Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging

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ABSTRACT

There is a great deal of heterogeneity in the impact of aging on cognition and cerebral functioning. One potential factor contributing to individual differences among the elderly is the cognitive reserve, which designates the partial protection from the deleterious effects of aging that lifetime experience provides. Neuroimaging studies examining task-related activation in elderly people suggested that cognitive reserve takes the form of more efficient use of brain networks and/or greater ability to recruit alternative networks to compensate for age-related cerebral changes. In this exploratory multi-center study, we examined the relationships between cognitive reserve, as measured by education and verbal intelligence, and cerebral metabolism at rest (FDG-PET) in a sample of 74 healthy older participants. Higher degree of education and verbal intelligence was associated with less metabolic activity in the right posterior temporoparietal cortex and the left anterior intraparietal sulcus. Functional connectivity analyses of resting-state fMRI images in a subset of 41 participants indicated that these regions belong to the default mode network and the dorsal attention network respectively. Lower metabolism in the temporoparietal cortex was also associated with better memory abilities. The findings provide evidence for an inverse relationship between cognitive reserve and resting-state activity in key regions of two functional networks respectively involved in internal mentation and goal-directed attention.

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Introduction

Advancing age has deleterious effects on cognitive processes, more particularly memory for personally experienced recent episodes and executive control processes (Park and Schwartz, 2000). This has been related to changes in brain structure and function, with most changes affecting the prefrontal cortex and the hippocampus (Gutchess et al., 2005; Raz, 2000; Raz et al., 2005). Importantly, however, there is a great deal of heterogeneity in cognitive performance among elderly healthy people. Actually, inter-individual variability in task performance increases as people age (Christensen et al., 1999). Whereas some older participants perform as well as young participants in memory or executive tasks, others show significant decline (Cabeza et al., 2002; Davidson and Glisky, 2002; Duarte et al., 2006; Glisky et al., 1995).

Neuroimaging studies of cognitive aging have related individual differences in cognitive performance to heterogeneity in the underlying cerebral functioning. Typically, these studies compared cerebral functioning in relation to task performance in high- and low-functioning elderly individuals classified on the basis of either their score on the task at hand or their performance in neuropsychological tests. Depending on the nature of the task, complex patterns of increased and decreased cerebral activity have been associated with good cognitive performance in aging. For instance, using FDG-PET, Hazlett et al. (1998) showed that older adults who performed well in a memory task demonstrated reduced frontal activity and more occipital activity than poor performers. Additionally, in older and young adults, performance in a verbal fluency task was found to correlate negatively with frontal, temporal and

parietal metabolic activity at rest (Boivin et al., 1992; Parks et al., 1988). In functional magnetic resonance imaging (fMRI) studies, it has been observed that, compared to low-functioning older participants, high-functioning elderly individuals recruit additional prefrontal regions when they engage in strategies that efficiently improve performance (for reviews, Grady, 2008; Reuter-Lorenz and Park, 2010).

Recently, there has been increasing interest in the factors that could contribute to individual differences in cognitive and cerebral aging. In particular, there is evidence that cognitive decline is attenuated in elderly people with high levels of intelligence, education, literacy, and occupational attainment (Albert et al., 1995; Christensen, 2001; Manly et al., 2005; Murray et al., 2011). The idea that individuals with stimulating lifetime experiences can cope better than others with age-related neural changes and thus minimize cognitive decline has been formalized in the cognitive reserve hypothesis (Steffener and Stern, 2012; Stern, 2002, 2006, 2009; Tucker and Stern, 2011). The hypothesis is that there is inter-individual variability in the brain networks or cognitive processes that underlie the performance of any task. This variability can take the form of differences in efficiency or capacity of the networks that can be invoked to perform a task (neural reserve). In healthy individuals, this will lead to variability in how these networks are recruited when coping with increased task demands. For tasks of low to moderate difficulty, high cognitive reserve will take the form of reduced – more efficient – activation of the network for an equivalent or even greater success in the task. For high-demanding tasks, individuals with high cognitive reserve will have a greater capacity, so that they can show greater increase in network activation to cope with increasing task difficulty. In case of brain disease, high cognitive reserve will help individuals to cope with brain pathology by making better use of brain networks. An individual whose networks are more efficient or have greater capacity might be more capable of coping with the disruption imposed by brain pathology. Alternatively, individuals suffering from brain pathology or age-related cerebral changes may use brain structures or networks (and thus cognitive strategies) not normally used by individuals with intact brain in order to compensate for brain damage (neural compensation).

Until now, most investigations of the neural implementation of cognitive reserve have examined how estimates of cognitive reserve modulate task-related activations as measured by PET or fMRI (Bartrés-Faz and Arenaza-Urquijo, 2011; Steffener and Stern, 2012). Typically, the construct of cognitive reserve is captured by measures of education and IQ, sometimes in combination with ratings of leisure activities and social life (Siedlecki et al., 2009). Then, the studies examine association between the cognitive reserve index and the degree of regional activation during task performance.

In healthy aging, evidence of cognitive reserve in the form of neural compensation mostly comes from comparison of cerebral activation during memory tasks in young and older participants as a function of cognitive reserve (Scarmeas et al., 2003b; Springer et al., 2005; Steffener et al., 2011; Stern et al., 2005). Using $H_2^{15}O$-PET, Scarmeas et al. (2003a, 2003b) showed that, compared to young adults, older participants showed a positive correlation between cognitive reserve and activation of the cuneus (reflecting the use of visual processes) during a nonverbal recognition memory task. In an fMRI study, Springer et al. (2005) observed that highly educated older people had greater frontal involvement during successful memory retrieval than less educated older participants, whereas there was a negative association between education and frontal activation in young adults. These findings indicate that healthy elders with high cognitive reserve are more prone than participants with less cognitive reserve to engage brain regions not typically involved in task performance by young adults in order to aid cognitive function.

