Metabolic and structural connectivity within the default mode network relates to working memory performance in young healthy adults

Igor Yakushev[a,b,#], Gael Chételat[c], Florian U. Fischer[a], Brigitte Landeau[c], Christine Bastin[d], Armin Scheurich[a], Audrey Perrotin[c], Mohamed Ali Bahri[d], Alexander Drzezga[b], Francis Eustache[c], Mathias Schreckenberger[e], Andreas Fellgiebel[a,*], Eric Salmon[d,*]

* *Equally contributed*

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

[b] Department of Nuclear Medicine, Technische Universität München, Munich, Germany

[c] Inserm-EPHE-Université de Caen, Caen, France

[d] Cyclotron Research Centre, University of Liège, Liège, Belgium

[e] Department of Nuclear Medicine, University Medical Center Mainz, Mainz, Germany

[#] Corresponding author:

Igor Yakushev, MD
Department of Nuclear Medicine
Klinikum rechts der Isar
Technische Universität München
Ismaninger Str. 22
D-81675 Munich
Germany
Tel: +49(0)89-4140-2964
Fax: +49(0)89-4140-4950
igor.yakushev@lrz.tum.de

Abstract

Studies of functional connectivity suggest that the default mode network (DMN) might be relevant for cognitive functions. Here, we examined metabolic and structural connectivity between major DMN nodes, the posterior cingulate (PCC) and medial prefrontal cortex (MPFC), in relation to normal working memory (WM).

DMN was captured using independent component analysis of [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) data from 35 young healthy adults (27.1±5.1 years). Metabolic connectivity, a correlation between FDG uptake in PCC and MPFC, was examined in groups of subjects with (relative to median) low (n=18) and high (n=17) performance on digit span backward test as an index of verbal WM. In addition, fiber tractography based on PCC and MPFC nodes as way points was performed in a subset of subjects.

FDG uptake in the DMN nodes did not differ between high and low performers. However, significantly (p=0.01) lower metabolic connectivity was found in the group of low performers. Furthermore, as compared to high performers, low performers showed lower density of the left superior cingulate bundle.

Verbal WM performance is related to metabolic and structural connectivity within the DMN in young healthy adults. Metabolic connectivity as quantified with FDG-PET might be a sensitive marker of the normal variability in some cognitive functions.

Key words: positron emission tomography, FDG PET, diffusion tensor imaging, posterior cingulate, cingulate bundle, independent component analysis

Introduction

In recent years, a set of brain regions called default mode network (DMN) has gained increasing attention in the field of cognitive neuroscience. This network – comprising typically the posterior cingulate (PCC), medial prefrontal (MPFC), and inferior parietal cortex – is significantly less active during cognitively demanding tasks than at rest or during passive tasks (Raichle et al., 2001). These areas overlap considerably with regions showing the highest level of metabolism and blood flow at rest (Raichle et al., 2001). Converging evidence from functional magnetic resonance imaging (fMRI) studies indicates, however, that DMN deactivation is not simply an epiphenomenon of goal-oriented brain activity. Instead, selective deactivation of the DMN might be as relevant for normal cognitive functioning as activation of task-dependent networks. E.g., failure to suppress DMN was related to decreased activity in task-relevant brain regions (Greicius and Menon, 2004; Sambataro et al., 2010) and, consequently, to attentional lapses and cognitive decrements (Sambataro et al., 2010; Weissman et al., 2006).

So far, the functional connectivity of the DMN and its relation to normal or pathological cognition has been studied mostly with fMRI. Neuronal activity is closely linked to glucose consumption that can be reliably measured *in vivo* using positron emission tomography with [18F]-fluorodeoxyglucose (FDG-PET, Phelps et al., 1983). As opposed to fMRI, FDG-PET captures neuronal activity that is in steady state in hourly terms and is independent of vascular coupling. This neuroimaging tool may hence be well suitable for exploring the baseline integrity of neuronal networks (Rocher et al., 2003) such as the DMN (Lee et al., 2008; Rilling et al., 2007). Although proposed more than 25 years ago (Clark et al., 1984; Horwitz et al., 1984; Metter et al., 1984), the method of interregional correlations has been validated for whole brain voxel-wise analyses only

