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

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Corresponding Author: Dr. Christine Bastin,

Corresponding Author's Institution: University of Liège

First Author: Christine Bastin

Order of Authors: Christine Bastin; Igor Yakushev; Mohamed Ali Bahri; Andreas Fellgiebel; Francis Eustache; Brigitte Landeau; Armin Scheurich; Dorothée Feyers; Fabienne Collette; Gael Chételat; Eric Salmon

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 elders 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 multi-centre 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.

**1. Cover Letter**

Liège, the 11th of June 2012

Ref.: NIMG-12-761

Dear Pr. Lustig,

Please find attached the revision of our manuscript entitled “Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging” that we submit for publication in NeuroImage.

We thank you for giving us the opportunity to revise our manuscript. We are also grateful to the Reviewers for their useful suggestions that have all been taken into account in this revised version. Changes to the text appear in bold in the manuscript.

Sincerely yours,

Christine Bastin and co-authors

Cyclotron Research Centre
University of Liège
Allée du 6 Août, 8, B30
B-4000 Liège
Belgium

Tel.: +32 4 366 23 27
Fax : +32 4 366 29 46
http://www.cyclotron.ulg.ac.be/

# Highlights

- Variability in cerebral metabolism is related to cognitive reserve in older people.
- The correlated regions were part of the default mode and dorsal attention networks.
- Higher cognitive reserve might refer to optimized resting-state brain functioning.

Revision of manuscript NIMG-12-761

Response to Reviews

Dear Pr. Lustig, dear Reviewers,

We thank you for giving us the opportunity to revise our manuscript. We are also grateful to the Reviewers for their useful suggestions that have all been taken into account in this revised version. Changes to the text appear in bold in the manuscript. Please find below detailed answers to each comment.

Reviewer #1

1. Reviewer 1 underlines the lack of clarity of the introduction with respect to the meaning of cerebral differences associated with cognitive reserve. We agree that decreased metabolic activity is not necessarily a positive outcome and that increased and decreased fMRI activity in aging may refer to beneficial or detrimental mechanisms depending on how this correlates with performance. We have rewritten most parts of the introduction in order to clarify the different concepts from the cognitive reserve hypothesis and we have enriched them with additional references and examples.

- More specifically, we have provided more arguments in favor of situations where decreased cerebral activity is beneficial. This is the case when, in healthy populations, cognitive reserve has been examined in reference to task difficulty or cognitive performance. “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 & Stern, 2012)” (p. 7). In healthy aging, fMRI studies showed that cognitive reserve was associated with decreased cerebral activity in the context of similar cognitive performance (p. 7). Moreover, studies on the neural basis of intelligence (which is included in indexes of cognitive reserve) demonstrated that brighter individuals show less cerebral activity and perform better in cognitive tasks than less intelligent individuals (pp. 7-8). Importantly, this was observed in a variety of cognitive tasks and with different neuroimaging methods (PET, fMRI and EEG).
In contrast, there are situations where decreased cerebral activity reflects neurodegeneration. This is the case of patients with Alzheimer’s disease. In this population, cognitive reserve has been examined in reference to dementia severity. “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, Zarahn, Anderson, Habeck, et al., 2003). 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.” (pp. 9-10).

- As suggested by Reviewer 1, we have added reference to evidence of relationship between metabolic activity and cognitive performance. More precisely, “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 on neuropsychological tests. Depending on the nature of the task, complex patterns of increased and decreased cerebral activity have been associated to 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 & Park, 2010)" (pp. 4-5).

- Although not enough studies have been conducted to provide a clear picture over a large variety of tasks, it seems that patterns of increased and decreased cerebral activity in relation to cognitive reserve appear in distinct regions and are specific to the task at hand. With regard to neural compensation, which takes the form of increased activity in relation to cognitive reserve, we have provided some examples: "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, Zarahn, Anderson, Hilton, et al., 2003; Springer, McIntosh, Winocur, & Grady, 2005; Steffener, Reuben, Rakitin, & Stern, 2011; Stern et al., 2005). Using $H_2{}^{15}O$-PET, Scarmeas et al. (2003) 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" (p. 6). With regard to neural efficiency, decreased activity is usually observed in regions typically associated with the task: "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" (p. 7). Thus, "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 & 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)" (p. 8).