A few studies have suggested that cognitive reserve in normal aging can also take the form of greater efficiency. For an equivalent or better level of performance or for an equal increase in task demand, someone with greater efficiency requires less of an increase in neural activity than does someone with less efficiency (Steffener and Stern, 2012). In older participants, evidence of greater neural efficiency in relation to cognitive reserve comes from findings indicating that the degree of cognitive reserve in older adults modulated the expression of a typical frontoparietal network during a working memory task in the face of cerebral atrophy (Steffener et al., 2011). When regions in the network were atrophied, older participants with low cognitive reserve showed higher expression of the network for equal performance as compared to those with high cognitive reserve whose functional network was expressed to a lower degree. In other words, cognitive reserve allowed maintaining efficiency of the functional networks in the presence of cerebral atrophy. Moreover, a series of fMRI studies in healthy aging showed that higher level of cognitive reserve was associated with reduced task-related activation in typically involved regions (Bartrés-Faz et al., 2009; Bosch et al., 2010; Solé-Padullés et al., 2009; Steffener et al., 2011). This was observed for different cognitive domains and in the context of similar level of performance. These findings resonate with the literature supporting the neural efficiency hypothesis of intelligence (Haier et al., 1992b). Brighter individuals (i.e., with higher IQ – as assessed by vocabulary scores or by a full psychometric battery such as the WAIS-R, notable measures also included in indexes of cognitive reserve) typically show less glucose cerebral consumption (as measured by FDG-PET) during cognitive task performance than less intelligent people. Such negative correlation between the amount of cortical involvement and IQ was observed in young and middle-aged participants, in a variety of cognitive tasks and with different neuroimaging methods (PET, fMRI and EEG) (Haier et al., 1992a, 1992b; Neubauer et al., 2005; Ruff et al., 2003; Vitouch et al., 1997; Vogt et al., 1998). Importantly, lower cerebral activation in relation to higher intelligence was associated with better cognitive performance (Ruff et al., 2003).

The fact that cognitive reserve can be associated with both increased and reduced activation in specific brain regions during task performance reflects the complexity of the neural expression of cognitive reserve (Steffener and Stern, 2012). For a given task, high cognitive reserve would be associated with reduced cerebral activation (neural efficiency) in regions typically engaged in task performance, whereas increased activation in less typical regions would reflect neural compensation. Previous work demonstrated the diversity of the cerebral sites manifesting neural reserve and compensation, suggesting some task-related specificity (although the idea of a generic cognitive reserve network has been put forward (Stern, 2009; Stern et al., 2008), see Discussion). Moreover, cognitive reserve may impact on the interaction between brain regions, in a way comparable to the relationship between individual differences in processing speed and the efficiency of interactions between brain regions (Rypma et al., 2006).

In aging, this idea of an impact of cognitive reserve on cerebral interactions is particularly pertinent if one considers that compromised cerebral functional connectivity also contribute to age-related changes. Indeed, the default mode network, a set of regions involved in internal mentation, as well as the attention networks, engaged in attention-demanding tasks, show reduced activity and altered intrinsic connectivity in elderly adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Lustig et al., 2003; Wu et al., 2011). One previous study showed that activity in the default mode network (comprising the medial and lateral temporal lobe, the medial prefrontal cortex, the precuneus/posterior cingulate cortex, and the posterior parietal cortex) is modulated by estimates of education, intelligence and leisure activities (Bosch et al., 2010). Indeed, the authors examined deactivations in regions of the default mode network during a language task and observed that elderly people with higher cognitive reserve deactivated this network less. Given that the default mode network deactivates more when demands in terms of cognitive control increase (Persson et al., 2007), these findings may reflect the fact that people with high cognitive reserve needed to engage less effortful resources and thus processed the language task more automatically than people with lower cognitive reserve.

In the current multi-center study, we investigated the influence of cognitive reserve in the cerebral functioning of healthy older

participants outside the context of a cognitive task, by examining resting-state functioning. The cerebral resting-state correlates of cognitive reserve were measured by means of FDG-PET. In comparison to fMRI, FDG-PET measures neuronal activity independently of vascular coupling and can be used to explore the baseline integrity of neuronal networks (Lee et al., 2008; Rocher et al., 2003).

Research on the influence of education, IQ and leisure activities on cerebral functioning at rest has mainly been conducted in patients with Alzheimer's disease (AD). Using FDG-PET or H_2 ^{15}O-PET, these studies consistently indicated that indexes of cognitive reserve correlate negatively with regional metabolism or blood flow, typically in posterior temporoparietal cortices, in patients of equivalent level of clinical severity (Alexander et al., 1997; Hanyu et al., 2008; Kemppainen et al., 2008; Perneczky et al., 2006; Scarmeas et al., 2003a). This was interpreted as evidence that patients with high level of cognitive reserve successfully compensate for early-stage AD pathology and need more advanced pathology before they exhibit clinical symptoms, so that for a given degree of dementia severity, high cognitive reserve patients have more pathology. Some of these studies included healthy elderly controls, but failed to find any significant correlation (Perneczky et al., 2006; Scarmeas et al., 2003a), possibly because the very small sample size (n = 16) did not give enough statistical power to detect any association. The current study thus aimed at re-examining the influence of cognitive reserve (as indexed by education and verbal intelligence) on resting-state cerebral metabolism in a large sample of healthy elderly participants. More importantly, this study considered resting-state data in the light of recent views that baseline brain activity consists of several functional networks of intrinsically correlated regions (Fox and Raichle, 2007). Thus, we interpreted regional correlations in terms of functional networks by taking advantage of available resting-state fMRI data. In line with the neural efficiency hypothesis of intelligence and considering previous evidence of more efficient cerebral functioning in older people with high level of cognitive reserve, we expected a negative association between measures of cognitive reserve and cerebral metabolism in regions pertaining to the default mode network. Nevertheless, the cognitive reserve hypothesis does not exclude that a positive relationship can be found in a different set of brain regions (Steffener and Stern, 2012).

Methods

Participants

The study included 74 healthy elderly participants (47 women) pooled across three research centers (Liège, Belgium, n = 21; Caen, France, n = 25; Mainz, Germany, n = 28). Age ranged from 60 to 86 years old (M = 70.6 ± 7.2) and did not differ between centers (F(2, 71) = 1.28, p > .28). Participants showed normal performance in a battery of neuropsychological tests, had no clinical evidence of psychiatric or neurological disorders, were free of medication that could affect cognitive functioning, and reported being in good health. Structural neuroimaging showed mild atrophy and leukoaraiosis consistent with aging. All participants gave informed consent to cognitive and neuroimaging assessments, which were approved by the local ethics committee in each center.