recently (Lee et al., 2008). In addition to the seed-based approaches as those mentioned above, covariance patterns in FDG-PET data can also be examined using multivariate analyses (Salmon et al., 2009; Zuendorf et al., 2003). A major (intrinsic) limitation of metabolic PET in connectivity research, however, has been availability of only one image per subject, as opposed to fMRI with availability of numerous scans, or time points, per subject. Thus, investigation of connectivity with (FDG-) PET has been considered as principally possible at a group level only. Yet, very recent evidence indicates encouraging properties of FDG-PET-based resting state connectivity at an individual level (Huang et al., 2010; Toussaint et al., 2012). To differentiate from functional connectivity as quantified with fMRI, here we use the term "metabolic connectivity" suggested by Lee et al. (2008).

A careful review of the fMRI literature indicates that working memory (WM) is a cognitive domain that might be specifically modulated by the DMN (Hampson et al., 2006; Esposito et al., 2009; Sambataro et al., 2010). Specifically, a stronger functional coupling between the MPFC and PCC nodes during rest was found to be associated with a better performance in a WM task. As fMRI researches themselves note, however (Hampson et al., 2006), it is well possible that the strength of the established functional-cognitive relationships is simply a reflection of the performance, rather than a predictor of it, given that the resting scans are interleaved with the WM scans (i.e., block design). Besides, the nature of the association between negative BOLD response and neuronal activity that itself relies on a complex interaction between metabolism and hemodynamics is still unclear, limiting interpretation of the above fMRI findings. Finally, it remains unknown whether the established role of DMN functional connectivity relies on structural connectivity.

In the present study, we combined FDG-PET and diffusion-tensor imaging (DTI; Le Bihan et al., 2001) to examine metabolic and structural connectivity between the PCC and MPFC as major

DMN nodes in relation to WM performance in healthy young adults. We hypothesized that individuals with higher WM performance would also demonstrate stronger connectivity as a reflection of a more efficient neuronal synchrony within the DMN.

Material and methods

Subjects

Two centers provided their data for the present work: Inserm-EPHE-Université de Caen, Caen, France (thereafter referred to as center 1) and University Medical Center Mainz, Mainz, Germany (thereafter referred to as center 2). All participants were recruited by advertisements posted in the hospitals of the participating centers and via newspaper announcements. From prospective studies conducted independently at each center, we retrospectively selected subjects according to the following criteria: age range 20-40 years, unremarkable clinical psychiatric and neurological examinations, presence of an FDG-PET scan, structural MRI scan, and neuropsychological testing including the digit span test. The tests and neuroimaging were conducted at different days. Exclusion criteria were a history or presence of any organic brain disease, substance abuse, all psychiatric diagnoses and diabetes mellitus. By these criteria, 16 subjects were included at center 1 and 19 subjects at center 2 (Table 1). Among 35 subjects, 3 were left-handed.

---------- **Table 1** about here ----------

Working memory assessment

Verbal working memory was assessed with the digit span test (Wechsler, 1997). This test requires the examiner to verbally present digits at a rate of one per second. The forward test requires

the participant to repeat the digits verbatim, while he/she has to repeat in reverse order for the backward one. The number of digits increases by one until the participant consecutively fails two trials of the same digit span length. Digit span forward is considered to be related to efficiency of attention, while digit span backward serves as a standard index of verbal WM with a high test-retest reliability (Waters and Caplan, 2003). It has been widely applied also in studies of young healthy adults (Turner et al., 2003; Zaninotto et al., 2009).

MRI

At center 1, a high-resolution T1-weighted anatomical image was acquired on a Philips (Eindhoven, The Netherlands) Achieva 3T scanner using a 3D fast field echo sequence (3D-T1-FFE sagittal; TR 20 ms, TE 4.6 ms, 180 slices; slice thickness 1 mm, FOV 256 mm, matrix size 256 x 256). Data acquisition at center 2 was performed on a Siemens Trio 3T scanner with the following parameters: TR 11.70 ms, TE 2.38 ms, 244 slices, slice thickness 0.82 mm, FOV 210 mm, matrix size 256 x 256.