2. Reviewer 1 raises also the issue of the interpretation of the current findings of a negative correlation between cognitive reserve measures and cerebral metabolism either in terms of neural efficiency or in terms of degree of pathology. As suggested by the Reviewer, in our control populations where care was taken to exclude as much as possible pathology, the association between decreased metabolism and better cognitive performance support an interpretation in terms of neural efficiency. In the Results section, we have specified: “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” (pp. 17-18). Rather than correlating cognitive performance with metabolic activity by separating participants in high and low cognitive reserve subgroups, we have preferred to retain information on individual variability in cognitive reserve by using a correlational approach. Therefore, “a stepwise forward regression analyses examined whether cognitive performance (respectively, memory sore 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, $p < .01$)” (p. 18). We have thus added in the Discussion: “there was some evidence of better memory functioning in individuals with high cognitive reserve and lower cerebral metabolism in the posterior temporoparietal cortex” (p. 21). An “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” (p. 24).

3. Reviewer 1 was concerned about the possibility that templates provided by NetBrainWork do not correspond to typical networks described in the resting-state literature, in particular the ventral and dorsal frontoparietal networks described by Corbetta and Shulman. In order to check whether the NetBrainWork templates represented most typical networks, we have contacted Vincent Perlbarg, the NetBrainWork developer, who provided us with updated and clearly identified templates which cover the typical resting-state networks. Moreover, we have tried to clarify the way we have proceeded and modified the text in the following way: “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, Srivastava, Reiss, & Menon, 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” (pp. 16-17). As the results of the template-matching procedure were slightly modified when using the updated templates, we have changed the text in the results section: “This analysis evidenced 19 independent components

which covered all grey 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 (Figure 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 (Figure 2 B, see Supplemental Figure 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, Figure 3 A). The intraparietal sulcus is a crucial part of the dorsal attention network, which supports goal-directed attention (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 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 (Figure 3 B), confirming that the latter is a good candidate (Supplemental Figure S2)" (p. 20).

4. Reviewer 1 understood that we argued that more efficient functioning of the dorsal attentional network may correspond to a generic cognitive reserve network, as suggested by Stern (2009). Actually, we did not wish to state that functional connectivity is more efficient, as we have no result addressing this hypothesis. Rather, we have shown that decreased activity in some specific regions (that we identified as part of the default mode network and dorsal attention networks) was associated with higher education and verbal intelligence and with better memory performance. Moreover, in line with the Reviewer's suggestion, we also wanted to put forward the idea that a generic cognitive reserve may not only involve controlled processes, but also a variety of internally-directed mental processes. This hypothesis should however be explored in future work. We have rephrased the paragraph to clarify this point (pp. 24-25).

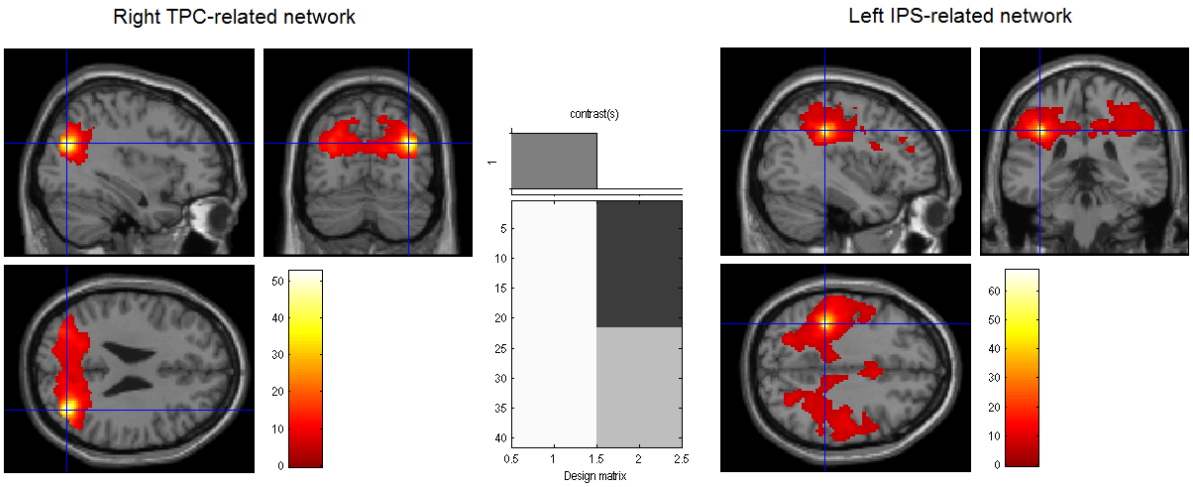
5. Reviewer 1 wonders why FDG-PET was chosen over task-related fMRI to study cognitive reserve. We used FDG-PET as "in comparison to fMRI, FDG-PET measures neuronal activity independently of vascular coupling and can be used to explore the baseline integrity of neuronal networks (Lee et al., 2008; Rocher, Chapon, Blaizot, Baron, & Chavoix, 2003)"(p. 9).

