 24 November 2014.

DOI 10.1002/hipo.22395

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).

with evidence of hippocampal degeneration outperformed those with an intact hippocampus. This superior performance was strongly correlated with greater expression of a posterior compensatory network (PCN) that includes co-ordinated brain activity in calcarine and posterior parietal cortical areas. We, therefore, introduce the PCN as a network with potential functional relevance to the successful performance of SWM in the context of low mnemonic load and incipient hippocampal neurodegeneration.

MATERIALS AND METHODS

Design

Two studies are reported here. In the first, we compare hippocampal volume and morphometry between individuals with Mild Cognitive Impairment (MCI, $n = 34$) versus healthy elderly with proficient cognition (PRO, $n = 22$) to define an appropriate volumetric threshold for hippocampal atrophy. In the second study, we examine memory-related functional networks exclusively in the PRO group, comparing those with (PRO_{ATR}) and without (PRO_{NIL}) hippocampal atrophy.

Subjects

MCI and PRO subjects were recruited from the Sydney Memory and Ageing Study. Detailed methodology for this study can be found in (Sachdev et al., 2010). All participants gave written informed consent and the study was approved by the University of New South Wales Human Research Ethics Committee. Subjects were aged between 70 and 85 yr, right-handed (mean Edinburgh handedness laterality index = 93; SD = 11.54) and of an English-speaking background. Exclusion criteria included diagnosis of dementia (DSM-IV; APA, 1995) or a Mini-Mental State Examination (MMSE) score- < 23 adjusted for age and education (Anderson et al., 2007), psychiatric disorder, central nervous system disorder, and acetylcholinesterase inhibitor treatment. Details about procedures for Clinical Diagnosis are provided in Supporting Information.

Imaging Protocol

Structural T1-weighted images were acquired using a Philips 3T Achieva Quasar Dual scanner. Standard sMRI protocol involved: (i) Scout mid-sagittal cut for AC-PC plane alignment, (ii) 3D T1-weighted structural (T1w TFE – turbo field echo) MRI, acquired coronally with repetition time TR = 6.39 ms, echo time TE = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view FOV = 256 × 256 × 190 mm^3, and slice thickness = 1 mm with no gap between; yielding 1 × 1 × 1 mm^3 isotropic voxels, (iii) T2-weighted fluid attenuated inversion recovery (FLAIR) sequence, acquired coronally with TR = 10,000 ms, TE = 110 ms, inversion time TI = 2800 ms; matrix size = 512 × 512; slice thickness = 3.5 mm with no gap between slices, yielding spatial resolution of 0.488 × 0.488 × 3.5 mm^3/voxel. Functional T2-weighted echoplanar images were acquired on a Philips (Achieva X) 3.0 Tesla scanner with an 8-channel SENSE head coil using an ascending slice sequence (29 axial slices, repetition time = 2,000 ms, echo time = 30 ms, 90° flip angle, matrix size = 112 × 128, field of view = 112 × 112 × 240 mm, voxel size = 2.14 × 2.73, slice thickness = 4.5 mm, 0-mm gap). Functional MRI (fMRI) preprocessing steps are provided in Supporting Information.

Hippocampus Structural Analyses

A combination of gold-stand manual hippocampal tracing, automated volume extraction, and surface-based deformation analysis were performed.

Manual hippocampal volumetry

Expert tracing the hippocampus, blinded to temporal or clinical information, was conducted using the "region of interest" (ROI) tool in Analyze 8.0 (Mayo Clinic) based on individual's T1-weighted structural MRI scans. All T1 images were normalized by rigid body transformation onto a common template to maximize standardization across subjects, and resliced coronally, orthogonal to the sagittal long-axis of the hippocampus. Tracing used a previously published protocol (Valenzuela et al., 2008) adapted from (Watson et al., 1997). Values were obtained for both the left and right hippocampi and summed for total hippocampal volume.

Automated hippocampal volume extraction

This process was carried out using SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). First, the original T1 scans were checked for obvious anatomical or positional abnormalities. Then images were bias-corrected, segmented, normalized to standard MNI space and modulated using the segmentation function of SPM5. Next, bilateral hippocampal volumes were extracted by applying a hippocampal mask generated from the Anatomical Automatic Labeling (AAL) template to each individual gray matter map (Tzourio-Mazoyer et al., 2002). Since we had both manual and automated hippocampal volumes for the fMRI sample (correlation: $r = 0.78$, $P < 0.001$), we were able to apply a study-specific adjustment coefficient to automated volumes of the larger MAS study to correct for template-based over-estimation. Whole brain volume was calculated as the sum of grey and white matter plus CSF using SPM5 segmentation tools as described previously (Wen et al., 2006).

Surface-based hippocampal morphometry

First, raw T1-weighted MRI scans were checked for obvious anatomical or positional abnormalities. Second, a brain mask was generated for each individual participant using SPM and the brain volume extracted by applying their brain mask on to the original image. Manual checking was performed to check against errors. Left and right hippocampi were then segmented using the Oxford Centre for Functional MRI of the Brain (FMRIB)'s Integrated Registration and Segmentation Tool

TABLE 1.

Sociodemographic and Clinical Descriptors of the fMRI Sample

Descriptor	MCI ($N = 34$)	PRO_{ATR}($N = 17$)	PRO_{NIL} ($N = 5$)	PRO_{ATR} VS PRO_{NIL} *P*-value
Age (yr)	78.0 (3.8)	77.9 (3.3)	74.7 (1.9)	0.057
Sex (%female)	60	58.8	40	0.46
Education (yr)	12.6 (3.9)	10.3 (2.5)	15.4 (4.8)	0.004
MMSE (/30)	27.9 (1.6)	29.4 (1.1)	29.2 (0.5)	0.76
Geriatric Depression Scale	1.1 (1.2)	2.62 (3.3)	1.8 (1.1)	0.61
APOE4 (presence %)	25.7	23.5	0	0.23
NART predicted IQ	107.2(10.3)	107.1 (7.8)	117.6 (7.3)	0.01

The PRO_{ATR} group had significantly lower years of education and estimated premorbid IQ than the PRO_{NIL} group, however, the direction of this difference was contrary to any possible explanation of their general cognitive proficiency. Chi-square tests were used to compare groups on sex and APOE 4. Independent *t*-tests were used to compare groups for the remaining continuous variables. NART predicted IQ is based on the National Adult Reading Test (Ed 2). The MMSE score includes adjustments for age and education.

(FIRST), found within FMRIB's Software Library (FSL) version 5.0.2. FIRST is a model-based procedure for subcortical segmentation and morphological modeling based on prior knowledge gained from a large number of manually segmented T1-weighted images (Patenaude et al., 2011). We used the same method as previously applied to elderly individuals (Erickson et al., 2009; Erickson et al., 2011). In brief, a standard spatial template (Montreal Neurological Institute, MNI) was affine co-registered to the original image and results individually manually checked. For each individual, left and right hippocampi were then segmented, followed by automated construction of a vertex-mesh model. Two group *t*-tests were performed based on vertex-to-vertex analyses on both the left and right hippocampus. Results were corrected for multiple comparison error using False Discovery Rate (FDR) correction.

fMRI SWM Paradigm

Subjects performed a visuo-spatial WM paradigm with progressively increasing levels of difficulty. Figure 2A depicts the events and timing of a single fMRI trial. Subjects were shown a 5 × 5 grid upon which pictures and filler items were placed. Subjects were asked to remember both the position and type of pictures depicted (termed "targets" chosen for not being readily named). During the maintenance epoch a fixation mask was presented before the response screen was shown. Subjects were asked to respond yes/no (via a button press) as quickly and accurately as possible as to whether any of the pictures were present in the same position as in the study screen. 14 such trials were conducted for each level of difficulty (easy, medium, and hard) per subject. This study was part of a larger paradigm, which has been previously reported in detail by (Kochan et al., 2011b). Examples of subjectwise SWM load calibration is available in Supporting Information.

