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Technical Note

Differential effects of global and cerebellar normalization on detection and differentiation of dementia in FDG-PET studies

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ABSTRACT

FDG-PET ([18F]fluorodeoxyglucose positron emission tomography) is frequently used to improve the differential diagnosis of dementia. However, a fundamental methodological issue of the reference area for the intensity normalization procedure is still unsolved. Here, we systematically compared the two most commonly used normalization methods to the cerebral and to the cerebellar metabolic rate for glucose with regard to detection and differentiation of dementia syndromes. FDG-PET imaging was performed on 19 subjects with early Alzheimer's disease, 13 subjects with early frontotemporal lobar degeneration and 10 subjects complaining of memory impairment, which had not been confirmed by comprehensive clinical testing. Images were normalized to either the cerebral or the cerebellar metabolic rate for glucose. Differences in relative regional glucose metabolism were assessed by voxelwise comparison. Analysis using the two normalization procedures revealed remarkable differential effects. Whereas cerebellar normalization was superior in identifying dementia patients in comparison to control subjects, cerebral normalization showed better results for differential diagnosis between types of dementia. These effects were shown for both, Alzheimer's disease and frontotemporal lobar degeneration. Relative hypermetabolism in comparison to the control group was only detected in both kinds of dementia using global normalization. The results indicate that normalization has a decisive impact on diagnostic accuracy in dementia. While cerebellar normalization seems to be more sensitive for early diagnosis, cerebral global normalization might be superior for differential diagnostic purposes in dementia syndromes.

Introduction

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are common kinds of dementia (Neary et al., 1998; Dubois et al., 2007, Schroeter et al., 2007). Recently, it was suggested to incorporate imaging markers into diagnostic criteria of specific neurodegenerative disorders (Dubois et al., 2007). Research investigating the contribution of positron emission tomography with [F18]fluorodeoxyglucose (FDG-PET) in detecting dementia disorders has revealed differential patterns of a reduced regional cerebral metabolic rate for glucose in different types of dementia (Mielke et al., 1994; Salmon et al., 2000; Sakamoto et al., 2002; Jeong et al., 2005; Mosconi et al., 2006; Jagust et al., 2007; Samuraki et al., 2007). While AD patients show reduced glucose consumption in parieto-temporal and posterior cingulate cortices (Ishii et al., 2001, 2005; Yakushev et al., 2008; Schroeter et al., 2009), the reduced glucose metabolism of patients with FTLD is predominately located in fronto-temporal and anterior cingulate cortices (Jeong et al., 2005; Schroeter et al., 2007, 2008).

Although the areas affected are sufficiently different in their anatomical distribution, it is necessary to run an intensity normalization procedure in order to compare their relative regional metabolic rate to those of healthy controls or with each other. This procedure removes interindividual differences in the absolute whole brain intensity by relativizing the absolute metabolic rate for glucose in the whole brain to a reference area. Such differences can, for example, result due to different amounts of radiocontrast agent injected.

At present, there is no consensus as to which reference region should be used. A review of the current literature revealed the use of the following areas for normalization of FDG-PET scans of dementia patients: the cerebral metabolic rate for glucose (CMRglc: Mielke et al., 1994; Salmon et al., 2000; Ishii et al.,, 2001; Herholz et al., 2002;

Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; CDR, Clinical Dementia Rating scale; CerMRglc, cerebellar metabolic rate for glucose; CMRglc, cerebral metabolic rate for glucose; FDG-PET, [18F]fluorodeoxyglucose-PET; FTLD, frontotemporal lobar degeneration; PET, positron emission tomography; SPM, Statistical Parametric Mapping; VOI, volume of interest.

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Mosconi et al., 2004; Samuraki et al., 2007; Del Sole et al., 2008; Yakushev et al., 2008, 2009), the cerebellum (Mielke et al., 1994; Minoshima et al., 1995; Ishii et al., 2001; Santens et al., 2001; Yakushev et al., 2008, 2009), the sensorimotor cortex (Minoshima et al., 1995; Santens et al., 2001; Sakamoto et al., 2002; Yakushev et al., 2008, 2009), the center of the midpontine slice (Minoshima et al., 1995; Mosconi et al., 2006), the visual cortex (Minoshima et al., 1995; Santens et al., 2001) and cluster-based normalization to the area with the highest activity in dementia patients (Yakushev et al., 2009).

As recently pointed out by Yakushev et al. (2008), the appropriate reference area should be maximally stable in patients and in healthy controls, minimally susceptible to external physiological stimuli, unaffected by the disease of interest and reliable and easy to determine. Moreover, because recent studies have shown that the chosen reference area is also important for diagnostic accuracy (Yakushev et al., 2008, 2009), we suggest adding a further criterion to this description for practical clinical reasons: The area should allow the most accurate distinction between different clinical diagnoses. This is the case if the reference area offers a maximum contrast of the differences in glucose metabolism between patients and healthy controls or between groups of patients with different disorders, so allowing easier detection and differentiation of these.