6. Reviewer 1 asked whether behavioral and neuroimaging protocols were the same across centers, other than those differences indicated in the manuscript. We have indeed described all the differences in the manuscript.

7. Reviewer 1 notices that statistical analyses of PET data and resting-state fMRI data were conducted by considering the potential confound of centers slightly differently. Indeed, in the analyses of PET data, we compute correlations between the index of cognitive reserve and cerebral metabolism across all 74 participants by including center as a covariate. This approach maximizes the statistical power. When computing correlations within each center, the numbers of observations are reduced respectively to 21 (Liège center), 25 (Caen center) and 28 (Mainz center). Conjunction

analyses looking at common correlational patterns across centers yielded no significant result, possibly due to lack of power.

With regard to the functional connectivity analyses using fMRI data, we have followed the Reviewer's suggestion and have also reported the results of an analysis where center is entered as a covariate, as in the PET data analyses. With this analysis, "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 centre as a covariate. 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" (p. 19).




8. As suggested by Reviewer 1, we have now reported scanner parameters in a uniform way across centers (pp. 13-14).

9. We thank Reviewer 1 for drawing our attention to a typo in the SPM version used. Processing of PET and fMRI data were performed with SPM5 and VBM5.

10. We thank the Reviewer for pointing out the wording mistake at the beginning of the "statistical analyses" section: individual PET images were indeed entered as dependent variable. We have corrected the sentence (p. 15).

11. Reviewer 1 asks why the statistical threshold was set at $p < .001$ uncorrected with a cluster size of 30 contiguous voxels. In the previous version of the manuscript, correlational analyses wit PET data were performed by setting an uncorrected threshold $p < .001$ because of the exploratory nature of the analysis. As pointed out by Reviewer 2, a threshold corrected for multiple comparison is however more appropriate. We have therefore discussed only the regions the metabolism of which correlated with cognitive reserve at a corrected statistical threshold, which was set at an exploratory threshold of $p < .10$ FWE-corrected for multiple comparisons. We have modified the text accordingly (p. 15, 17, 25). The minimum cluster size was set at 30 voxels, so that it is superior to twice the FWHM in order to avoid casual correlation between voxels (p. 15).

12. We thank the Reviewer for identifying a mistake in the description of filtering fMRI time-series. What has actually been done is that "data were temporally band-passed filtered (0.008-0.1 Hz) using a Gaussian temporal filter" (p. 15).

13. Reviewer 1 wonders whether there is any interaction with center in the analyses of the neural correlates of cognitive reserve. There was no difference across center in the analyses of fMRI data, as indicated in the text of the manuscript. As for PET data, the results were similar when center was not entered as a covariate in the SPM regression analyses. When we computed correlations within each center, there was no significant result for any center, possibly as a result of the small number of participants (see point 7). Altogether, this suggests that center did not influence the results and that combining data from multiple centers was helpful to increase power in the statistical analyses.

14. As suggested by Reviewer 1, we have added a supplemental figure presenting goodness of fit scores in the matching procedure (Figure S2).

Reviewer #3

1. Reviewer 3 underlines the fact that the negative correlations between metabolism of specific regions and cognitive reserve were at best moderate as found at an uncorrected statistical threshold of $p < .001$. We agree with the Reviewer that correction for multiple comparisons in neuroimaging analyses is important. Therefore, we discussed only the regions the metabolism of which correlated with cognitive reserve at a corrected statistical threshold. However, as the current investigation should be considered as exploratory, we set the statistical threshold at $p < .10$ FWE-corrected for multiple comparisons with an extent threshold of 30 contiguous voxels (i.e., superior to twice the FWHM) (p. 15). The same statistical threshold was used when exploring the correlation between cognitive reserve and grey matter density (p. 17). In addition, we indicated in the discussion section that caution is needed in the interpretation of the findings and replication would allow confirming this exploratory study (p. 25).