Partial Least Squares (PLS) Network Analysis

PLS analysis produces a number of latent variables (LVs) that attempt to maximally account for co-variance within the neuroimaging × behavioral matrix. These LVs represent 4D functional brain networks (varying across brainspace and the temporal evolution of the task). Each LV has its own significance (tested by permutation and bootstrap tests) and cross-block covariance (the percentage of total covariance accounted by the LV).

Expression units in a Group-PLS are termed "Design Scores" by PLS software co-author McIntosh (McIntosh et al., 1996, 2004; McIntosh and Lobaugh, 2004). These represent relative expression of a given spatiotemporal network when aggregated across subjects and across trials for a prescribed group, and in this case also at different mnemonic loads.

Expression units in a Behavioral-PLS are termed "Brain Scores." These represent relative expression of a given spatiotemporal network at the individual subject level across trials for a given mnemonic load.

These two different expression units are in arbitrary units (AUs) and cannot be compared between types of PLS (nor even between different experiments using the same type of PLS). The absolute nature of the AUs is strongly influenced by the degree of brain-behavior covariance in the data, and so will be analysis-specific. Rather, like all PLS analyses, the units are intended solely for revealing relative differences.

Group-wise or task-based PLS analysis was conducted on the PRO group only using version 5.1102011 of the "plsgui" program (http://www.rotman-baycrest.on.ca/index.php?section = 84) for MATLAB. Analysis involved separating the PRO_{ATR} and PRO_{NIL} groups and loading the respective pre-processed fMRI and behavioral data files. Significance was tested after 500 permutation tests and 100 bootstraps (Efron and Tibshirani, 1986). Further analytical details about PLS Latent Variables, as well as Behavioral PLS and Seed PLS are presented in Supporting Information.

Statistical Analysis

Behavioral and sociodemographic data were analyzed using the *T*-test or Chi-square procedures (controlling alpha at 0.05).

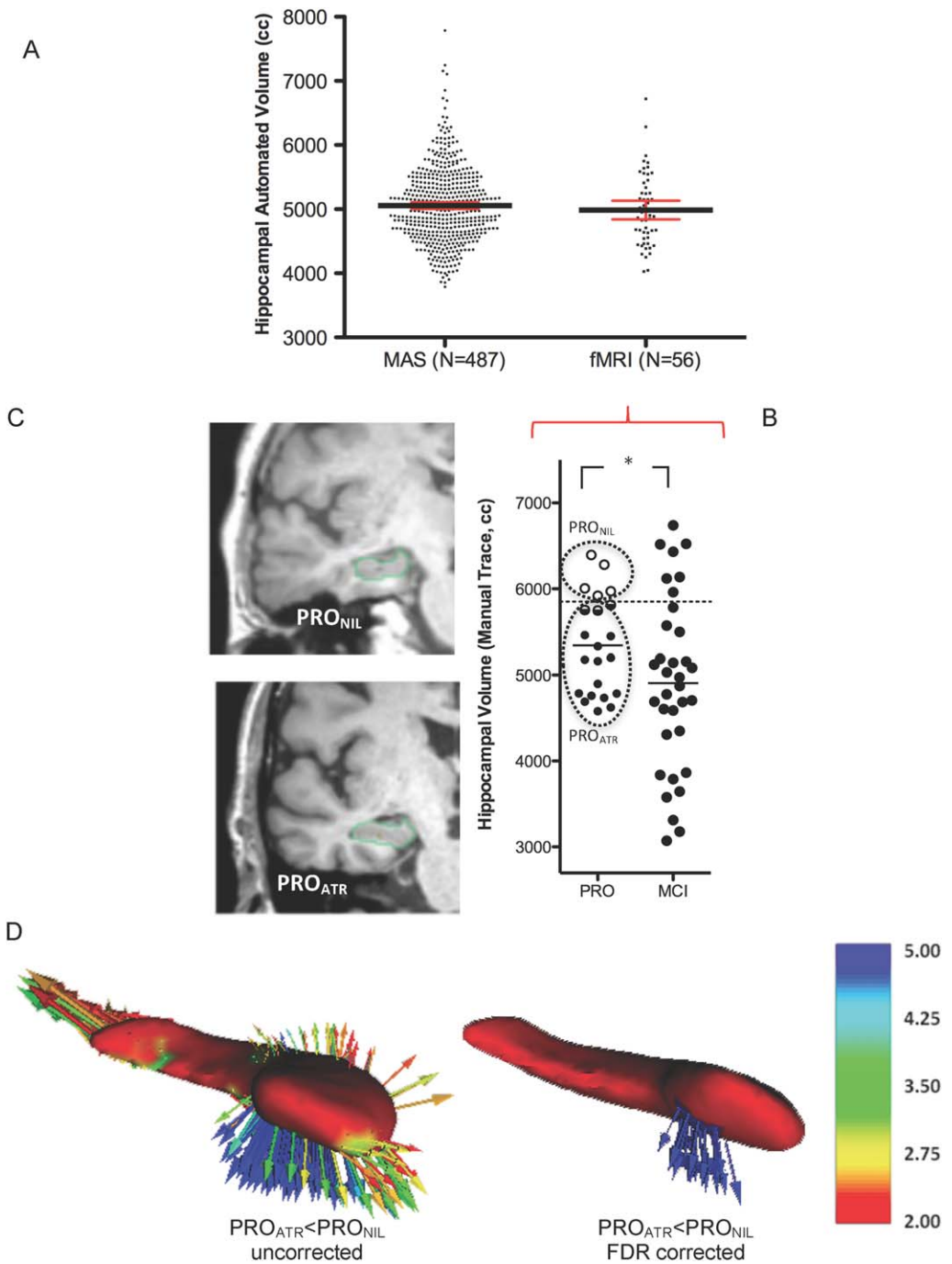

FIGURE 1. Hippocampal volumes in fMRI subsample in comparison to population-based cohort. (A) Template-based automatic extraction of hippocampal volume in the larger population-based Memory and Ageing Study (MAS) in comparison to volumes in those individuals in the fMRI substudy. There were no significant differences between these groups (mean and 95% confidence interval shown). (B) Within the fMRI subsample ($N = 57$), based on blinded manual tracing, individuals with Mild Cognitive Impairment (MCI, $n = 35$) had significantly lower hippocampal volume than those with supra-normal cognition (PRO, $n = 22$, group means indicated by solid horizontal line). Within the PRO group, discriminant analysis resulted in a volume threshold (dashed horizontal line) that separated a subgroup with MCI-like hippocampal atrophy (PRO_{ATR}, filled circles) from a subgroup without hippocampal atrophy (PRO_{NIL}, unfilled circles). Three individuals near the threshold (half filled circles) were progressively included in sensitivity analyses to establish that subsequent results were not dependent on this arbitrary volume. (C) Examples of a PRO_{NIL} individual without hippocampal degeneration and PRO_{ATR} individual with hippocampal volume loss. (D) FSL-FIRST hippocampal surface morphometric analysis found selective left-sided subicular atrophy in PRO_{ATR} group compared to PRO_{NIL} group. Left: uncorrected results, where arrows point from modeled PRO_{ATR} vertex toward matched PRO_{NIL} vertex, that is, direction of change. Arrow colors depict statistical *F*-values, moving from warm (non-significant) to cool (highly significant). Right: Results after False Discovery Rate correction are focused on ventral surface of hippocampal head. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Correlations (Pearson's) and discriminant analysis were calculated using the PASW statistics 20.0 statistical software package.