Materials and procedure

Cognitive reserve

Education and vocabulary abilities were used as proxies of cognitive reserve. Education was measured as the total number of years of education that the participant completed. Vocabulary abilities were measured with the French version of the Mill Hill vocabulary test (part B, Deltour, 1993) in French-speaking participants (Liège and Caen centers) and with the Wortschatztest (Schmidt and Metzler, 1992) in German-speaking participants (Mainz center). Education

and vocabulary measures were each converted into z-scores using the mean and standard deviation of each center as reference in order to reflect inter-individual variability. Both z-scores were combined into a mean z-score to best capture the contribution of the two variables to cognitive reserve (Stern, 2002, 2009).

Cognitive testing

Elderly participants performed within normal range in a battery of neuropsychological tests including assessments of episodic memory and executive functions. We considered inter-individual variability in memory ability and in executive and attention function, as these functions are the main domains of age-related cognitive changes (Craik and Salthouse, 2000; Park and Schwartz, 2000). Individual differences in memory were indexed by the participants' z-score in verbal learning performance (word-pair learning in Liège (Bastin et al., 2012), Encoding Storage Retrieval ESR test (Eustache et al., 1998) in Caen and Verbal Learning and Memory Test VLMT (Helmstaedter et al., 2001) in Mainz). As for variability in the general domain of executive function and attention, a composite z-score was calculated including forward and backward digit span, and Trail Making Test performance in Caen and Mainz centers, and performance in the Reading span test (Desmette et al., 1995), the Hayling test (Andrés and Van der Linden, 2000) and the attention subtest from the Mattis DRS (Mattis, 1973) in Liège center.

Resting-state neuroimaging

Cerebral metabolism. In each center, brain metabolic activity was measured during quiet wakefulness with eyes closed and ears unplugged after intravenous injection of an average of 180 MBq of 18F-2-fluoro-2-deoxy-D-glucose (FDG). In Liège, PET images were acquired on a Siemens/CTI (Knoxville, TN) ECAT HR+ scanner (3D mode; 15.2 cm axial field of view; 4.4 mm axial resolution). In Caen, PET data were acquired on a Discovery RX VCT 64 PET-CT device (General Electric Healthcare) (15.7 cm field of view; 4.9 mm axial resolution). In Mainz, PET data were acquired using a Philips Gemini TF PET/CT-Scanner (Philips Medical Systems, Eindhoven, NL) (18 cm axial field of view; 4.7 mm axial resolution).

Images of the tracer distribution in the brain were used for analysis; the minimum scan starting time was 30 min after tracer injection. Scan duration was 10 min in Caen center and 20 min in Liège and Mainz centers. Images were reconstructed using the filtered backprojection method (Liège), 3D ordered-subset expectation maximization (3D-OSEM) (Mainz) or 3D-RAMLA algorithm (Caen) including corrections for measured attenuation, random effects and scatter using the standard software supplied by the various scanner manufacturers.

Magnetic resonance imaging. MRI was performed within three months of the PET exam. Subjects were equipped with earplugs and their heads were stabilized with foam pads to minimize head motion. In all participants, a high-resolution T1-weighted anatomical image was acquired. In Liège center, data were acquired on a 3 T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil [TR 7.92 ms, TE 2.4 ms, FA 15°, 176 sagittal slices, FoV 256 × 224 mm², slice thickness 1 mm, matrix size 256 × 224 (Deichmann et al., 2004)]. In Mainz, acquisition was performed on a 3 T Siemens Trio MRI scanner [TR 1170 ms, TE 2.38 ms, FA 15, 244 sagittal slices, FoV 256 × 210 mm^2, slice thickness 0.82 mm, matrix size 256 × 256]. In Caen, images were acquired on a Philips (Eindhoven, The Netherlands) Achieva 3 T scanner using a 3D fast field echo sequence [TR 20 ms, TE 4.6 ms, FA 20°, 170 sagittal slices, FoV 256 × 256 mm^2, slice thickness 1 mm, matrix size 256 × 256].

In a subset of 41 healthy elderly participants (Liège, n = 21; Caen, n = 20), resting-state fMRI time series were acquired. During this acquisition, which was the last one of the MRI scanning session, subjects were asked

to relax, lie still in the scanner and keep their eyes closed while not falling asleep. In Liège, multislice T2*-weighted functional images were acquired with a gradient-echo EPI sequence using axial slice orientation and covering the whole brain [TR 2130 ms, TE 40 ms, FA 90°, 32 slices, slice thickness 3 mm, gap 30%, matrix size 64×64, FoV 220×220 mm², in-plane resolution 3.4×3.4 mm², 250 volumes]. The initial three volumes were discarded to avoid T1 saturation effects. In Caen, resting-state functional acquisitions were obtained using an interleaved 2D T2*SENSE (SENSitivity Encoding) EPI sequence designed to reduce geometrical distortions by using parallel imaging, shorter echo time, and smaller voxels [SENSE factor = 2, TR 2382 ms, TE 30 ms, FA 80 , 42 slices, slice thickness 2.8 mm, no gap, matrix size 80×80, FoV 224×224 mm², in-plane resolution 2.8×2.8 mm², 280 volumes]. The first six volumes were discarded due to saturation effects.

Functional cerebral image preprocessing and analyses

Image preprocessing

Preprocessing of PET data was performed with SPM5 (Wellcome Department of Cognitive Neurology, London, UK). For each participant, the structural MRI image was segmented by means of the VBM5 toolbox (Structural Brain Mapping Group, Christian Gaser, Department of Psychiatry, University of Jena, Germany) and normalized to the MNI stereotactic space. A mean image of all participants' normalized MRI image and a mean image of all participants' normalized gray matter segmented image were computed (to be used as masks in the statistical analysis). Each subject's PET image was coregistered to the corresponding MRI image and normalized by applying parameters from the spatial normalization of the MRI data. All normalized PET images were used to compute a mean PET image. Mean whole-brain and gray matter MRI volumes were then resliced to the mean PET image space. In order to control for individual variation in global ^{18}FDG uptake, each normalized PET image was divided by the values extracted from a region of interest in the pons. Then the resulting individual PET images were divided by the mean of all PET images from the corresponding center to account for inter-center effects. Finally, the images were smoothed with an isotropic 12 mm full-width half-maximum (FWHM) Gaussian kernel.

