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Relationships between brain metabolism decrease in normal aging and changes in structural and functional connectivity

Gaël Chételat [a,b,c,d,*,1], Brigitte Landeau [a,b,c,d,1], Eric Salmon [e], Igor Yakushev [f,g], Mohamed Ali Bahri [e], Florence Mézenge [a,b,c,d], Audrey Perrotin [a,b,c,d], Christine Bastin [e], Alain Manrique [h], Armin Scheurich [f], Mathias Scheckenberger [i], Béatrice Desgranges [a,b,c,d], Francis Eustache [a,b,c,d], Andreas Fellgiebel [f]

[a] INSERM, U1077, Caen, France
[b] Université de Caen Basse-Normandie, UMR-S1077, Caen, France
[c] Ecole Pratique des Hautes Etudes, UMR-S1077, Caen, France
[d] CHU de Caen, U1077, Caen, France
[e] Cyclotron Research Centre, University of Liège, Allée du 6 Août, 8, B30, 4000 Liège, Belgium
[f] Department of Psychiatry and Psychotherapy, University Medical Centre Mainz, Mainz, Germany
[g] Department of Nuclear Medicine, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany
[h] Department of Nuclear Medicine, CHU de Caen, Caen, France
[i] Department of Nuclear Medicine, University Medical Center Mainz, Mainz, Germany

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ABSTRACT

Normal aging is characterized by brain glucose metabolism decline predominantly in the prefrontal cortex. The goal of the present study was to assess whether this change was associated with age-related alteration of white matter (WM) structural integrity and/or functional connectivity. FDG-PET data from 40 young and 57 elderly healthy participants from two research centers (n = 49/48 in Center 1/2) were analyzed. WM volume from T1-weighted MRI (Center 1), fractional anisotropy from diffusion-tensor imaging (Center 2), and resting-state fMRI data (Center 1) were also obtained. Group comparisons were performed within each imaging modality. Then, positive correlations were assessed, within the elderly, between metabolism in the most affected region and the other neuroimaging modalities. Metabolism decline in the elderly predominated in the left inferior frontal junction (LIFJ). LIFJ hypometabolism was significantly associated with macrostructural and microstructural WM disturbances in long association fronto-temporo-occipital fibers, while no relationship was found with functional connectivity. The findings offer new perspectives to understand normal aging processes and open avenues for future studies to explore causality between age-related metabolism and connectivity changes.

Introduction

In vivo cross-sectional ^{18}FDG-PET studies in normal healthy individuals have consistently shown decreased cerebral glucose metabolism with age, with a differential effect across brain regions, the frontal cortex showing the greatest effects (Garraux et al., 1999; Herholz et al., 2002; Hsieh et al., 2012; Kalpouzos et al., 2009; Moeller et al., 1996; Petit-Taboué et al., 1998; Zuendorf et al., 2003). The most frequently reported areas are the ventral and dorsal lateral prefrontal/inferior frontal cortex, the anterior cingulate cortex, medial prefrontal areas and precentral and perisylvian areas. Decreased metabolism is also reported, though less consistently, in the caudate nuclei and the (superior) lateral temporal cortex. The neurophysiological mechanisms underlying these metabolic changes with age are still unknown. It is possible however that connectivity disruption is involved.

Indeed, normal aging process is also characterized by changes within the WM. In addition to WM hyperintensities (e.g. Maillard et al., 2012), structural and functional connectivity changes occur and alterations of WM tract integrity have been consistently reported. Thus, histopathological studies have shown age-related loss of myelinated fibers and degeneration of myelin in the WM (Marner et al., 2003; Peters, 2002). Diffusion tensor imaging (DTI) allows in-vivo investigation of WM microstructure integrity (Le Bihan, 2003) with fractional anisotropy (FA) being the best established DTI indices for the quantification of structural integrity and connectivity. DTI studies in normal aging have reported significant decrease in FA in the whole brain (Rovaris et al., 2003), with greater FA decline in frontal compared to posterior WM regions (Abe et al., 2002; Ota et al., 2006; Pfefferbaum et al., 2000, 2005; Salat et al., 2005; Sullivan et al., 2006). In general, an anterior–posterior gradient is found, for example with the genu of the corpus callosum being more significantly altered than the splenium

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter LIFJ, left inferior frontal junction; PVE, partial volume effects; SPM, statistical parametric mapping; VBM, voxel-based morphometry; WM, white matter.

* Corresponding author at: Unité de Recherche U1077, Centre Cyceron, Bd H. Becquerel, BP 5229, 14074 Caen Cedex, France. Fax: +33 2 31 47 02 75.
E-mail address: chetelat@cyceron.fr (G. Chételat).

[1] Equally contributed.

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(Kochunov et al., 2007, 2012; Pfefferbaum et al., 2000; Sullivan et al., 2001). Also, highest rates of decline are reported for the late thinly myelinated associative tracts, while the thickly myelinated motor and sensory tracts are more resistant to normal aging processes (Bartzokis et al., 2001, 2003, 2004; Kochunov et al., 2007; Tang et al., 1997), giving rise to the developmental theory. In addition to microstructure changes, macroscopic changes in WM structural integrity can also be assessed using T1-weighted MRI and measures of WM volume for example using voxel-based morphometry (VBM; Good et al., 2001). Thus, voxelwise WM volume decrease with age has been reported in the frontal lobe, optic radiations, and posterior limb of internal capsule (Good et al., 2001). Finally, in addition to these WM structural changes, resting-state fMRI studies in normal aging consistently reported functional connectivity disruption with age specifically along the anterior–posterior axis of the brain (Andrews-Hanna et al., 2007; Biswal et al., 2010; Grady et al., 2010; Jones et al., 2011; Meunier et al., 2009; Mevel et al., 2013; Wu et al., 2011), though they mainly focused on midline structures of the default mode network (Raichle et al., 2001).