RESULTS

Study 1: Hippocampal Volumetric Threshold Between MCI and Cognitively Proficient Elderly

Two groups of older individuals were recruited for a fMRI substudy from the Sydney Memory and Ageing Study (MAS). The first comprised those with overtly proficient cognition by virtue of all test results on a comprehensive neuropsychological battery falling above the 15th percentile according to published norms: PRO, $n = 22$, mean age 77 yr, 46% male, 39% of subjects in the MAS population-based cohort met this criteria.

The second group comprised individuals meeting Mild Cognitive Impairment (MCI) criteria (Winblad et al., 2004), including amnestic and nonamnestic subtypes (MCI $n = 35$, mean age 78 yr, 60% female; further sociodemographic and clinical details can be found in Table 1). Although not all individuals with MCI will develop dementia over time, those affected have a significantly higher risk (Petersen, 2004), particularly when accompanied by biomarker evidence of AD pathology (Jack et al., 2011), including hippocampal atrophy (Jack et al., 1999), cortical fibrillar amyloid on molecular imaging (Jack et al., 2008), or CSF-based AD protein changes (Shaw et al., 2009).

On the basis of automated extraction of hippocampal volume, we first compared our entire fMRI sample ($N = 57$) to the larger population-based MAS cohort with MRI data ($N = 487$) and found no significance difference (Fig. 1A). Hippocampal volume in our fMRI sample was, therefore, representative of the general aged population in our geographical area. Next, whole brain volume (WBV) was calculated using automated segmentation of structural MR images in addition to (blinded) manual tracing of hippocampal volume. As expected, we observed an 8% reduction in total (left+right) hippocampal volume in the MCI group (manual trace average 4907.2 mm^3 ± SD 1009.0) compared to the PRO group (5342.3 ± 571.7, T-value = 2.05, P-value = 0.045 – Fig. 1B). In the absence of any significant WBV differences (T-value = 0.37, P-value = 0.71), this was suggestive of selective hippocampal degeneration. Loss of hippocampal volume is a well established in vivo AD biomarker, independently contributing to prediction of prospective dementia (Jack et al., 1999) as well as closely tied to post mortem measures of AD pathology (Gosche et al.). However, given the large amount of overlap in manually traced volumes between the PRO and MCI groups in our fMRI sample, we employed an empirically based linear discriminant analysis to determine the optimal threshold for predicting group membership using this measure alone. This cut-off was 5900 mm^3 (Figs. 1B,C), and resulted in an overall classificatory accuracy of 57%.

Study 2: Cognitive Proficiency Despite Hippocampal Atrophy

Henceforth, our focus is solely on the PRO group, and we used the hippocampal volume threshold above to distinguish between two types of cognitively-proficient older individuals (Fig. 1B): PRO without hippocampal volume loss (PRO_{NIL}, $n = 5$), and PRO with MCI-like hippocampal volume loss (PRO_{ATR}, $n = 17$). Because no group differences were noted on WBV (T-value = 1.1, $P = 0.28$), we considered atrophy as an explanation for their significantly lower hippocampal volume (Fig. 1C). To support this interpretation, hippocampal morphology in the PRO_{ATR} and PRO_{NIL} groups was analyzed using an automated surface-based mesh modeling approach [FSL's FIRST pipeline (Patenaude et al., 2011)]. We found strong evidence for subicular deflation in the left hippocampus of the PRO_{ATR} group in comparison to the PRO_{NIL} group, a result that survived vertex-based multiple comparison correction (Fig. 1D). Accordingly, a large proportion of our PRO sample had evidence of hippocampal atrophy similar in magnitude to that seen in MCI, but no clinical or sociodemographic explanation for their general cognitive proficiency (see Table 1). In fact, when specifically comparing the PRO_{ATR} group with the PRO_{NIL} on a panel of neuropsychological tests, performance on only a single test was found to be significantly worse (without multiple comparison correction – see Supporting Information).

Distinct Functional Memory Networks in Those With Proficient Cognition and Hippocampal Degeneration

A customized and graded spatial working memory (SWM) fMRI paradigm was used to examine memory networks during parametric variation of mnemonic load (Kochan et al., 2010, 2011a,b; Fig. 1D). Using this paradigm, we have shown that the hippocampus is specifically engaged during encoding of the task and is implicated in feature-binding spatial position with visual details (Kochan et al., 2010), that behavioral performance degrades in MCI individuals compared to healthy elderly and exhibit increased deactivation of default mode network areas as memory load increases (Kochan et al., 2010), and that this pattern can independently contribute to prediction of further functional decline (Kochan et al., 2011a).

Partial Least Squares (PLS) multivariate fMRI analysis was used to characterize whole-brain spatial and temporal network differences between PRO_{NIL} and PRO_{ATR}. PLS aims to identify a parsimonious set of latent variables (LVs) that summarize the interaction between brain states (e.g., fMRI timeseries) and an experimental factor of interest (e.g., experimental condition or performance on a test; McIntosh et al., 1996; McIntosh and Lobaugh, 2004; McIntosh et al., 2004). Like other multivariate techniques (Gonzalez-Castillo et al., 2012), PLS is a data-driven approach well suited to studying distributed brain processes.

We first used task-PLS analysis to identify latent variables that maximally distinguished our two PRO groups across the

three SWM load conditions (easy, medium, and hard). This yielded two significant latent variables (Fig. 2A): LV_1 was highly expressed in the PRO_{NIL} group, but virtually absent in the PRO_{ATR} group; LV_2 was highly expressed in the PRO_{ATR} group but absent in PRO_{NIL}. Both networks followed an "inverted U" polynomial-shaped function with increasing load