Preprocessing of fMRI data was performed with SPM5. After slice timing correction, each subject's functional images were spatially realigned to the mean functional image using rigid body transformations. The mean functional image was coregistered to the anatomical image, and then spatially normalized to the MNI space using the same normalization parameters as applied to the structural MRI (see above). The normalized images were smoothed with an isotropic 6 mm FWHM Gaussian kernel. Data were temporally band-passed filtered (0.008–0.1 Hz) using a Gaussian temporal filter.

Statistical analyses

The main statistical analyses involving cognitive reserve concerned FDG-PET images. They consisted of a multiple regression where individual PET images were entered as dependent variable, the cognitive reserve index (mean education and vocabulary z-score) as covariate of interest, and center and age as nuisance variables. In order to isolate the metabolic correlates of cognitive reserve, linear contrasts were used to identify the brain regions where metabolism was either positively or negatively correlated with the level of cognitive reserve across participants. Given the exploratory nature of the analysis, the height threshold was set at $p < .10$ FWE-corrected for multiple comparisons with an extent threshold of 30 contiguous voxels (i.e., superior to twice the FWHM).

In order to identify the resting-state network to which the regions observed in the above-mentioned correlation analyses belonged, resting-state fMRI images were submitted to two distinct connectivity analyses. First, the peak coordinates of regions showing significant correlations with the level of cognitive reserve were entered in

seed-voxel analyses in SPM. The seed-voxel analysis was done as reported elsewhere (Boly et al., 2009; Fox et al., 2005). In each subject, the first eigenvariate of the time courses of voxels in 8-mm spherical ROIs centered on each seed-region coordinates was extracted. Similar time course extractions were performed for white matter (MNI coordinates: $x = -22$, $y = 16$, $z = 32$) and CSF in a ventricle ($x = -6$, $y = 20$, $z = 10$). The two latter time courses and the global brain signal changes across time, then their derivatives as well as the movement parameters were used as nuisance covariates in a statistical model. Serial correlations were then estimated with a restricted maximum likelihood algorithm using an intrinsic autoregressive model during parameter estimations. The effects of interest were tested by linear contrasts, generating statistical parametric maps [SPM(T)] in each subject. A contrast image was computed for each subject and for each seed-region, identifying regions correlating positively with the selected seed-region after removal of the sources of spurious variance cited above.

Individual summary statistics images were submitted to the second-level analysis corresponding to random effects model in which subjects are considered as random variables and the center as a between-subject factor. This analysis allowed identifying regions functionally connected to each seed at a statistical threshold of $p < .05$ FWE-corrected for multiple comparisons at the voxel level.

Second, preprocessed resting-state fMRI images were also submitted to an Independent Component Analysis (ICA) with the NetBrainWork toolbox (Vincent Perlbarg, Inserm U678, UMRS 678 PARIS, http://sites.google.com/site/netbrainwork). In order to detect functional networks at the group level, a spatial ICA was applied to individual functional images with the maximum number of components set at 40, and then hierarchical clustering was used to gather similar components across subjects. In order to find the independent component that most closely matched the regions showing metabolic activity correlated to cognitive reserve and their seed-related network, goodness of fit was measured as the differences between the average z-score of voxels from the seed-related network outside the components and the average z-score of voxels inside the components (Greicius et al., 2004). These components were compared to descriptions of resting-state networks previously found in normal aging in order to identify the functional networks to which they correspond. For confirmation purposes, this was complemented by a template-matching procedure where components were compared to templates independently obtained with NetBrainWork (Vincent Perlbarg, personal communication), with the caveat that these templates come from young adults. The 12 templates represented respectively auditory, basal ganglia, default mode, executive control, limbic, motor, salience, visual/lingual, visual/primary, dorsal attention, left and right ventral attention networks.

Voxel-based morphometry

To assess whether the relationship between regional metabolism and cognitive reserve could be accounted for by atrophy, the 74 participants' images of gray matter density obtained from the processing of anatomical images with VBM5 were smoothed (12 mm FWHM) and introduced into a multiple regression design in SPM in order to examine the correlation between regional gray matter density and level of cognitive reserve. Intracranial volume, center and age served as nuisance variable. The statistical threshold was set at $p < .10$ FWE-corrected for multiple comparisons at the voxel level.