2. Reviewer 3 wishes that other regions showing a negative correlation with cognitive reserve are presented in a Figure. We have added an illustration of these results in supplemental Figure S1.

Sincerely yours,

Christine Bastin and co-authors

Cyclotron Research Centre
University of Liège
Allée du 6 Août, 8, B30
B-4000 Liège
Belgium

Tel.: +32 4 366 23 27
Fax : +32 4 366 29 46
http://www.cyclotron.ulg.ac.be/

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

Christine Bastin[a], Igor Yakushev[b,c], Mohamed Ali Bahri[a], Andreas Fellgiebel[c], Francis Eustache[d], Brigitte Landeau[d], Armin Scheurich[b], Dorothée Feyers[a], Fabienne Collette[a], Gael Chételat[d]* & Eric Salmon[a]*

[a] Cyclotron Research Centre, University of Liège, Allée du 6 Août, 8, B30, 4000 Liège, Belgium

[b] Department of Nuclear Medicine, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

[c] Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Mainz, Germany

[d] Inserm-EPHE-Université de Caen, Boulevard Becquerel, 14000 Caen, France

* Equally contributed

Corresponding author: Christine Bastin, Cyclotron Research Center, University of Liege, Allée du 6 Août, B30, 4000 Liège, Belgium, Telephone: 32 4 366 23 27, Fax: 32 4 366 29 46, Email: Christine.Bastin@ulg.ac.be

# Highlights

- Variability in cerebral metabolism is related to cognitive reserve in older people.
- The correlated regions were part of the default mode and dorsal attention networks.
- Higher cognitive reserve might refer to optimized resting-state brain functioning.

## 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 elders 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 multi-centre 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.


Keywords: aging, cognitive reserve, FDG-PET, resting-state fMRI, memory.

1. Introduction

**Advancing age has deleterious effects on cognitive processes, more particularly memory for personally experienced recent episodes and executive control processes (Park & 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, i**nter-individual variability in task performance increases as people age (Christensen et al., 1999). Whereas some older participants perform as well as young participants on memory or executive tasks, others show significant decline (Cabeza, Anderson, Locantore, & McIntosh, 2002; Davidson & Glisky, 2002; Duarte, Ranganath, Trujillo, & Knight, 2006; Glisky, Polster, & Routhieaux, 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 on neuropsychological tests. Depending on the nature of the task, complex patterns of increased and decreased cerebral activity have been associated to 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 & 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, Schupf, Tang, & Stern, 2005; Murray et al., 2011). The idea that individuals with stimulating lifetime experience can cope better than others with age-related neural changes and thus minimize cognitive decline has been formalized in the cognitive reserve hypothesis (Steffener & Stern, 2012; Stern, 2002, 2006, 2009; Tucker & Stern, 2011). **The hypothesis is that there is inter-individual variability in the brain networks or cognitive processes that underlie the performance in 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 & Arenaza-Urquijo, 2011; Steffener & 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, Zarahn, Anderson, Hilton, et al., 2003; Springer, McIntosh, Winocur, & Grady, 2005; Steffener, Reuben, Rakitin, & Stern, 2011; Stern et al., 2005). Using $H_2{}^{15}O$-PET, Scarmeas et al. (2003) 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 & 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 were 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, Siegel, Tang, Abel, & Buchsbaum, 1992a). Brighter individuals (i.e., with higher IQ –as assessed by vocabulary scores or by a full psychometric battery such as the WAIS-R-, of note 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; Haier, Siegel, MacLachlan, et al., 1992; Neubauer, Grabner, Fink, & Neuper, 2005; Ruff, Knauff, Fangmeier, & Spreer, 2003; Vitouch, Bauer, Gittler, Leodolter, & Leodolter, 1997; Vogt, Klimesch, & Doppermayr, 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 & 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 less this network. Given that the default mode network deactivates more when demands in terms of cognitive control increase (Persson, Lustig, Nelson, & Reuter-Lorenz, 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-centre 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, Chapon, Blaizot, Baron, & Chavoix, 2003).**

Research on the influence of education, IQ and leisure activities on cerebral functioning at rest have 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, Zarahn, Anderson, Habeck, et al., 2003). 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, Zarahn, Anderson, Habeck, et al., 2003), 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 & 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 & Stern, 2012).