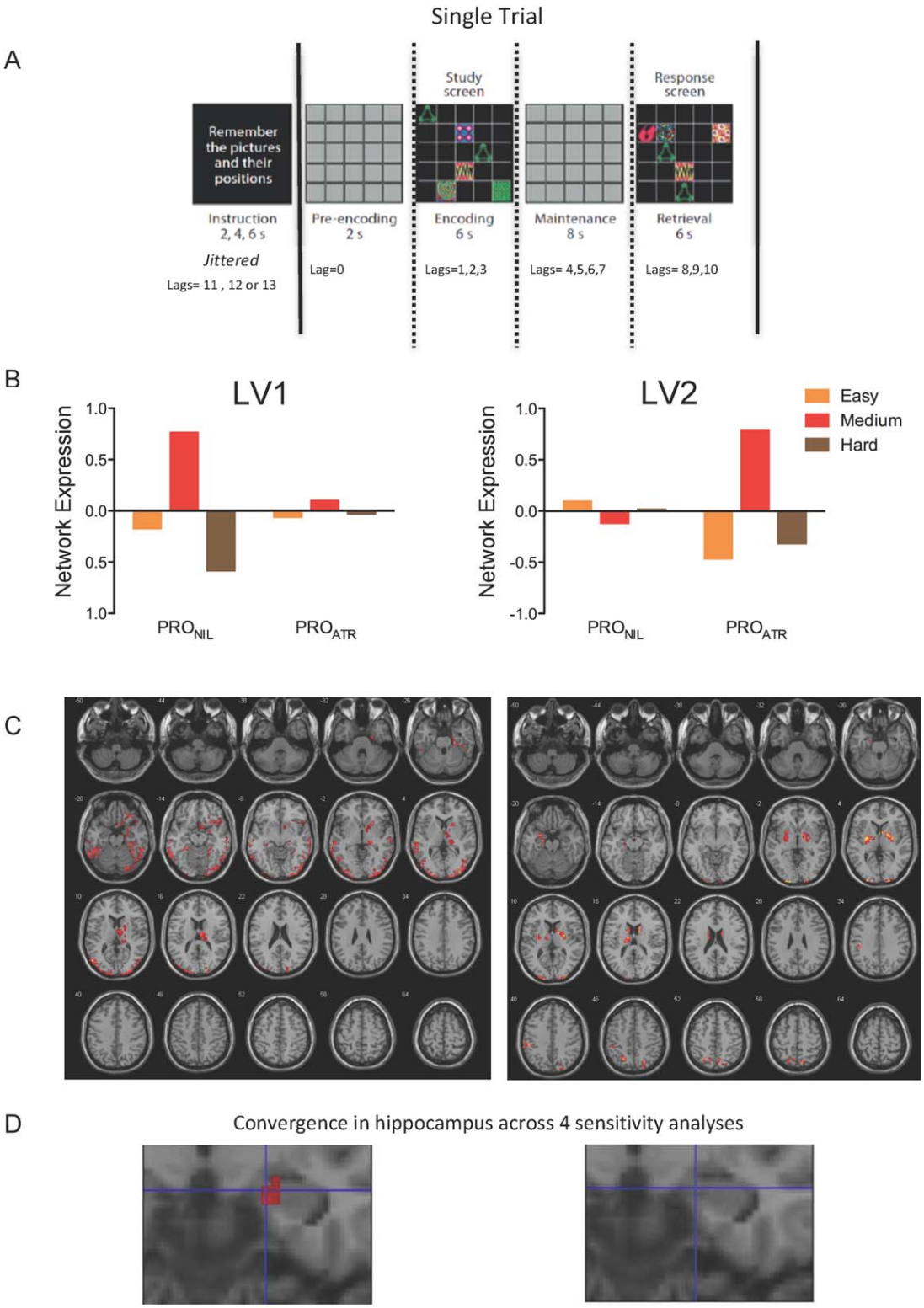

FIGURE 2.

TABLE 2.

Faster Spatial Working Memory Responses in Cognitively Proficient Elderly With Hippocampal Atrophy Than in Those Without

	PRONIL		PROATR	
	Response time (secs)	Accuracy (%)	Response time (secs)	Accuracy (%)
Easy	1.61 (0.19)	97.1 (3.8)	1.26 (0.24) ***	96.7 (6.7)
Medium	2.60 (0.61)	68.6 (9.6)	2.45 (0.67)	78.7 (12.6)
Hard	2.88 (0.60)	64.3 (10.1)	2.67 (0.66)	70.1 (14.9)

Average (SD) response times and accuracy rates during SWM paradigm across 14 trials per memory load. All group *T*-tests at $P < 0.05$ significance and were non-significant except for PRO_{ATR} vs PRO_{NIL} on response times at easy level (*** $P < 0.001$).

as previously described in several working memory studies (Leung et al., 2004; Todd and Marois, 2004), however, with very different spatial distributions (Fig. 2B). There was prominent and replicable hippocampal involvement in the PRO_{NIL} related LV_1 network (accounting for 43.9% of covariance), consistent with intact medial temporal lobe anatomy in this group (Fig. 2C). By contrast, there was no consistent hippocampal involvement in the PRO_{ATR} related LV_2 network (12.0% covariance), in agreement with observed atrophy of this brain structure (Fig. 2D).

Sensitivity Analyses

To exclude the possibility that the particular hippocampal volume threshold we used to define hippocampal atrophy had led to arbitrary results, we carried out a set of sensitivity analyses – in effect three additional task-PLS analyses where the threshold between PRO_{NIL} and PRO_{ATR} was systematically lowered (see Fig. 1B). Whereas our first task-PLS was based on 17 PRO_{ATR} subjects (and 5 PRO_{NIL}), these sensitivity analyses included 16 PRO_{ATR} subjects (6 PRO_{NIL}), or 15 PRO_{ATR} (7 PRO_{NIL}) or 14 PRO_{ATR} (8 PRO_{NIL}). The particular threshold had no major influence on our results. These were highly concordant, and in Figure 2D we show overlapping brain regions from across all four task-PLS analyses. There was consistent hippocampal involvement during SWM in PRO_{NIL} subjects and no hippocampal involvement in PRO_{ATR} subjects.

Posterior Compensatory Network Mediates Fast Basic Spatial Working Memory

A number of criteria have been suggested in order to better define a compensatory functional network (Valenzuela et al., 2007). First, evidence of disease or injury is required, and second, a change in network expression from the norm. We have attempted to address these above. The third criterion is that individual differences in compensatory network expression should predict variation in a preserved cognitive domain. Accordingly, we compared SWM performance in the PRO_{ATR} and PRO_{NIL} groups at easy, medium and hard memory load. Contrary to all expectations, response times were significantly faster in the PRO_{ATR} group (with hippocampal atrophy) than in the PRO_{NIL} group (without hippocampal atrophy), but only during basic-level (i.e., one target) SWM (Table 2). Furthermore, PRO_{ATR} individuals committed the same number of errors as PRO_{NIL} individuals, and hence their increased response speed was not by virtue of sacrificing accuracy. Despite faster response times in the PRO_{ATR} group compared

FIGURE 2. Differential network expression in cognitively proficient individuals with and without hippocampal atrophy during graded spatial working memory task. (A) Graded spatial working memory task. Figure shows timing of stimuli and example of a "medium" or "hard" task (depending on individual performance level) comprised 4 memory features. (B) LV1 network is highly expressed in PRO_{NIL} group ($n = 5$) and follows an "inverted U" shaped function as SWM load moves from easy to medium to hard; LV1 is negligibly expressed in PRO_{ATR} group. Conversely, LV2 network is highly expressed in PRO_{ATR} group ($n = 17$), follows a similar "inverted U" shaped function with load and is negligibly expressed in the PRO_{NIL} group. (C) Spatial distribution of LV1 (left) and LV2 (right) networks in axial plane at a single timepoint during paradigm (lag = 2, cluster threshold > 500 voxels for LV1 and 100 voxels for LV2, bootstrap correction $P < 0.05$). Salient parts of LV1 network include right hippocampus, entorhinal cortex, middle occipital gyrus, superior and inferior temporal gyrus and right thalamus. LV2 areas include bilateral caudate and putamen, left superior parietal lobe, left middle occipital gyrus. Left entorhinal cortex and hippocampus was also implicated in LV2 in this analysis, but was not consistent across sensitivity analyses as shown below. (D) Intersection across four different task-PLS sensitivity analyses in coronal plane (PRO_{NIL} $n = 5/6/7/8$ vs PRO_{ATR} $n = 17/16/15/14$), highlighting consistent participation of right hippocampus in LV1 network and absence in L2 network. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to PRO_{NIL} at the easy SWM level, when compared to response times in our previous study of younger adults (Kochan et al., 2011b), there was still evidence for age-related slowing on this task (see Supporting Information).

We next performed a behavioral-PLS analysis in the PRO_{ATR} group specifically to identify a network whose expression was related to spatial working memory response times under different levels of memory load. A single significant LV was found (multivariate $P = 0.04$, 37.9% covariance) predominantly expressed under low memory demand. In fact, in these conditions the correlation between brain expression of this network and faster SWM response times was exceptionally strong, $r = -0.96$ ($P < 0.0001$, Fig. 3B). No significant correlation between network expression and SWM was observed at the medium ($r = 0.50$, $P = 0.06$) or hard memory conditions ($r = 0.05$, $P = 0.86$). Interestingly, the largest cluster within this network comprised >9000 voxels, with a broad posterior distribution inclusive of several occipital areas, posterior cingulate, superior parietal cortex and vermis (Figs. 3A,C).