Results

Correlation between cerebral metabolism and cognitive reserve

At the exploratory statistical threshold of p<.10 FWE-corrected and extent threshold of 30 voxels, there was no positive correlation between
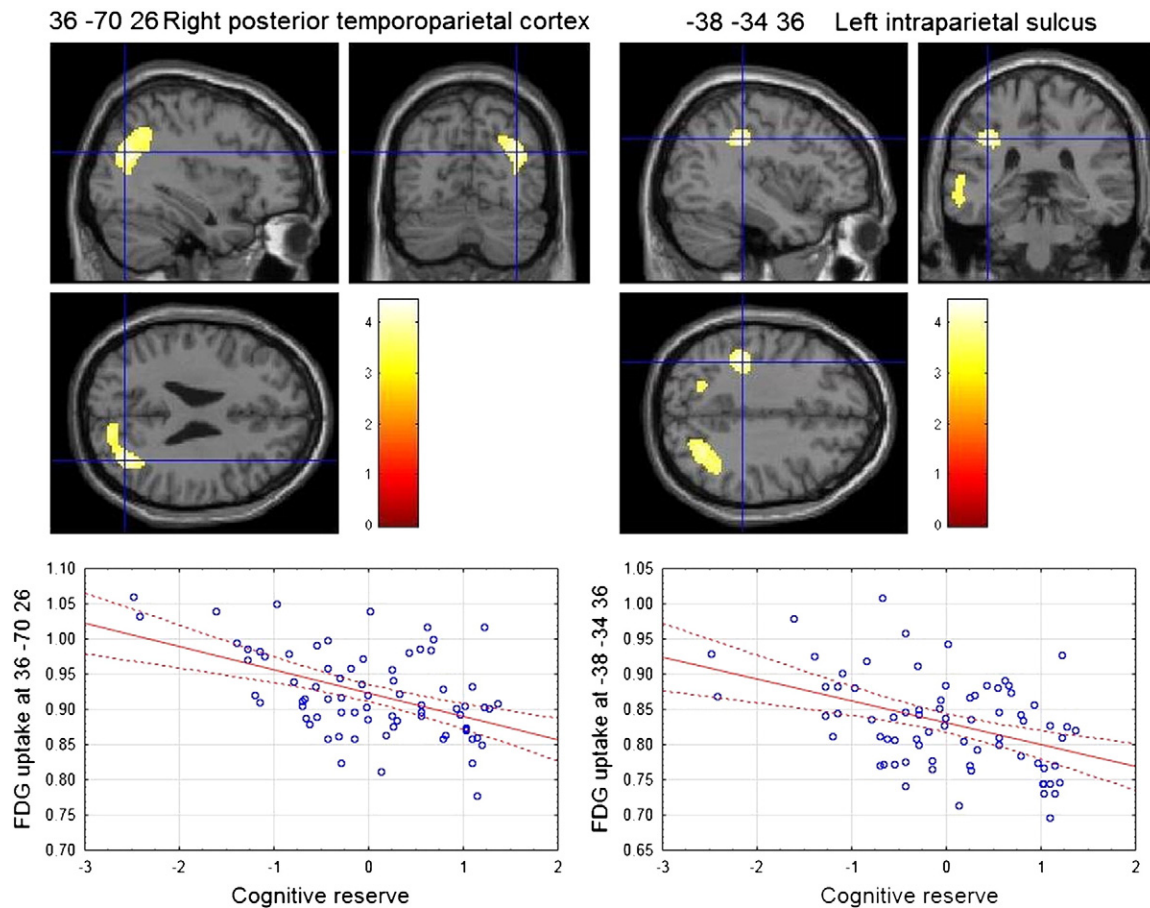
Fig. 1. SPM results of the negative correlation between cerebral metabolism and level of cognitive reserve (mean education and vocabulary z-score), $p<.10$ FWE-corrected for multiple comparisons. Significantly correlated clusters are projected on a canonical T1-weigthed MRI. Scatter plots represent FDG-uptake values in each cluster against level of cognitive reserve.

metabolism and level of cognitive reserve in this multi-center study. In contrast, negative correlations were observed in the right posterior temporoparietal cortex [right TPC, MNI coordinates: $x=36$, $y=-70$, $z=26$, $T=4.38$, $k=1243$] and the left anterior intraparietal sulcus [left IPS, MNI coordinates: $x=-38$, $y=-34$, $z=36$, $T=4.44$, $k=261$] (Fig. 1). At a more liberal threshold of $p<.001$ uncorrected, there were also negative correlations in the precuneus, the left middle temporal gyrus and the occipital cortex (see supplemental Fig. S1).

As indexes of cognitive reserve have been related to the level of cognitive performance in older adults, in particular in the domain of memory and executive function (Manly et al., 2005) and given that the neural efficiency hypothesis relates decreased cerebral activity to better cognitive performance (e.g., Ruff et al., 2003), we further explored the relationships between the neural correlates of cognitive reserve and cognitive performance. In the current sample, participants with higher level of education and vocabulary had higher memory abilities (Bravais–Pearson correlation between cognitive reserve and memory z-score, $r=.35$, $p<.05$) and also higher or a trend for higher executive/attention function (correlation between cognitive reserve and composite executive/attention z-score, Liège: $r=.50$, $p<.05$, Caen-Mainz, $r=.23$, $p<.077$). Thus, we performed two additional correlational analyses by including the memory z-score and the composite executive/attention z-score respectively as confounding variables in the design matrix in order to check whether the neural correlates of cognitive reserve are independent or not of memory and executive/attention abilities. The results showed that metabolic activity in the right posterior temporoparietal cortex and the left anterior intraparietal sulcus remained correlated with the level of cognitive reserve when executive/attention inter-individual variability was controlled [right TPC, $x=36$, $y=-68$, $z=26$, $T=4.38$, $k=1475$,

p FWE-corrected at voxel level$<.054$; left IPS, $x=-38$, $y=-34$, $z=36$, $T=4.19$, $k=181$, p FWE-corrected at voxel level$<.094$], but was weaker when memory inter-individual variability was controlled [right TPC, $x=36$, $y=-70$, $z=26$, $T=3.82$, $k=442$; left IPS, $x=-38$, $y=-36$, $z=36$, $T=4.12$, $k=124$, p uncorrected at voxel level$<.001$].

Furthermore, a stepwise forward regression analyses examined whether cognitive performance (respectively, memory score and composite executive/attention score) can be predicted on the basis of cognitive reserve and metabolic activity in right TPC and left IPS. Memory scores were significantly positively associated with cognitive reserve (beta$=.29$) and negatively associated with metabolism in the right TPC (beta$=-.14$, $R^2=.14$, $p<.01$). The composite executive/attention score was mainly associated with cognitive reserve (beta$=.30$, $R^2=.09$, $p<.01$).

Resting-state fMRI networks

As resting-state fMRI data were acquired in a subset of participants, we first checked that the negative correlation between cognitive reserve and metabolism in the right TPC and left IPS could still be observed in this reduced sample. This was indeed the case, although the smaller sample size reduced the statistical significance. There was a negative correlation in the right posterior temporoparietal cortex [$x=32$, $y=-72$, $z=26$, $T=3.66$, $k=166$, p uncorrected$<.001$] and the left IPS [$x=-42$, $y=-30$, $z=40$, $T=3.62$, $k=42$, p uncorrected$<.001$].

