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Hypometabolism of the posterior cingulate cortex is not restricted to Alzheimer's disease

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ABSTRACT

When differential diagnosis of dementia includes both Alzheimer's disease (AD) and the behavioural variant of frontotemporal dementia (bvFTD), distribution of cerebral glucose metabolism as measured using [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography ([^{18}F]FDG-PET) may be helpful. One important clue for differentiation is the presence of hypometabolism in the posterior cingulate cortex (PCC), usually associated with AD. PCC hypometabolism however, could also be present in bvFTD. Therefore, the specificity of PCC hypometabolism was examined. Based on visual reading PCC hypometabolism was present in 69–73/81 probable AD patients, in 10–16/33 probable bvFTD patients, and in 0–1/22 cognitive normal (CN) subjects. Findings were validated using a PCC to reference tissue [^{18}F]FDG standard uptake value ratio (SUVr) cut-off, which was derived from the receiver operating characteristic (ROC) separating probable AD from CN, resulting in 9–14/33 bvFTD patients having PCC hypometabolism, depending on the reference tissue used. In conclusion, PCC hypometabolism is not restricted to AD.

1. Introduction

Reduced uptake of [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) in the posterior cingulate cortex (PCC) is a characteristic feature of Alzheimer's disease (AD)(Herholz, 2014; Kato et al., 2016; Landau et al., 2011; Minoshima et al., 1997). However, PCC hypometabolism may not be restricted to AD and can also be seen in other dementias such as the behavioural variant of frontotemporal dementia (bvFTD), which is characterized by most prominent hypometabolism in the frontal lobe (Diehl et al., 2004). Previous studies reported inconsistent findings regarding involvement of the PCC in bvFTD, and involvement of the PCC mostly coincided with more advanced stages of the disease (Broe et al., 2003; Diehl-Schmid et al., 2007; Ishii et al., 1998; Kato et al., 2016; Whitwell et al., 2004). Little is known about the prevalence of PCC hypometabolism at time of bvFTD diagnosis, nor about its association with clinical phenotype. The aim of this study was therefore to assess the prevalence of PCC hypometabolism in AD, bvFTD, and cognitive normal (CN) subjects using visual reading. A second objective was to explore associations between PCC standard uptake value ratio (SUVr; using both cerebellum and pons as reference regions) and clinical characteristics.

2. Methods

2.1. Subjects

A total of 136 subjects from the Amsterdam dementia cohort were included(van der Flier et al., 2014). AD subjects (n = 81) met clinical criteria for probable AD and had CSF tau/Aβ_{1-42} > 0.52, implying high likelihood for underlying AD pathology (Duits et al., 2014;

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Mckhann et al., 2011). BvFTD subjects (n = 33) met clinical criteria for probable bvFTD and diagnosis was confirmed by a neurologist specialised in bvFTD (YP) (Rascovsky et al., 2011). Furthermore, all bvFTD patients had CSF $A\beta_{1-42}$ > 550 pg/mL, implying a low likelihood for underlying amyloid pathology (Mulder et al., 2010). CN subjects (n = 22) performed normally on an extensive neuropsychological test battery, and showed no abnormalities on MRI indicative of underlying neurodegeneration, as evaluated by an experienced neuroradiologist (FB). All CN subjects had CSF tau/$A\beta_{1-42}$ < 0.52, implying a low likelihood for underlying AD pathology (Duits et al., 2014). The local Medical Ethics Review Committee approved the study. All subjects provided written informed consent prior to inclusion.

2.2. Neuropsychological assessment

A standard neuropsychological test battery was used to assess major cognitive functions (van der Flier et al., 2014). Test scores were transformed into z-scores, and inverted where appropriate, so that higher scores represented better performances. Compound scores were calculated for each cognitive domain investigated. In addition, Mini-Mental State Examination (MMSE), Clinical Dementia Rating scale (CDR), and Neuropsychiatric Inventory (NPI) were included.