A posterior compensatory network (PCN) was, therefore, expressed in cognitively proficient older individuals who simultaneously exhibit hippocampal degeneration. This PCN predicted rapid and efficient response times during simple SWM tasks. To further explore potential functional relevance, we tested whether PCN expression during the easy memory load was correlated with performance on other cognitive tests. PCN expression was significantly correlated to superior Digit Symbol coding performance ($r = 0.57$, $P = 0.04$ – Fig. 4A), independent of age (partial $r = 0.57$, $P = 0.04$), and showed near-significant trends with better Trails Making B time ($r = -0.50$, $P = 0.07$) and letter fluency ($r = 0.46$, $P = 0.09$). When these two tests of executive function were combined into a summary domain score, the correlation with PCN expression was near-significant ($r = 0.53$, $P = 0.06$ – Fig. 4B). These results were based on the PRO_{ATR} grouping of $n = 14$, and when subject to sensitivity analyses were not completely consistent (correlations with Digit Symbol varied from 0.37 to 0.57, and correlations with Executive Function varied from 0.43 to 0.53). By contrast, expression during moderate or difficult SWM was not correlated with cognitive performance on any neuropsychological test.

Calcarine is a Key Spatial Component of Posterior Compensatory Network

Given the broad posterior distribution of the proposed PCN, our next step was a series of seed-PLS analyses designed to determine whether certain regions within this network served as key spatial components, that is, individual cortical areas whose covariance pattern resembled the covariance pattern of the wider PCN. Six brain ROIs were analyzed based on their maximal voxelwise significance level in the preceding analysis – the cuneus, calcarine cortex, precuneus, and different parts of the parietal cortex.

As seen in Figures 4C–F, based on the Spatial Goodness of Fit measure (Seeley et al., 2009) the network defined by a right calcarine seed was spatially most similar to the overall PCN, by a factor of almost 2-to-1. When combined with our observation that calcarine cortical activity was correlated with faster SWM response times during easy tasks (right Calcarine $r = -0.73$, left Calcarine $r = -0.84$, see Fig. 3C), this brain region is likely to have an important functional role within the PCN.

DISCUSSION

Cortical compensation in response to damage to medial temporal lobe structures may be a key process in the maintenance of cognitive function in later life but a more precise neuronal network explanation has proven elusive. For the first time, we show that a posterior compensatory network (PCN) is selectively engaged by older individuals with hippocampal atrophy, who despite this neuronal vulnerability, maintain neuropsychological proficiency. Moreover, expression of this network is strongly correlated with more efficient basic-level SWM performance, to the extent that these individuals are faster and no less accurate on this task than their peers without hippocampal atrophy. The calcarine occipital region and posterior parietal cortex are key components of this newly described PCN.

In the realm of AD and brain ageing, biomarker research has almost exclusively focused on in vivo estimation of neurodegenerative disease burden (Jack et al., 2010), with an underlying assumption that cognition in late life is a function of the build-up (or absence) of disease. We used a degree of hippocampal volume loss commensurate with that seen in a population-based cohort with MCI to define hippocampal atrophy, an interpretation further supported by selective deflation of the subiculum, a consistent finding in ageing studies (Frisoni et al., 2008; Thomann et al., 2013). Yet for some time post mortem studies have emphasized a disconnect between AD pathology and antemortem cognitive state (Davis et al., 1999; Price and Morris, 1999; CFAS-MRC, 2001; Knopman et al., 2003). These studies indicate that about 30% of individuals with significant AD pathology at death were cognitively intact in life. The role of adaptive cortical reorganization in response to chronic and progressive brain damage has by comparison received much less attention. Quite contrary to expectations, our data shows it is indeed possible to have superior mnemonic performance, albeit only at low mnemonic load, in the presence of hippocampal atrophy when accompanied by engagement of the PCN. A comprehensive approach to the prognosis of cognitive function in aged individuals may, therefore, require consideration of both disease burden and compensatory brain processes.

The PCN identified here as relevant to basic-level SWM in the presence of hippocampal atrophy does not appear to be strongly expressed normatively. There was no evidence of a similar network pattern being functionally relevant to SWM in healthy older adults without hippocampal atrophy, however, we recognize that this group was small. Our data suggest that these