## 2. Methods

### 2.1. Participants

The study included 74 healthy elderly participants (47 women) pooled across three research centres (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 centres ($F(2, 71) = 1.28$, $p > .28$). 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 centre.

## 2.2. Materials and procedure

### 2.2.1. 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 centres) and with the Wortschatztest (Schmidt & Metzler, 1992) in German-speaking participants (Mainz centre). Education and vocabulary measures were each converted into z-scores using the mean and standard deviation of each centre as reference in order to reflect interindividual 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).

### 2.2.2. Cognitive testing

Elderly participants performed within normal range on a battery of neuropsychological tests including assessments of episodic memory and executive functions. We considered interindividual variability in memory ability and in executive and attention function, as these functions are the main domains of age-related cognitive changes (Craik & Salthouse, 2000; Park & 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, Desgranges, & Lalevée, 1998) in Caen and Verbal Learning and Memory Test VLMT (Helmstaedter, Lendt, & Lux, 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 centres, and performance on the Reading span test (Desmette, Hupet, & Van der Linden, 1995), the Hayling test (Andrés & Van der Linden, 2000) and the attention subtest from the Mattis DRS (Mattis, 1973) in Liège centre.

### 2.2.3. Resting-state neuroimaging

#### *2.2.3.1. Cerebral metabolism*

In each centre, 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 centre and 20 min in Liège and Mainz centres. 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.

#### *2.2.3.2. 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 centre, data were acquired on a 3T 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, Schwarzbauer, & Turner, 2004)]. In Mainz, acquisition was performed on a 3T 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 3T 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 mm$^2$, in-plane resolution 3.4 × 3.4 mm$^2$, 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 was used **[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 mm$^2$, in-plane resolution 2.8 × 2.8 mm$^2$, 280 volumes]**. The first six volumes were discarded due to saturation effects.

2.3.Functional cerebral image preprocessing and analyses

2.3.1. 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 normalised to the MNI stereotactic space. A mean image of all participants' normalised MRI image and a mean image of all participants' normalised grey 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 normalised by applying parameters from the spatial normalisation of the MRI data. All normalised PET images were used to compute a mean PET image. Mean whole-brain and grey 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 centre to account for inter-centre 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.**

2.3.2. 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 centre 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 centred 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 centre 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, Srivastava, Reiss, & Menon, 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.**

2.4. 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 grey 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 grey 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**.

3. Results

3.1. 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 metabolism and level of cognitive reserve in this multi-centre 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] (Figure 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 Figure 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 interindividual 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 interindividual 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 sore 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, $R^2 = .09$, $p < .01$).**

3.2. 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].

3.2.1. 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 centre (Liège>Caen or Caen>Liège), so we explored voxels where BOLD signal covaried with each seed activity across time in participants from both centres 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 centre 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.**

3.2.2. Independent Component Analysis

This analysis evidenced 19 independent components which covered all grey 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 (Figure 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 (Figure 2 B, see Supplemental Figure 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, Figure 3 A). **The intraparietal sulcus is a crucial part of the dorsal attention network, which supports goal-directed attention (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 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 (Figure 3 B), confirming that the latter is a good candidate (Supplemental Figure S2).**

3.3. Voxel-based morphometry

**There was no correlation between grey 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 grey matter density.

## 4. 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, Zarahn, Anderson, Habeck, et al., 2003). In the current multi-centre 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 & 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, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner, Andrews-Hanna, & Schacter, 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 & Maguire, 2007; Schacter, Addis, & Buckner, 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 & 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 indicate 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 & 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 & 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 characterised by spontaneous low-frequency fluctuations that are anticorrelated 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 refer 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 & 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, Zarahn, Anderson, Habeck, et al., 2003), 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 been ruled out by longitudinal follow-up assessment of cognitive functioning of the participants.**

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There is no conflict of interest for any of the authors.