Seed-voxel analysis

This analysis aimed at identifying regions that are functionally connected to the right TPC and the left IPS respectively. First of all,

there was no effect of center (Liège > Caen or Caen > Liège), so we explored voxels where BOLD signal covaried with each seed activity across time in participants from both centers via a null conjunction analysis (Table 1). The results indicated that the activity in the right temporoparietal cortex covaried with activity in a large cluster extending medially from the right TPC and joining the contralateral area, as well as with the posterior cingulate cortex. As for the left anterior intraparietal sulcus, its activity covaried with that of the right intraparietal sulcus, the precuneus, the precentral gyrus and the postcentral gyrus bilaterally, as well as the middle cingulate cortex.

It should be noted that the seed-voxel networks were very similar and slightly larger when the networks were identified by means of a one-sample *t*-test including the center as a covariate (data not shown). Thus, the right TPC seed-related network extended to the contralateral TPC and included the posterior cingulate cortex. The left IPS activity covaried with that in the right IPS, precentral gyrus, postcentral gyrus and frontal eye field bilaterally, and middle cingulate cortex.

Independent Component Analysis

This analysis evidenced 19 independent components which covered all gray matter areas and corresponded to resting-state networks across participants. Among these components, the best fit to the cluster in the right posterior temporoparietal cortex (goodness of fit: 1.70) and its seed-related network (goodness of fit: 3.42) was a component that encompassed the posterior cingulate cortex/precuneus, the posterior temporoparietal cortex, the parahippocampal cortex and bilateral inferior parietal lobules (Fig. 2 A). This component is close to the posterior default mode network previously identified in older adults (Damoiseaux et al., 2008). The next best fit (2.78) was a component that may correspond to the anterior default mode network as identified by Damoiseaux et al. (2008) and which included the medial prefrontal cortex, the posterior cingulate cortex and posterior parietal cortices. This was subsequently confirmed by the template-matching procedure which showed high fit of these components to the default mode network (Fig. 2 B, see Supplemental Fig. S2 for measures of goodness of fit). As for the cluster in the left anterior intraparietal sulcus and its seed-related network, they best fitted one bilateral component comprising the intraparietal sulcus extending to the precuneus (goodness of fit: cluster = 1.60; network = 1.44, Fig. 3 A). The intraparietal sulcus is a crucial part of the dorsal attention network, which supports goal-directed attention (Corbetta and Shulman,
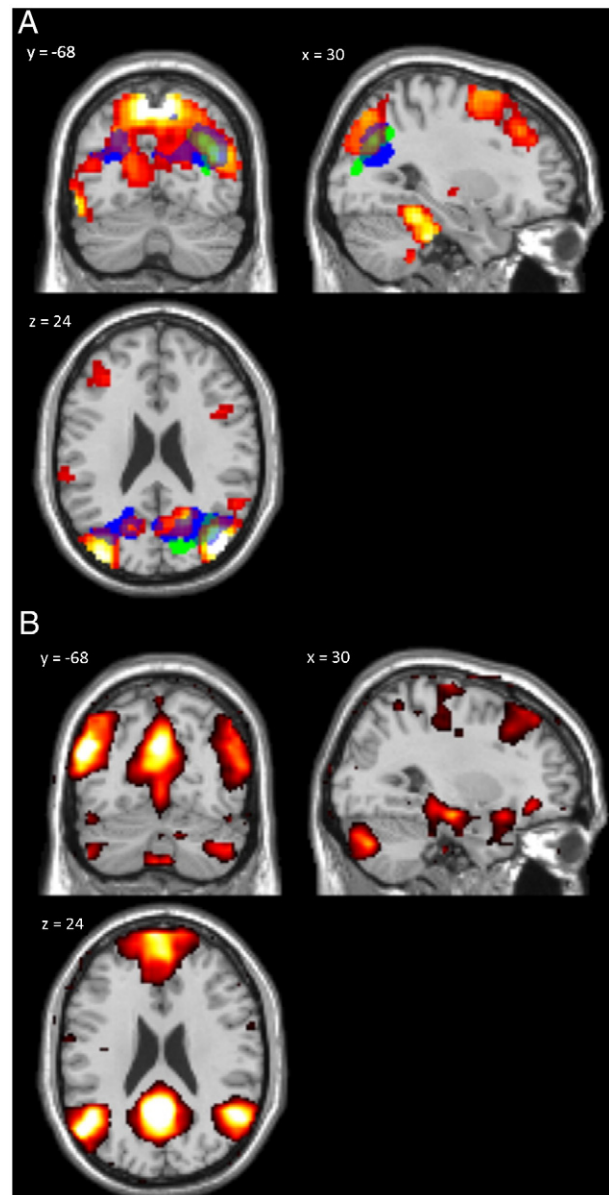
Fig. 2. Results of the Independent Component Analysis (NetBrainWork) at the group level. A. Component (hot colors) that best fitted with the right posterior temporoparietal region whose metabolism is negatively correlated with level of cognitive reserve (green) and with the corresponding seed-related network (blue). B. NetBrainWork template for the default mode network.

2002; Fox et al., 2006) and is affected by aging (Andrews-Hanna et al., 2007). The template-matching provided two best-fits for this component: the limbic template, which includes the precuneus as the independent component, and the dorsal attention network (Fig. 3 B), confirming that the latter is a good candidate (Supplemental Fig. S2).

Voxel-based morphometry

There was no correlation between gray matter density and cognitive reserve at $p < .10$ FWE-corrected. At a more liberal threshold of $p < .001$ uncorrected for multiple comparisons, there was a negative correlation in the left precental gyrus [$x = -45$, $y = -17$, $z = 45$, $T = 3.66$, $k = 1842$]. Consequently, the results of the metabolic correlational analysis were not driven by variation in gray matter density.

Table 1
Resting-state fMRI: results of the seed-voxel analyses showing regions where BOLD signal covaries with activity in the right posterior temporoparietal cortex and the left anterior intraparietal sulcus.