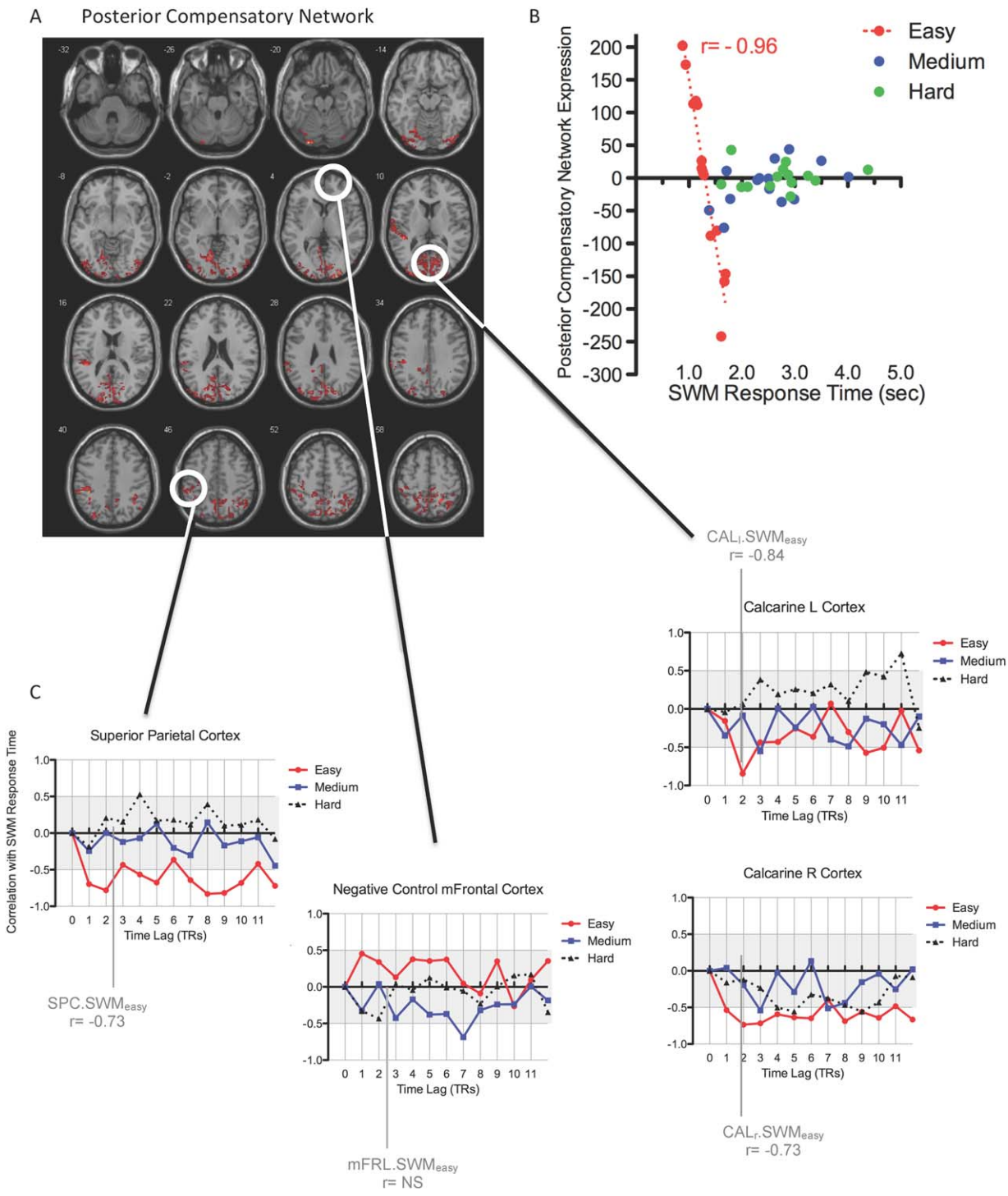

FIGURE 3. Posterior Compensatory Network (PCN) expression predicts fast and accurate spatial working memory performance during easy tasks in individuals with proficient cognition and hippocampal atrophy. Spatial distribution of PCN in axial plane at acquisition time of lag = 2 is heavily posterior, including bilateral secondary occipital cortex and posterior parietal lobe, and the cerebellum (cluster threshold > 500 voxels, bootstrap correction $P < 0.05$). PCN expression at lag = 2 is strongly correlated with fast and accurate completion of a SWM task when easy, but not at more challenging memory demands. Spatial and temporal characteristics of PCN. Three salient parts of the PCN (right and left calcarine cortex, CAL, and superior parietal cortex, SPC) and a negative control non-PCN region (right middle frontal lobe, mFRL) are highlighted. Each graphs show how the correlation between BOLD signal change (with respect to initial baseline signal) and SWM performance changes across the duration of the trial (i.e., total of 13 whole-brain echoplanar acquisitions per trial, labeled here as lags 0–12) and is distinct for each level of memory load. For all parts of the PCN, there were strong negative correlations with SWM (i.e., predictive of faster performance) at easy mnemonic load, particularly early in the course of each trial at Lag 2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

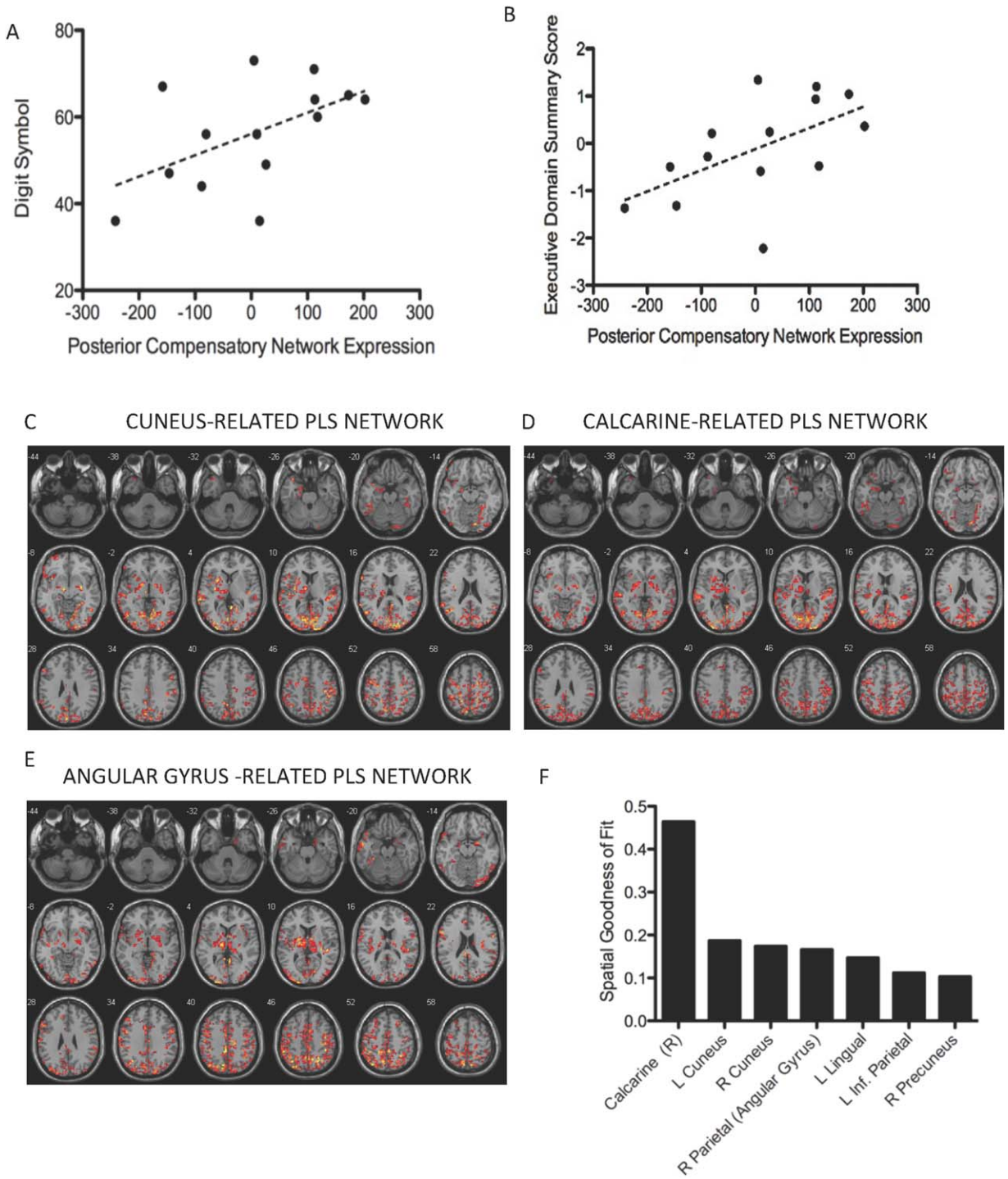

FIGURE 4. PCN expression may be linked to general cognitive functions and calcarine occipital cortex is a dominant spatial component. Scatterplots depict correlation between expression of PLS-defined Posterior Compensatory Network during easy spatial working memory task and: (A) Digit Symbol test and (B) Executive function summary score ($PRO_{ATR} = 14$). Seed-PLS was also used to define: (C) right calcarine-related, (D) cuneus-related, and (E) right angular gyrus-related networks (Lag = 2, cluster threshold > 100 voxels, bootstrap correction $P < 0.05$). (F) Spatial Goodness of Fit analyses found that the calcarine-related network most closely matches the spatial distribution of the entire PCN in Figure 3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

individuals tended to engage a hippocampus-inclusive network, particularly at intermediate memory demand levels. Normal cognition in the aged may, therefore, arise from a "healthy brain" that employs normative functional networks, or from a brain with incipient degeneration reliant on the effective engagement of the PCN and no doubt other compensatory

networks. By implication, longitudinal studies and clinical trials that recruit "cognitively normal" aged individuals are at risk of confounding two qualitatively different brain states that are likely to exhibit distinct natural histories.

On the basis of spatial and functional criteria, the calcarine cortex and posterior parietal regions were key parts of the PCN. Activity in both these areas were strongly correlated to faster SWM response times, specifically at elementary memory load. Calcarine cortex is generally regarded as important for primary and secondary visual processing, however, under atypical conditions, this region can undergo profound functional plasticity. Transient, tactile-dependent activation of calcarine cortex was found in young adults after being blindfolded for 5 days (Merabet et al., 2008), consistent with the observation of primary and secondary visual cortex activation in blind individuals upon the tactile stimulus of braille (Cohen et al., 1997; Hamilton et al., 2000; Kupers et al., 2007). Stern et al. (2000) also identified calcarine cortex as an important part of a compensatory network that predicted relatively conserved recognition memory in AD patients.