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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

| | | MNI coordinates | | | | |
|---|---|---|---|---|---|---|
| Side | Anatomical region | x | y | z | Z | K |
| | 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.

Figure legends

Figure 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.

**Figure 2.** Results of the Independent Component Analysis (NetBrainWork) at the group-level. A. Component (hot colours) 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.

**Figure 3**. Results of the Independent Component Analysis (NetBrainWork) at the group-level. A. Component (hot colours) 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.

**Supplemental Figures**

**Figure S1. SPM results of the negative correlation between cerebral metabolism and level of cognitive reserve (mean education and vocabulary z-score), p < .001 uncorrected for multiple comparisons, extent threshold > 30 voxels. 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.**

**Figure S2. Goodness of fit measures for (A) seed-related networks (left intraparietal sulcus –LIPS- network and right temporoparietal cortex –RTPC- network) versus independent components matching; (B) independent components versus NetBrainWork templates matching.**

**9. Figure**

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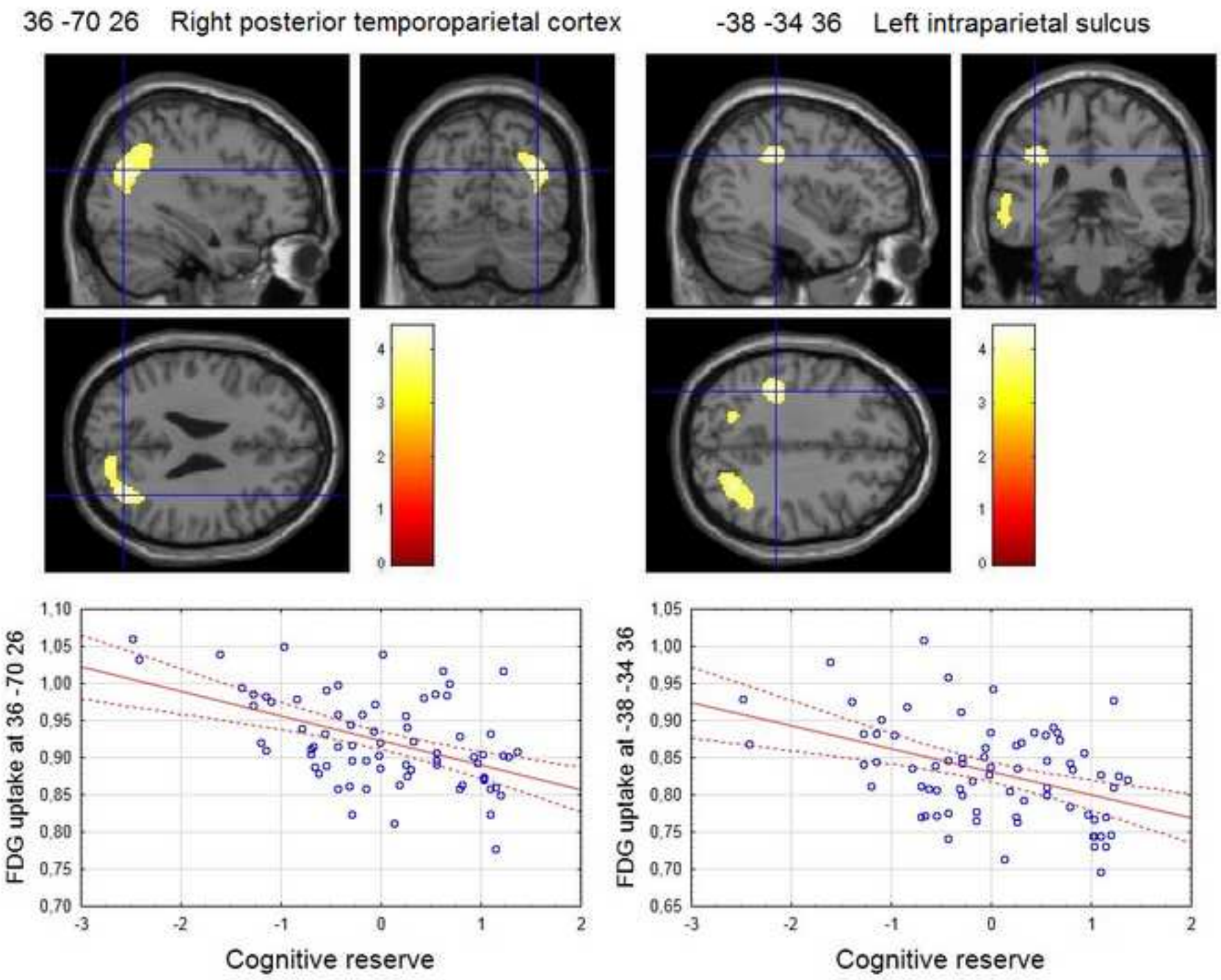