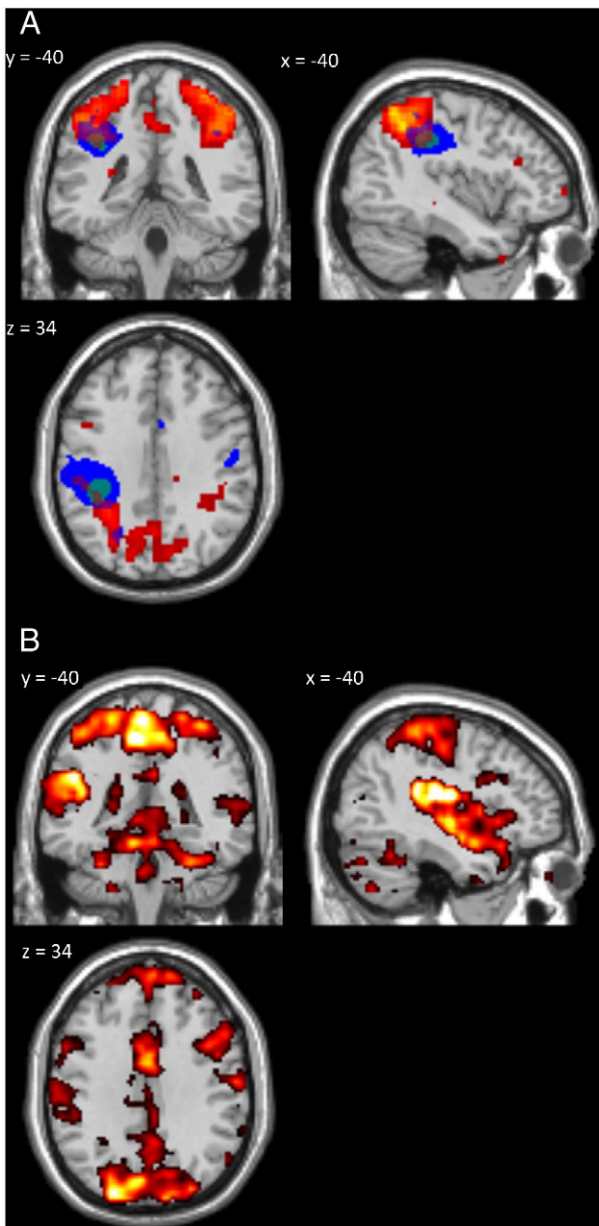| Side	Anatomical region	MNI coordinates			z	k
		x	y	z		
Seed: right posterior temporoparietal cortex [36 −70 26]						
R	Temporoparietal cortex	36	−72	26	inf	2438
L	Angular gyrus	−32	−74	*30*	*6.91*	
L	Posterior cingulate cortex	−8	−64	50	4.85	3
Seed: left anterior intraparietal sulcus [−38 34 36]						
L	Intraparietal sulcus	−38	−36	36	inf	2317
L	Postcentral gyrus	−58	−26	*44*	*6.40*	
L	Precentral gyrus	−44	−20	*38*	*7.45*	
R	Intraparietal sulcus	40	−34	46	5.44	34
R	Postcentral gyrus	54	−12	32	6.25	88
R	Precentral gyrus	56	−24	44	6.06	43
R	Precuneus	28	−62	40	6.34	117
R	Middle cingulate	4	10	36	5.60	17

Results at $p < 0.05$ FWE-corrected for multiple comparisons at the voxel level. L/R = left/right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). k = cluster size. In italics are sub-peaks of the above-mentioned cluster.

Fig. 3. Results of the Independent Component Analysis (NetBrainWork) at the group level. A. Component (hot colors) that best fitted with the left anterior intraparietal sulcus whose metabolism is negatively correlated with level of cognitive reserve (green) and with the corresponding seed-related network (blue). B. NetBrainWork template for the dorsal attention network.

Discussion

This study examined whether cognitive reserve relates to resting-state cerebral metabolism in aging. Previous studies failed to identify any such association, but had very small sample sizes (Perneczky et al., 2006; Scarmeas et al., 2003a). In the current multi-center study, a large group of healthy older participants were scanned with FDG-PET during quiet wakefulness with eyes closed. The novelty of this work consisted in considering resting-state metabolic correlates of cognitive reserve at the light of current knowledge on functional networks (Fox and Raichle, 2007). We anticipated an association between cognitive reserve and activity in regions within the default mode network because one earlier study focusing on task-related deactivation of the default mode network suggested that cognitive reserve modulates the extent to which older participants deactivate the default mode regions in order to engage resources

in the service of the task (Bosch et al., 2010). In the current study, the main finding was that higher education and vocabulary abilities were related to lower metabolic activity in the right posterior temporoparietal cortex and the left anterior intraparietal sulcus. Functional connectivity analyses of resting-state fMRI data showed that these regions belong respectively to the default mode network and the dorsal attention network. Moreover, there was some evidence of better memory functioning in individuals with high cognitive reserve and lower cerebral metabolism in the posterior temporoparietal cortex.

The default mode network comprises two distinct subsystems that interact with a midline core (Andrews-Hanna et al., 2010; Buckner et al., 2008). The medial temporal lobe (MTL) subsystem includes the hippocampus, the parahippocampal cortex, the ventral medial prefrontal cortex, the posterior inferior parietal lobule and the retrosplenial cortex. This subsystem preferentially activates when people remember events they experienced in the past, but also when they imagine what they will do in the future (Hassabis and Maguire, 2007; Schacter et al., 2007). The second subsystem, the dorsomedial prefrontal subsystem, includes the dorsomedial prefrontal cortex, the temporoparietal junction, the lateral temporal cortex and the temporal pole. It is mainly recruited when people reflect about themselves or infer the mental states of other people (D'Argembeau et al., 2012; Saxe and Kanwisher, 2003). Both subsystems are strongly related to a core set of hubs, the posterior cingulate cortex and the anterior medial prefrontal cortex, the widespread connectivity of which supports integration across subsystems during internal mentation (Buckner et al., 2009). The right posterior temporoparietal region that correlated here with the level of cognitive reserve is very close to the coordinates of the posterior parietal region that Andrews-Hanna et al. (Andrews-Hanna et al., 2010) found to be part of the MTL subsystem. The seed-voxel analysis further indicates that the right TPC is functionally connected to posterior midline regions, including the posterior cingulate cortex, from the midline core.