DTI data were acquired at center 2 only using a diffusion weighted single shot spin-echo echoplanar based sequence: 30 directions; b=1000 s/mm2; matrix 128x128; section thickness, 3 mm; voxel size, 1.5x1.5x3 mm; TR/TE, 7100 ms/102 ms (Wolf et al., 2012).

FDG-PET

At both centers, PET examinations were performed under standard resting conditions after the participants had fasted for at least 6 h before scanning. At center 1, a 10-min PET scan was acquired on a Discovery RX VCT 64 PET/CT device (General Electric Healthcare) about 50 min after i.v. injection of approximately 180 MBq FDG. The device has a resolution of 3.76 x 3.76 x 4.9 mm (field of view 15.7 cm). Images were reconstructed using the 3D ordered-subset expectation

maximization (3D-OSEM) method with a voxel size of 2.7 x 2.7 x 3.27 mm, after corrections for scatter and attenuation. At center 2, a 15-min PET scan was acquired in list mode on a Philips Gemini TF PET/CT scanner (Philips Medical Systems, Eindhoven, NL) about 30 min after i.v. injection of approximately 150 MBq FDG. The PET camera has an axial field of view of 18.0 cm and an axial resolution of 4.7 mm. Images corrected for scatter and attenuation were reconstructed to 5 mm slices using a 3D-RAMLA algorithm.

Image preprocessing

Preprocessing of image data was performed with the statistical parametric mapping toolbox (SPM5, Wellcome Department of Cognitive Neurology, London, UK). First, structural T1-MRI images were segmented and spatially normalized into the MNI space using voxel based morphometric toolbox, VBM5 (Ashburner and Friston, 2005) as implemented SPM5.

Individual PET images were coregistered to the corresponding MRI images and using a mutual information approach as implemented by default in SPM. Afterward, PET images were spatially normalized by applying parameters estimated from normalization of the MRI data. Individual variations in global FDG uptake were adjusted for by dividing each image by the value of the pons (Mevel et al., 2007). The resultant individual PET images were then divided by the mean of all PET images per center to account for inter-center effects. This procedure allowed abolishing any main effect of centre, while the group effects remained unchanged (Chetelat et al., 2013). Since PET data from two centers had a distinct original spatial resolution, a differential smoothing was applied to equalize the effective smoothness (Chételat et al., 2008; Villain et al., 2010). A Gaussian kernel of 9.3 x 9.3 x 8.7 (x, y, z) mm^3 was used for the PET data at center 1, while a kernel of 9.3 x 9.3 x 9.3 mm^3 for the data at center 2.

Definition of the default mode network

To identify a coherent spatial activity related to the DMN, preprocessed PET images (n=35) were subjected to a group ICA algorithm (GIFT, http://icatb.sourceforge.net). Its major steps include data reduction by means of principal component analysis (PCA), ICA itself, and back-reconstruction (Calhoun et al., 2001). Prior to PCA, the optimal number of components as estimated using the GIFT dimensionality estimation tool was set to five. To display voxels that contributed most strongly to a particular IC, intensity values in each spatial map were converted to Z-values (Calhoun et al., 2001). As a result of these analyses, we obtained 5 spatial ICs that were classified as following: default mode, sensorimotor, auditory, cerebellar, and subcortical networks (Di and Biswal, 2012) The DMN component included the PCC, frontal (MPFC and partially lateral prefrontal), and inferior parietal cortices bilaterally. Subsequently, the clusters except the frontal one were converted to binary images at a z-value of 1.5. To restrict the frontal cluster to the MPFC, a z-threshold of 2.0 was applied there. Thus, we obtained a binary mask of typical DMN regions of a comparable size. Finally, relative FDG uptake from the PCC and MPFC nodes was extracted across all subjects using MarsBar toolbox (http://marsbar.sourceforge.net).