To further understand the processes underlying age-related brain changes, it seems of particular interest to assess whether there is any relationship between cerebral metabolism decline with age, and alterations in structural and functional WM connection tracts. It is likely that glucose metabolism may impact on myelin integrity as reflected by FA measurements as maintaining myelin is energy demanding; conversely, myelin disruption is expected to impact on metabolism and functioning of connected brain regions (Bartzokis, 2004). The density and volume of WM fibers, that probably influences both FA and VBM measures of WM volume, are also very likely to impact on the projection sites; it has been shown for example in Alzheimer's disease that the profile of hypometabolism is at least partly due to disconnection processes, i.e., disruption of WM tracts that project to these metabolically affected regions (Villain et al., 2008, 2010a). Finally, local metabolic dysfunction may be due to, or may lead to, disruption in the functional connectivity with distant brain regions.

Although showing a correlation between two processes does not allow to infer causality between these processes, assessing the relationships between brain metabolism in regions typically affected by normal aging on the one hand, and structural and functional connectivity on the other hand, is a first step to further our understanding of the physiological mechanisms underlying age-related metabolic decline. A few studies assessed the links between microstructural WM changes and metabolism (Inoue et al., 2008; Kochunov et al., 2009; Kuczynski et al., 2010), but there has been no study to date that used a multimodal approach to assess whether metabolism decrease with age is related to microscopic or macroscopic structural or functional connectivity changes.

The objective of the present study was thus to assess the relationships between age-related gray matter (GM) decrease of glucose metabolism measured with FDG-PET, focusing on the region with the strongest effect, and macrostructural (with VBM-WM volume), microstructural (with DTI), and functional (with resting-state fMRI) connectivity voxelwise throughout the whole brain.

Material and methods

Participants

The study included 97 healthy participants separated in young (<40 years old) and elderly (>60 years old) individuals pooled across two research centers (Center 1 = Caen in France, and Center 2 = Mainz in Germany) in the framework of a tripartite collaborative project that already gave rise to a publication (Bastin et al., 2012). Participants showed normal performances for age in a battery of neuropsychological tests, had no clinical evidence of psychiatric or neurological disorders, no severe brain lesion on T2-weighted or FLAIR MRI images, were free of medication that could affect cognitive functioning, and reported being in good health. All participants gave informed consent to cognitive and neuroimaging assessments, which were approved by the local ethics committee in each center.

The number of participants per group and center and their corresponding demography are provided in Table 1. All participants from both centers had an FDG-PET scan. Structural T1-MRI images from Center 1 were used to assess WM volume as a reflect of WM macroscopic structural integrity. DTI-FA data were available in all individuals from Center 2, allowing to assess WM microscopic structural integrity. Finally, resting-state fMRI data were available in all individuals from Center 1, allowing to measure functional connectivity.

Neuroimaging data acquisition

FDG-PET data

In both centers, PET data were acquired under standard resting conditions after participants had fasted for at least 6 h. In 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 intravenous injection of 180 MBq FDG. The device has a resolution of 3.76 × 3.76 × 4.9 mm (field of view = 157 mm). Images were reconstructed with a resultant voxel size of 2.7 × 2.7 × 3.27 mm. In 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 intravenous injection of approximately 150 MBq FDG. The PET camera has an axial field of view of 18 cm and an axial resolution of 4.7 mm. Images corrected for scatter and attenuation were reconstructed to 5 mm slices. In each center, brain metabolic activity was measured during quiet wakefulness with eyes closed and ears unplugged.

MRI data

MRI was performed within three months of the PET exam. Subjects were equipped with earplugs and their heads was stabilized with foam pads to minimize head motion. In Center 1, images were acquired on a Philips (Eindhoven, The Netherlands) Achieva 3T scanner. In Center 2, data acquisition was performed on a Siemens Trio 3T scanner.

T1-weighted structural MRI

A T1-weighted anatomical image was obtained in all participants of both Centers. In Center 1, high-resolution T1-weighted images were obtained using the 3D fast field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms, echo time = 4.6 ms, 170 slices; slice thickness 1 mm, field of view = 256 mm, matrix size 256 × 256). In Center 2, acquisition was performed with the following parameters: repetition time = 1170 ms, echo time = 2.38 ms, 244 slices, slice thickness 0.82 mm, field of view = 210 mm, matrix size 256 × 256.

DTI data

In Center 2, diffusion-weighted images were also obtained in all young and elderly participants. Images were obtained using a diffusion-weighted single-shot spin-echo echoplanar based sequence (30 directions; b = 1000 s/mm^2; matrix 128 × 128; section thickness, 3 mm; voxel size, 1.5 × 1.5 × 3 mm; repetition time = 7100 ms, echo time = 102 ms).

Table 1
Demographic characteristics of the samples.

	Center 1	Center 2
Young	N = 21	N = 19
Age	28.7 ± 5.5 (21–37)	25.5 ± 4.1 (22–37)
Education	13.7 ± 2.6 (10–19)	13.5 ± 1.6 (13–18)
Elderly	N = 28	N = 29
Age	69.9 ± 6.5 (60–84)	69.2 ± 8.2 (60–85)
Education	11.3 ± 3.6 (7–20)	12.5 ± 3.6 (9–18)

Age and education are indicated in years as mean ± standard deviation (minimum, maximum).