Regarding attention networks, a distinction is made between the dorsal attention network, involving the intraparietal sulcus and superior frontal regions, which supports goal-directed attention, and the ventral attention network, comprising the supramarginal gyrus and the ventral orbitofrontal cortex, which is activated when a salient, unexpected stimulus catches attention (Corbetta and Shulman, 2002). Spontaneous activity in the dorsal attention network is negatively correlated with activity in the default mode network (Fox et al., 2005), reflecting the opposition between attention to the external world and mental processes oriented to oneself. The anterior intraparietal sulcus that correlated with cognitive reserve in the current study has also been found to be activated across different executive tasks (Collette et al., 2005) and in verbal and visual short-term memory (Majerus et al., 2010, 2012). It appears to be a central region of the dorsal attention network and may have the function of an attentional pointer which points to representations to be maintained in the focus of attention (Cowan, 2011). In the current study, the anterior IPS is functionally connected to precentral and postcentral regions, that also form part of the dorsal attention network (Corbetta and Shulman, 2002; Fox et al., 2006).

The negative association between cognitive reserve and resting-state metabolism of regions within the default mode and dorsal attention networks could be interpreted by considering rest as involving cognitively active states. Indeed, when resting in the scanner with eyes closed, healthy participants were found to switch from internally-oriented thoughts to attention to external stimulation on average every 20 s (Vanhaudenhuyse et al., 2011). Importantly, the intensity of internal and external awareness was related to the activation of regions within the default mode and dorsal attention networks respectively. This alternation of internally- and externally-oriented thoughts thus corresponds to the observation that, at rest, the brain activity is characterized by spontaneous low-frequency fluctuations that are anti-correlated in the dorsal attention network and the default mode network (Fox et al., 2005). Whereas our resting-state fMRI data allowed evidencing, in the sample,

the involvement of distinct functional networks underlying respectively internal mentation and goal-directed attention, the PET data represent the amplitude of metabolic activity in specific regions within each network over a 10 to 20-min period. The metabolic correlations thus point to key regions where the level of activity covaries across participants with their index of cognitive reserve. Consistently with previous task-related activation studies showing that higher cognitive reserve is related to lower (and thus more efficient) cerebral functioning (Bartrés-Faz et al., 2009; Bosch et al., 2010; Solé-Padullés et al., 2009; Steffener et al., 2011), the current findings suggest that individuals with higher education and vocabulary levels need less activity in specific brain regions of functional networks allowing mental processes oriented to the self and attention to the external world during rest. Such interpretation in terms of neural efficiency was reinforced by the results of the regression analysis showing that decreased metabolic activity in the TPC was associated with better memory performance.

An alternative interpretation refers to the notion of a generic cognitive reserve network. More precisely, Stern et al. (2008) identified similar task-related activations associated with proxy measures of cognitive reserve across two tasks with distinct cognitive demands. They speculated that cognitive reserve may have a specific neural substrate, such that people with high level of cognitive reserve would be able to engage this network in the service of any task. In other words, there would be a cognitive reserve network observed for any type of cognitive domain and which would be associated to the overall ability to cope with age-related changes or brain pathology in general. As the regions found to correlate with cognitive reserve independently of the task were in the prefrontal cortex, Stern (2009) suggested that the generic cognitive reserve network may be related to control processes. In the current study, decreased activity in specific posterior parietal regions was associated with higher education and verbal intelligence and with better memory performance. The implication of the intraparietal sulcus from the dorsal attentional network is consistent with the idea that the generic cognitive reserve network would be associated with control processes (Stern, 2009). However, the finding of more efficient activity of a region from the default mode network in relation to cognitive reserve opens the possibility that the generic cognitive reserve network also provides efficient functioning of a variety of internally directed cognitive processes. More research is needed in order to explore the hypothesis that the generic cognitive reserve network refers actually to the efficient interaction between several functional networks. In particular, a further step would be to examine how cognitive reserve influences the functional coupling of the anti-correlated default mode and dorsal attention networks during rest.

As the current study was exploratory, we observed negative correlations between cerebral metabolism and cognitive reserve at a statistical threshold that reduces the risk of false negatives (p<.10), but still corrected for multiple comparisons. Future work should replicate these findings and further examine how cognitive reserve is implemented in terms of interactions between resting-state neural networks. Considering previous literature on the neural expression of cognitive reserve, it is very likely that positive and negative correlations exist in different parts of the brain (Steffener and Stern, 2012) and that they would be more or less put forward depending on the method used for measuring cognitive reserve and for analyzing neuroimaging data (such as partial volume effect correction or the scaling method that has been shown to have a strong impact on metabolism measurement (Mevel et al., 2007)).

Finally, given that we observed a negative correlation between measures of cognitive reserve and metabolism in the temporoparietal cortex, as did previous studies on Alzheimer's disease (Alexander et al., 1997; Hanyu et al., 2008; Kemppainen et al., 2008; Perneczky et al., 2006; Scarmeas et al., 2003a), one needs to consider the possibility that the decreased metabolic activity observed in healthy older participants with more education and greater vocabulary abilities may reflect the presence of more cerebral pathology than in participants with less education and poorer vocabulary performance. Several points argue against this interpretation. First, the characteristics of the current sample do not indicate that individuals with high cognitive reserve were closer to dementia than others. Indeed, there was no sign of cognitive decline in any participant. Additionally, considering that age is a risk factor for dementia, there was no correlation between age and the estimate of cognitive reserve ($r = -.07$, $p > .54$). So high and low cognitive reserve individuals did not differ in terms of age. Moreover, participants with more education and greater vocabulary abilities had better memory and executive performance. Second, decreased metabolism in the temporoparietal cortex was associated with better memory performance. Therefore, it seems unlikely that in a sample of healthy older participants of similar age, those who have higher level of education and vocabulary as well as better cognitive performance in association with reduced temporoparietal metabolism actually have more brain pathology. Nevertheless, the hypothesis of an interaction between cognitive reserve and decreased regional brain metabolism for anticipating cognitive deterioration in elderly individuals could only have been ruled out by longitudinal follow-up assessment of cognitive functioning of the participants.

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