Fiber tracking

Diffusion weighted data were processed using FSL 4.1 (FMRIB Analysis Group, Oxford, UK) following the procedures: (i) motion and eddy current correction, (ii) adjustment of gradients according to the rotational part of resulting affine transformations, (iii) smoothing using a Gaussian kernel with a sigma of 0.75 mm, and (iv) removal of the skull and non-brain tissue using brain extraction tool (BET). Fiber tracking of the superior cingulate bundle (CB) that is known to connect the PCC with MPFC was performed as in detail reported elsewhere (Fischer et al., 2012). In brief, whole brain fiber tracking was conducted in native space using fiber assignment by continuous

tracking (FACT) with a fixed step size and local tensor interpolation as implemented in CAMINO v2 (Microstructural Imaging Group, University College London, UK, http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php). Stopping criteria were set to value of fractional anisotropy (FA) ≥ 0.15 and curvature $\leq 50°$. As we did not expect any artifactual streamlines due to neurodegenerative changes as those in e.g., Alzheimer's disease, we skipped the step of weighting (Fischer et al., 2012). The above defined PCC and MPFC nodes served as additional way points for fiber isolation. Specifically, binary images of the above DMN nodes in MNI space were i) transformed to subject-specific native space using inverse transformation of the spatial normalization and ii) dilated in a few millimeters to ensure their contact with white matter (Greicius et al., 2009; van den Heuvel et al., 2009). Finally, we calculated FA, mean diffusivity (MD), density (number of streamlines per voxel), and volume of the isolated fiber tracts, separately for the right and left hemisphere (Fischer et al., 2012).

Statistical analyses

In analogy with previous studies, test performance was adjusted for variance of no interest by calculating standardized residuals (Z scores) after effects of center, age, gender, and education had been regressed out (Kravariti et al., 2012; Walhovd and Fjell, 2007). Subjects were then categorized into groups with high and low test performance by the common method of a median split (Düzel et al., 2011; Jaeggi et al., 2008).

Subsequently, we assessed metabolic connectivity between the PCC and MPFC nodes in the whole sample, as well as separately in the group of low and high performers. Hereby, we applied a concept of metabolic connectivity proposed by Lee et al. (2008) as implemented elsewhere (Cilia et al., 2011; Fouquet et al., 2009; Morbelli et al., 2012). Specifically, metabolic connectivity was quantified by calculating linear correlations between regional FDG values (in our case, those

extracted from the DMN nodes) across groups. Resultant correlation coefficients (one per group) were compared by means of Fisher's z test. To address the issue of specificity, we a) conducted the same analyses for the sub-test digit span forward, and b) calculated metabolic connectivity of the PCC and MPFC with the sensorimotor cortex (SMC). Individual regional values of the SMC were extracted using automated anatomical labeling (Tzourio-Mazoyer et al., 2002).

Structural connectivity between the PCC and MPFC nodes in subjects from center 2 was assessed by calculating tractography indices (see above) of the reconstructed CB. In contrast to FDG-PET, DTI analyses yielded 4 outcome measures per subject, such that these were compared between the groups by means of a one-sided t-test. I.e., we hypothesized that subjects with lower test performance would have lower connectivity than those with high test performance. Differences were considered significant at $p<0.05$ uncorrected for multiple comparisons. We examined uncorrected results, as in the present small sub-sample of young, healthy and well-educated adults the effects were expected to be weak.

Results

Distribution of individual scores from the digit span backward test (after median split) in each subgroup is shown in Fig. 1. As expected, there was a strong difference in test performance between the groups (Table 2).

---------- **Figure 1** about here ----------

---------- **Table 2** about here ----------

The resultant binary mask of the typical DMN regions of is illustrated in Fig. 2.

---------- **Figure 2** about here ----------

There was no difference in relative FDG-uptake between low and high group in either DMN node (p's>0.4 in t-test). However, there was a strong correlation (Pearson correlation coefficient r=0.85, p<0.001) between PCC and MPFC tracer uptake in the whole sample (n=35). The correlation was significantly stronger (Fischer's z=-3.1, p=0.01) in the group of high performers (r=0.92, p<0.001) than that in the group of low performers (r=0.66, p=0.003) at WM test. The same analyses conducted for the sub-test digit span forward did not result in any significant differences between the groups (low r=0.84, high r=0.87, n.s.). A correlation between FDG uptake in the PCC and SMC was similar among the groups of high and low performers (low r=0.74, high r=0.80, n.s.). The same was true for the correlation between MPFC and SMC uptake (r=0.78, r=0.83, n.s.).