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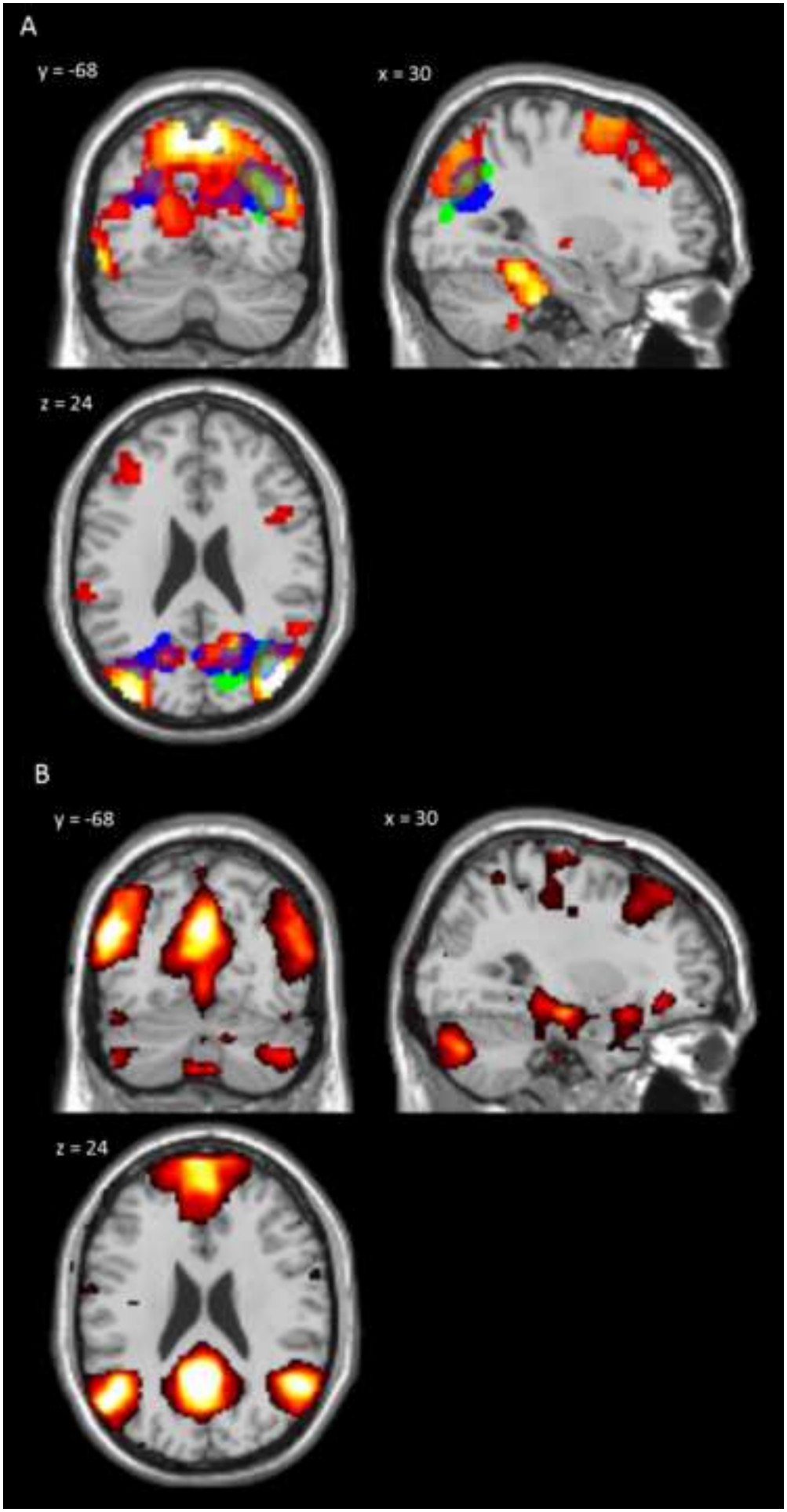