Our findings are hence in stark contrast to those studies that have reported bilateral prefrontal cortical activity in the aged as part of a compensatory process (Park and Reuter-Lorenz, 2009). It is noteworthy that these results were generally based on declarative verbal memory tasks (e.g., Cabeza et al., 2002), whereas our PCN results are based on a visuospatial working memory task and so may represent a potential reason for this difference. However, it remains unresolved whether frontal "bilateralization" is related to better (suggestive of a compensatory process) or worse cognitive outcomes (network dysfunction; Grady, 2012). One of the few fMRI studies to assess for disease burden in their aged subjects (in the form of hippocampal atrophy) also noted greater bilateral frontal activation under memory demand, however, this combination was linked with declining memory proficiency (Persson et al., 2006). As far as we are aware, our findings in support of a posterior compensatory network are the first to show: (a) memory-related network change in cognitively-intact aged subjects, that are (b) dependent on presence of hippocampal atrophy, and (c) whose expression positively predicts conserved (and even superior) memory function under tightly defined condition of simplistic task demands.

These findings provoke some theoretical questions. First, it is possible that individuals with hippocampal atrophy and posterior compensation may in the future decompensate. For example, this could occur through subtle disease or dysfunction targeting these same posterior cortical areas. Classical AD pathology has for example been reported in the posterior cingulate early in the disease process (Pengas et al., 2010) and is suggested to underlie default mode dysfunction in MCI and early AD (Greicius et al., 2004; Rombouts et al., 2005). The posterior cingulate can be found within our PCN, and hence degenerative disease that targets this brain region could potentially be harmful to successful functional compensation. Second, in those with hippocampal atrophy, the putative stimulus for functional reorganization is a progressive lesion. Our cross-sectional data, therefore, presents a limitation for we cannot determine the temporal sequencing of hippocampal atrophy and functional reorganization. We also cannot fully account for the general cognitive proficiency of our subjects with hippocampal atrophy on the sole basis of engagement of the PCN. The PCN was highly specified for the mediation of basic-level SWM, with only a suggestion of possible relevance to cognitive control processes. Outside of more automatic stimulus-driven working memory demands (i.e., when encoding and retention of more than a single image-location pair was required), the PCN was not expressed (Fig. 3) and there was no corresponding performance advantage (Table 2). This is related to a general limitation of PLS analyses, whereby the first latent variable that accounts for the majority of brain-behavior covariance is most likely to be statistically robust. In our PLS analyses the primary latent variable was relevant to only low level spatial working memory, whereas secondary and tertiary latent variables with possible relevance to medium and hard memory load were also found but did not meet statistical threshold. It is, therefore, likely that other as yet unidentified compensatory networks interact with the PCN to help maintain cognition in those with asymptomatic hippocampal atrophy. Finally, the multivariate PLS approach implemented here does not model the haemodynamic response function, and so whether the PCN is more specifically active during easy-level encoding, retention or retrieval SWM processes is not determinate. Further research will be required to clarify this issue.

Overall, our findings cast new light on the role of potentially compensatory brain processes in individuals with hippocampal atrophy. Surprisingly, when this PCN is strongly engaged, performance on a basic-level spatial working memory task in those with hippocampal atrophy can exceed performance in those with a fully intact hippocampus. Accurate interpretation of an older individual's current brain state, as well as their future mental prospects, may therefore, benefit from combining information about cognitive function, disease burden, and scope for compensatory functional reorganization.

REFERENCES

Anderson TM, Sachdev PS, Brodaty H, Trollor JN, Andrews G. 2007. Effects of sociodemographic and health variables on Mini-Mental State Exam scores in older Australians. Am J Geriatr Psychiatry 15:467–476. doi:10.1097/JGP.0b013e3180547053.

Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, Yassa MA, Bassett SS, Shelton AL, Gallagher M. 2012. Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron 74: 467–474. doi:10.1016/j.neuron.2012.03.023.

Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. 2000. Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med 343:450–456. doi:10.1056/NEJM200008173430701.

Brayne C, Ince PG, Keage HA, McKeith IG, Matthews FE, Polvikoski T, Sulkava R. 2010. Education, the brain and dementia: Neuroprotection or compensation? Brain 133 (Part 8):2210–2216. doi: 10.1093/brain/awq185.

Buckner RL. 2004. Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. Neuron 44:195–208. doi:10.1016/j.neuron.2004.09.006.

Cabeza R, Anderson N, Locantore J, McIntosh A. 2002. Aging gracefully: Compensatory brain activity in high-performing older adults. Neuroimage 17:1394–1402.

Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. 2004. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 14:364–375.

CFAS-MRC. 2001. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of Medical Research Council Cognitive Function and Aging Study. Lancet 375:169–175.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, Honda M, Sadato N, Gerloff C, Catala MD, Hallett M. 1997. Functional relevance of cross-modal plasticity in blind humans. Nature 389:180–183. doi:10.1038/38278.

Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, Kase CS, Benjamin EJ, Polak JF, O'Donnell CJ, Yoshita M, D'Agostino RB, DeCarli C, Wolf PA. 2008. Prevalence and correlates of silent cerebral infarcts in the framingham offspring study. Stroke 39:2929–2935. doi:10.1161/strokeaha.108.516575.

Dauer W, Przedborski S. 2003. Parkinson's disease: Mechanisms and models. Neuron 39:889–909.

Davis DG, Schmitt FA, Wekstein DR, Markesbery WR. 1999. Alzheimer neuropathologic alterations in aged cognitively normal subjects. J Neuropathol Exp Neurol 58:376–388.

Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, Dale AM, Stern CE, Blacker D, Albert MS, Sperling RA. 2004. Medial temporal lobe function and structure in mild cognitive impairment. Ann Neurol 56:27–35. doi:10.1002/ana.20163.

Efron B, Tibshirani R. 1986. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat Sci 1:54–75.

Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wojcicki TR, McAuley E, Kramer AF. 2009. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19:1030–1039. doi:10.1002/hipo.20547.

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H., White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. 2011. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108:3017–3022. doi: 10.1073/pnas.1015950108.

Frisoni GB, Ganzola R, Canu E, Rub U, Pizzini FB, Alessandrini F, Zoccatelli G, Beltramello A, Caltagirone C, Thompson PM. 2008. Mapping local hippocampal changes in Alzheimer's disease and normal ageing with MRI at 3 Tesla. Brain J Neurol 131 (Part 12): 3266–3276. doi:10.1093/brain/awn280.

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA. 2012. Whole-brain, time-locked activation with simple tasks revealed using massive averaging and model-free analysis. Proc Natl Acad Sci USA 109:5487–5492. doi:10.1073/pnas.1121049109.

Gosche KM, Mortimer JA, Smith CD, Markesbery WR, Snowdon DA. 2002. Hippocampal volume as an index of Alzheimer neuropathology: Findings from the Nun Study. Neurology 58:1476–1482.

Grady C. 2012. The cognitive neuroscience of ageing. Nat Rev Neurosci 13:491–505. doi:10.1038/nrn3256.

Grady C, McIntosh A, Beig S, Keightley M, Burian H, Black S. 2003. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's Disease. J Neurosci 23:986–993.

Grafman J, Jonas BS, Martin A, Salazar AM, Weingartner H, Ludlow C, Smutok MA, Vance SC. 1988. Intellectual function following penetrating head injury in Vietnam veterans. Brain 111 (Part 1): 169–184.

Greicius MD, Srivastava G, Reiss AL, Menon V. 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. Proc Natl Acad Sci USA 101:4637–4642. doi:DOI 10.1073/pnas.0308627101.

Hamilton R, Keenan JP, Catala M, Pascual-Leone A. 2000. Alexia for Braille following bilateral occipital stroke in an early blind woman. Neuroreport 11:237–240.

Jack C, Petersen R, Xu Y, et al. 1999. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 52:1397–1403.

Jack CR, Jr., Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, Knopman DS, Boeve BF, Klunk WE, Mathis CA, Petersen RC. 2008. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain 131 (Part 3):665–680. doi:10.1093/brain/awm336.

Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 9:119–128. doi: 10.1016/S1474–4422(09)70299-6.

Jack CR, Jr., Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH. 2011. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:257–262. doi: 10.1016/j.jalz.2011.03.004.

Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, Smith GE, Dickson DW, Johnson KA, Petersen LE, McDonald WC, Braak H, Petersen RC. 2003. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 62:1087–1095.

Kochan NA, Breakspear M, Slavin MJ, Valenzuela M, McCraw S, Brodaty H, Sachdev PS. 2010. Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge. Dement Geriatr Cogn Disord 30:553–568. doi:10.1159/000322112.

Kochan NA, Breakspear M, Valenzuela M, Slavin MJ, Brodaty H, Wen W, Trollor JN, Turner A, Crawford JD, Sachdev PS. 2011a. Cortical responses to a graded working memory challenge predict functional decline in mild cognitive impairment. Biol Psychiatry 70:123–130. doi: 10.1016/j.biopsych.2011.03.006.

Kochan NA, Valenzuela M, Slavin MJ, McCraw S, Sachdev PS, Breakspear M. 2011b. Impact of load-related neural processes on feature binding in visuospatial working memory. PLoS One 6: e23960. doi:10.1371/journal.pone.0023960.

Kupers R, Pappens M, de Noordhout AM, Schoenen J, Ptito M, Fumal A. 2007. rTMS of the occipital cortex abolishes Braille reading and repetition priming in blind subjects. Neurology 68: 691–693. doi: 10.1212/01.wnl.0000255958.60530.11.

Leung HC, Seelig D, Gore JC. 2004. The effect of memory load on cortical activity in the spatial working memory circuit. Cogn Affect Behav Neurosci 4:553–563.

McIntosh A, Lobaugh N. 2004. Partial least squares analysis of neuroimaging data: Applications and advances. Neuroimage 23:S250–S263.

McIntosh AR, Bookstein FL, Haxby JV, Grady CL. 1996. Spatial pattern analysis of functional brain images using partial least squares. Neuroimage 3:143–157. doi:10.1006/nimg.1996.0016.

McIntosh A, Chau W, Protzner A. 2004. Spatiotemporal analysis of event-related fMRI data using partial least squares. Neuroimage 23:764–775.

Merabet LB, Hamilton R, Schlaug G, Swisher JD, Kiriakopoulos ET, Pitskel NB, Kauffman T, Pascual-Leone A. 2008. Rapid and reversible recruitment of early visual cortex for touch. PLoS One 3:e3046. doi:10.1371/journal.pone.0003046.

Morcom AM, Good CD, Frackowiak RS, Rugg MD. 2003. Age effects on the neural correlates of successful memory encoding. Brain 126 (Part 1):213–229.

Park D, Reuter-Lorenz P. 2009. The adaptive brain: Aging and neurocognitive scaffolding. Annu Rev Psychology 60:173–196.

Patenaude B, Smith SM, Kennedy DN, Jenkinson M. 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56:907–922. doi:10.1016/j.neuroimage.2011.02.046.

Pengas G, Hodges JR, Watson P, Nestor PJ. 2010. Focal posterior cingulate atrophy in incipient Alzheimer's disease. Neurobiol Aging 31:25–33. doi: 10.1016/j.neurobiolaging.2008.03.014.

Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, Buckner RL. 2006. Structure-function correlates of cognitive decline in aging. Cereb Cortex 16:907–915. doi: 10.1093/cercor/bhj036.

Petersen RC. 2004. Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183–194. doi:10.1111/j.1365–2796.2004.01388.x.

Price JL, Morris JC. 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 45:358–368.

Putcha D, Brickhouse M, O'Keefe K, Sullivan C, Rentz D, Marshall G, Dickerson B, Sperling R. 2011. Hippocampal hyperactivation associated with cortical thinning in Alzheimer's disease signature regions in non-demented elderly adults. J Neurosci 31:17680–17688. doi:10.1523/JNEUROSCI.4740-11.2011.

Quiroz YT, Budson AE, Celone K, Ruiz A, Newmark R, Castrillon G, Lopera F, Stern CE. 2010. Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease. Ann Neurol 68:865–875. doi:10.1002/ana.22105.

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, Koeppe RA. 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 12:174–187.

Reuter-Lorenz PA, Stanczak L, Miller AC. 1999. Neural recruitment and cognitive aging: Two hemispheres are better than one, especially as you age. Psychol Sci 10:494–500.

Rombouts SARB, Barkhof F, Goekoop R, Stam CJ, Scheltens P. 2005. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: An fMRI study. Hum Brain Map 26:231–239. doi:Doi 10.1002/Hbm.20160.

Sachdev PS, Brodaty H, Reppermund S, Kochan NA, Trollor JN, Draper B, Slavin MJ, Crawford J, Kang K, Broe GA, Mather KA, Lux O. 2010. The Sydney Memory and Ageing Study (MAS): Methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70–90 years. Int Psychogeriatrics/IPA 22:1248–1264. doi:10.1017/S1041610210001067.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron 62:42–52. doi: 10.1016/j.neuron.2009.03.024.

Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ. 2009. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 65:403–413. doi:10.1002/ana.21610.

Stern Y. 2002. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 8:448–460.

Stern Y, Moeller J, Anderson K, Luber B, Zubin N, DiMauro A, Park A, Campbell C, Marder K, Bell K, et al. 2000. Different brain networks mediate task performance in normal aging and AD - Defining compensation 606. Neurology 55:1291–1297.

Stevens WD, Hasher L, Chiew KS, Grady CL. 2008. A neural mechanism underlying memory failure in older adults. J Neurosci 28:12820–12824. doi: 10.1523/JNEUROSCI.2622-08.2008.

Thomann PA, Wustenberg T, Nolte HM, Menzel PB, Wolf RC, Essig M, Schroder J. 2013. Hippocampal and entorhinal cortex volume decline in cognitively intact elderly. Psychiatr Res 211:31–36. doi:10.1016/j.pscychresns.2012.06.002.

Todd JJ, Marois R. 2004. Capacity limit of visual short-term memory in human posterior parietal cortex. Nature 428:751–754. doi:10.1038/nature02466.

Tononi G, Sporns O, Edelman G. 1999. Measures of degenerecy and redundancy in biological networks. Proc Natl Acad Sci USA 96:3257–3262.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289. doi:10.1006/nimg.2001.0978.

Valenzuela M, Breakspear M, Sachdev P. 2007. Complex mental activity and the ageing brain: Molecular, cellular and cortical network mechanisms. Brain Res Rev 56:198–213.

Valenzuela M, Sachdev P, Wen W, Chen X, Brodaty H. 2008. Lifespan mental activity predicts diminished rate of hippocampal atrophy. PLoS One 3:e2598.

Vernooij MW, Ikram MA, Tanghe HL, Vincent AJPE, Hofman A, Krestin GP, Niessen WJ, Breteler MMB, van der Lugt A. 2007. Incidental findings on brain MRI in the general population. N Engl J Med 357:1821–1828. doi:doi:10.1056/NEJMoa070972.

Watson C, Jack C, Cendes F. 1997. Volumetric magnetic resonance imaging: Clinical applications and contributions to the understanding of temporal lobe epilepsy. Arch Neurology 54:1521–1531.

Wen W, Sachdev PS, Chen X, Anstey K. 2006. Gray matter reduction is correlated with white matter hyperintensity volume: A voxel-based morphometric study in a large epidemiological sample. Neuroimage 29:1031–1039. doi: 10.1016/j.neuroimage.2005.08.057.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. 2004. Mild cognitive impairment–beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256:240–246. doi:10.1111/j.1365–2796.2004.01380.x.