---------- **Figure 3** about here ----------

Using tractography, CB could be reconstructed in all subjects from center 2 (Fig.4). Tractography indices in each group are reported in Table 3. The direction of effects was in accord with our hypothesis for most indices, but the difference reached the pre-defined level of significance only for left CB density (Table 3). I.e., it was lower in the low performers as compared to the high performers group.

---------- **Figure 4** about here ----------

---------- **Table 3** about here ----------

Discussion

In the present multimodal imaging study, we examined metabolic and structural connectivity between major nodes of the DMN in healthy young adults, in relation to WM. As the major finding, both metabolic and structural connectivity was found to be greater in individuals with higher performance in a standard verbal WM test.

The pattern of the DMN (MPFC, PCC, inferior parietal cortex) we observed is well in agreement with previous resting state metabolic PET (Rilling et al., 2007) as well as fMRI (for a review see van den Heuvel and Hulshoff Pol, 2010) studies. Consistent with the definition of the DMN, the above regions are typically deactivated during performance of a WM task in fMRI experiments (Anticevic et al., 2010; Hampson et al., 2006; Tomasi et al., 2006). Due to the complex nature of WM, the pattern of task-related, or activated, regions is rather variable, but it typically includes lateral prefrontal, premotor and lateral posterior parietal cortices (Collette et al., 1999; Owen et al., 2005). Thus, our data suggest an association of verbal WM with connectivity within (in narrow sense) task-unrelated network. Although rather unexpected at first blush, this finding is overall in line with growing fMRI literature on a specific modulating role of the DMN in cognitive processes. Indeed, spontaneous activity within the DMN persists across both experimental and rest conditions (Greicius and Menon, 2004). While DMN activity is clearly suppressed during a WM task, there is a substantial amount of spontaneous signal fluctuations within the DMN (Fransson, 2006; Mayer et al., 2010), indicating that the network is still active in the "deactivation mode". Even more intriguingly, and in line with the present work, dedicated fMRI studies found that a stronger functional coupling between the MPFC and PCC nodes during rest was associated with a better performance in a WM task (Esposito et al., 2009; Hampson et al., 2006; Sambataro et al., 2010). As mentioned above, there are limitations in interpretation of these fMRI findings. Most importantly, cognitive fMRI studies typically implement comparisons between two states that are closely spaced in time, i.e. block-design. In such a case, it is possible that the established BOLD-

task relationship is a reflection of the task itself rather than a predictor of it (Hampson et al., 2006). Besides, very recent evidence indicates that functional connectivity of intrinsic resting state networks including the DMN is a subject to systematic artifacts due to head motion (Power et al., 2012; Van Dijk et al., 2012). Yet, our FDG-PET data support the evidence provided by fMRI. Namely, they suggest the presence of a relatively stable (in time and space) synchronous neuronal connectivity within the DMN, with the strength of the correlation being related to cognitive performance as measured outside the scanner. In no way, however, this means that functional and metabolic connectivity as indexed by fMRI and FDG-PET provide analogous information. Although there is a certain overlap, each imaging modality traces unique covariance patterns, as predicted by the distinct nature of the measured signal and distinct temporal resolution (Yakushev et al., in preparation).

The observed findings can be interpreted at least in two complementary ways. First, and most obviously, effective coordination between the PCC and MPFC might be a key prerequisite of synchronous deactivation of the DMN during cognitive tasks. Such a deactivation would allow the brain to focus attentional resources on the incoming (sensory) information. Second, the efficient coordination between the DMN nodes might be necessary to differentially modulate activity in task-related networks. Indeed, causality analyses by Uddin et al. (2009) indicated that the PCC and MPFC exerted greater influence on their anticorrelated networks than the other way around, suggesting that these two major nodes may directly modulate activity in task-related networks. Overall, both explanations are well in line with the concept of deficient resource allocation. I.e., both activation in task-related networks and efficient deactivation within the DMN are important for allocation of the attentional resources necessary for the performance of a cognitive task (Sonuga-Barke and Castellanos, 2007; Wermke et al., 2008; Sambataro et al., 2010).