As most studies use either intensity normalization to the CMRglc (mean metabolic rate for glucose in the whole brain) or to cerebellar glucose consumption, we compared these two methods with respect to their superiority in both detecting dementia and also in differentiating between different types of dementia. These aspects are not necessarily the same, because normalizing the data to a specific region can either increase or decrease the power of statistical tests between different groups (Ishii et al., 2001; Yakushev et al., 2008, 2009). This strongly depends on the differences between groups in the reference areas. These are not the same for the comparison of clinical patients to healthy controls or to groups of patients with different disorders. For example, an earlier study showed the cerebellar glucose uptake to be little affected in patients with AD while the CMRgluc was significantly reduced compared to healthy controls (Kushner et al., 1987). For that reason, we hypothesize differential effects of normalization for either the diagnosis or differentiation of dementia syndromes.

Methods

Subjects

We analyzed FDG-PET data of 19 patients (Table 1) with an early stage of probable AD, 13 patients with an early stage of FTLD and 10 control subjects. Probable AD was diagnosed according to the original and revised NINCDS-ADRDA criteria (McKhann et al., 1984; Dubois et al., 2007). Diagnosis of FTLD was based on the criteria suggested by Neary et al. (1998). The control group included people who visited the Day Clinic of Cognitive Neurology at the University of Leipzig with subjective memory complaints, which were not objectively confirmed by a comprehensive neuropsychological and clinical evaluation. FDG-PET for these subjects was conducted for diagnostic reasons within the clinical assessment. This control group was chosen because, in clinical practice it is crucial to discriminate between these subjects and patients with an early stage of dementia. Informed consent was obtained from all subjects. The research protocol was approved by the ethics committee of the University of Leipzig, and was in accordance with the latest version of the Declaration of Helsinki.

Table 1
Subject group characteristics.

	Controls	AD	FTLD	ANOVA (*df*, *F*, *p*)
Number	10	19	13	–
Male/Female	6/4	7/12	6/7	–
Age (years)	55.1 ± 5.0	62.6 ± 6.0	61.1 ± 6.6	2, 5.26, 0.009
CDR (score)	0.25 ± 0.26	0.87 ± 0.47	0.81 ± 0.43	2, 7.77, 0.001
CMRglc/CerMRglc ratio	1.20 ± 0.06	1.08 ± 0.06	1.11 ± 0.08	2, 7.52, 0.002

Mean ± standard deviation. AD Alzheimer's disease, ANOVA analysis of variance, CerMRglc cerebellar metabolic rate for glucose, CMRglc cerebral metabolic rate for glucose, CDR Clinical Dementia Rating scale, FTLD frontotemporal lobar degeneration.

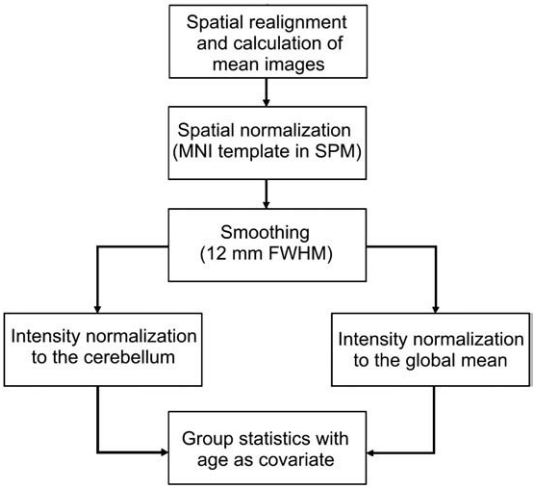

Fig. 1. Schematic representation of the procedure for FDG-PET data handling and processing steps.

FDG-PET imaging

All PET data were acquired on a Siemens ECAT EXACT HR+ scanner (CTI/Siemens, Knoxville, TN, USA) under a standard resting condition in 2-dimensional (2D) mode. The 2D acquisition mode was used because it allows a better quantification of the PET data due to lower scatter radiation. Sixty-three slices were simultaneously collected with an axial resolution of 5 mm full width at half maximum (FWHM) and in-plane resolution of 4.6 mm. After correction for attenuation, scatter, decay and scanner-specific dead time, images were reconstructed by filtered back-projection using a Hann-filter of 4.9 mm FWHM. The 63 transaxial slices obtained had a resolution of 128 * 128 voxels with an edge length of 2.45 mm.

PET data analysis

The resultant ECAT volume files were separated into single frames (ANALYZE-format) using the import tool from the program MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html) and the last three frames à 10 min, starting from 30 to 60 min post injection, of each patient were chosen for further analysis. SPM5 (Statistical

Table 2
Extension of hypometabolic brain regions for different contrasts with global and with cerebellar normalization.

Contrast	Global normalization		Cerebellar normalization	
	Cluster extent	Maximal *p*-value	Cluster extent	Maximal *p*-value
AD<Controls	7988	3.05E−010	14649	2.25E−013
FTLD<Controls	11,089	1.34E−013	17742	1.11E−016
Controls<AD	7268	1.95E−009	n.s.	n.s.
Controls<FTLD	7863	1.62E−009	n.s.	n.s.
FTLD<AD	20,069	<1.0E−20	4419	8.42E−05
AD<FTLD	25,704	<1.0E−20	8533	3.04E−10

The size is represented by the sum of all clusters (in voxels) which exceeded an uncorrected threshold $p<0.001$ on the voxel level with cluster extension $k\geq 30$ voxels and $p<0.05$ (corrected) on the cluster level. AD Alzheimer's disease, FTLD frontotemporal lobar degeneration, n.s. not significant.