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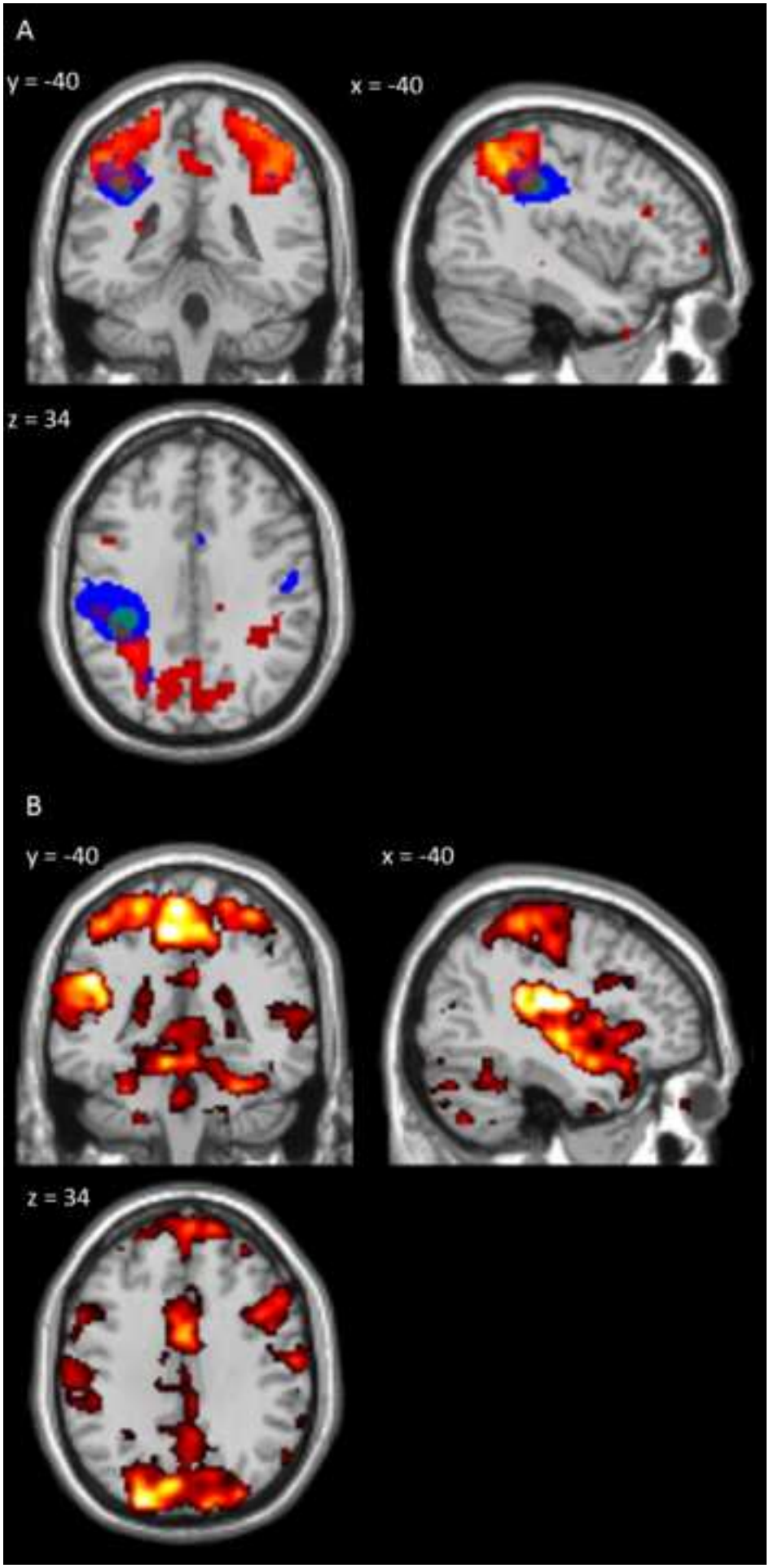

**10. Supplementary Material**

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