So far, this concept relied on functional data provided by fMRI. Thus, it has been unclear whether this network interplay exists only at the functional level or if there is a structural substrate that, at least partially, subserves such relations. Indeed, the presence of functional connectivity does not automatically imply the presence of structural connectivity (Greicius et al., 2009; Honey et al., 2009). In this context, our DTI findings are of particular interest. Specifically, a higher fiber density of the CB, a path that interconnects the PCC with MPFC (Greicius et al., 2009; van den Heuvel et al., 2009) was found in subjects with higher WM performance. This observation is in accord with increasing evidence according to which tractography-specific indices that are based on the number of fibers may be useful measures of neuronal structural connectivity (Schott et al., 2011; Shao et al., 2012). Overall, our DTI data suggest that not only functional, but also structural integrity within a "task-unrelated" network such as the DMN might be of relevance for a given task/function.

Interestingly, the positive link between CB integrity and WM as observed here is supported by existing, although limited, DTI/MRI literature. As the CB is not typically considered a part of the structural network underlying WM, all studies that reported findings in respect to the CB had applied a hypothesis-free whole brain analysis. Remarkably, Carlton et al. (2010) found that FA in the left fronto-parietal tract that include the CB explained the largest proportion of variance in the digit span backward test in healthy middle aged and elderly individuals. Besides, lesions exactly in the CB correlated most strongly with performance in a verbal WM test in patients with multiple sclerosis (Sepulcre et al., 2009). The association between WM measures and integrity of the (left) CB in multiple sclerosis was independently reported by another group (Dineen et al., 2009).

While the field of functional brain connectivity as quantified with fMRI has been rapidly expanding in the last years, PET is still traditionally applied for measuring local brain metabolism and perfusion, typically in a diseased state. In the present study, regional as well as whole brain (data not shown) tracer uptake did not differ as a function of WM, while regional connectivity did.

The findings thus strongly suggest that examination of metabolic connectivity patterns, over and above metabolic activity patterns, can provide critical information about mechanisms of brain functioning. In fact, the approach of interregional correlation analysis (Lee et al., 2008) applied here shows specific, plausible patterns of metabolic connectivity in healthy middle aged adults. Of note, the approach is rather robust to the seed size and seed definition method (Lee et al., 2008), favoring its use also for exploring pathological connectivity (Morbelli et al., 2012).

In our study, the established structural-functional association was not strong. I.e., the difference in CB density between high and low performers would not survive a correction for multiple comparisons. Further, a parametric correlation between the test scores and tractography indices revealed only a trend ($p<0.09$) for density and volume of the left CB (data not shown). It should be explicitly noted, however, that we studied a rather small sample of young (age range 21-37 years) and well-educated adults without evidence for any neurological or psychiatric disorder and with fairly normal cognitive performance. Obviously, in such a sample, statistical power is rather limited, due to low variance in both structural and cognitive measurements.

This study has several limitations. First, metabolic connectivity as presently quantified allows reasonable inferences only at a group level. However, recent advances in functional connectivity modeling have allowed identifying brain connectivity networks from PET data at a single subject level (Huang et al., 2010). Once a group-level based connectivity model is available, the method enables to classify new subjects on the basis of their individual connectivity profile. Second, we cannot exclude that the present metabolic and structural relationships with verbal WM are not driven by more global cognitive characteristics such as general intelligence (Ackerman et al., 2005). Yet, additional analyses with vocabulary as proxy of verbal intelligence (Baddeley et al., 1993; Bastin et al., 2012) did not reveal any significant relationships (data not shown). Finally, we cannot exclude that the differences in data acquisition protocols between two centers have influenced our

PET findings. However, the application of a sophisticated methodology including double scaling and differential smoothing has allowed us to minimize the corresponding sources of variance (Chetelat et al., 2013).

In conclusion, we found that metabolic connectivity between the PCC and MPFC as major DMN nodes is related to verbal WM performance in healthy young adults. DTI analyses further suggested that this link was subserved by structural integrity of the CB, a major white matter tract interconnecting the above brain regions. Along with functional connectivity as measured with fMRI, PET-based metabolic connectivity may serve a useful tool for investigating brain networks underlying individual cognitive differences. Subsequently, it could provide critical diagnostic information across a range of mental disorders that are accompanied with cognitive deficits (e.g., Morbelli et al., 2012).

Funding

The French Caen study was supported by Agence Nationale de la Recherche (ANR LONGVIE 2007), Programme Hospitalier de Recherche Clinique (PHRC National 2011), Région Basse Normandie and Institut National de la Santé et de la Recherche Médicale (INSERM). The German study was supported by the Research Focus on Interdisciplinary Neurosciences IFSN of the University of Mainz, Germany. The Inter-University Attraction Pole [grant number P6/29] and the French-speaking Community of Belgium [ARC 06/11-340] supported CB and DF's positions. The Belgian National Funds for Scientific Research and the University of Liège supported MRI and PET acquisition costs for the Belgian study.

Acknowledgments

The authors are grateful to B. Desgranges, V. de La Sayette, M. Fouquet, N. Villain, R. La Joie, K. Mevel, F. Mézenge, S. Egret, C. Schupp, J. Dayan, A. Quillard, L. Barré, A. Manrique, C. Lebouleux, M.H. Noel & M.C. Onfroy for their help in data acquisition and processing and/or in the conception of the study.

Disclosure Statement

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

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Tables

Table 1. Demographic characteristics of subjects

	All subjects	Center 1	Center 2	P[1]
N (female)	35 (20)	16 (10)	19 (10)	0.734[2]
Age, years	27.1±5.1	29.1 ±5.7	25.5±4.1	0.048
Education, years	13.3 ± 1.9	13.1± 2.3	13.5 ± 1.6	0.504
Digit span forward	6.5 ± 1.2	6.3 ± 1.1	6.6 ± 1.2	0.282
Digit span backward	5.4 ± 1.5	5.6±1.3	5.2±1.6	0.417

Mean ± SD. [1] T-test and [2] Chi-square test for comparison between subjects from center 1 and center 2

Table 2. Demographic characteristics of subjects according to performance in digit span backward test

	Low	High	P[1]
N (female)	18 (11)	17 (9)	0.738[2]
Age, years	27.0 ± 4.7	27.3 ± 5.7	0.869
Education, years	13.6 ± 2.1	13.1 ± 1.8	0.456
Digit span backward*	-0.78 ± 0.5	0.83 ± 0.5	<0.001

Mean ± SD. [1] T-test and [2] Chi-square test for comparison between low and high groups.

*Standardized residuals (Z scores) after effects of center, age, gender, and education had been regressed out

Table 3. Tractography indices of the cingulate bundle (center 2 only)

	Low (n=9)	High (n=10)	p[1]
FA L	0.48 (0.03)	0.50 (0.03)	0.158
MD L	740 (15)	750 (35)	0.224
Density L	26 (9)	36 (12)	**0.026**
Volume L	2816 (628)	3319 (695)	0.058
FA R	0.47 (0.02)	0.47 (0.03)	0.495
MD R	724 (12)	729 (26)	0.313
Density R	30 (6)	30 (10)	0.491
Volume R	2363 (722)	2807 (891)	0.126

[1]One-sided T-test for comparison between low and high performers. L – left, R – right

Figure captions

Figure 1.

Individual scores for performance in digit span backward test adjusted for center, age, sex, and education (z scores). Open circles indicate subjects from center 1, filled circles from center 2

Figure 2.

A mask of DMN regions as overlaid onto a standard MRI template

Figure 3.

Correlation between relative FDG uptake extracted from the PCC and MPFC nodes. Open circles indicate subjects from center 1, filled circles from center 2

Figure 4.

Fibers of the superior cingulate bundle as isolated using the PCC and MPFC nodes as way points