2.3. APOE genotype and CSF biomarkers

Collection and analysis of APOE genotype and CSF biomarkers were performed as described previously (van der Flier et al., 2014). For inclusion of bvFTD subjects, the cut-off for normal CSF $A\beta_{1-42}$ was set at > 550 pg/mL. For inclusion of AD patients, the cut-off for abnormal CSF tau/$A\beta_{1-42}$ was set at > 0.52, and for CN subjects < 0.52 (Duits et al., 2014). Finally, associations between CSF biomarkers and PCC SUVr were assessed using continuous variables.

2.4. MRI protocol

T1-weighted 3D MPRAGE images were acquired for co-registration, segmentation, and region of interest definition. Images were obtained on a 1.5 T Sonata scanner (Siemens, Erlangen, Germany; slice thickness 1.5 mm, 160 slices, matrix size 256 × 256, voxel size 1 × 1 × 1.5 mm, echo time 3.97 ms, repetition time 2700 ms, flip angle 8°) or a 3 T SignaHDxt scanner (General Electric, Milwaukee, Wisconsin, USA; slice thickness 1 mm, 180 slices, matrix size 256 × 256, voxel size 1x1x1.5 mm, echo time 3 ms, repetition time 708 ms, flip angle 12°).

2.5. PET protocol

Prior to injection of ~185 MBq [^{18}F]FDG, patients were required to rest for 10 min with eyes closed and earplugs in a dimly lit room. [^{18}F]FDG PET emission scans were acquired at 45 min post injection using either an ECAT EXACT HR + (Siemens/CTI, Knoxville, TN) or a Gemini TF-64 PET/CT (Philips, Best, The Netherlands) scanner. In addition, in case of the HR +, a 10 min transmission scan or, in case of the Gemini, a low dose CT scan was acquired prior to the emission scan to correct emission data for tissue attenuation. Image acquisition, pre-processing and the reconstruction protocol have been described elsewhere (Verfaillie et al., 2015).

2.6. Imaging analysis

T1 weighted MR images were co-registered to corresponding [^{18}F]FDG PET data using the Vinci software package (version 2.56.0). Using PVElab together with the Hammers template, regions of interest (ROI) were delineated on the MRI scans and superimposed onto the dynamic PET scan to generate regional time activity curves (TAC). (Hammers et al., 2002; Svarer et al., 2005) Since the pons is not a standard region in this template, it was delineated manually on the co-registered T1w MR image using in-house built software in IDL, and superimposed onto the dynamic PET images. The manual delineation was performed based on voxel intensity differences between the pons and the remaining part of the brainstem on the T1w MR image. Using SPM segmentation, pons white matter volumes were extracted from which a 95% CI of pons white matter volume was calculated for quality insurance of the manual delineation. Outliers were checked on both their delineation and segmentation, and when necessary corrected. PCC SUVr was calculated as PCC to reference region ratio, by dividing the images by the reference region value. For the reference tissue cerebellum grey matter (further referred to as 'cerebellum') and pons white matter (further referred to as 'pons') TACs were assessed separately.

Two nuclear medicine physicians, blinded for clinical diagnosis, performed visual reading. The level of experience in visual reading of [^{18}F]FDG brain images differed between readers. Reader A was very experienced, reading multiple [^{18}F]FDG images weekly, whilst reader B recently completed training to be nuclear medicine physician. PCC hypometabolism was considered to be present when the PCC (defined using anatomical boundaries that are described elsewhere (Minoshima et al., 1994)) was isointense – since healthy brain metabolism is associated with highest glucose uptake in the PCC (Loessner et al., 1995) – or hypointense compared with other cortical regions by thresholding the SUVr image to identify the area in the brain with the highest activity concentration (Minoshima et al., 1997).

2.7. Statistical analyses

Statistical analyses were performed using SPSS for Windows version 22.0 (IBM Corp. Armonk, NY). Clinical characteristics were compared between diagnostic groups (AD, bvFTD and CN) using chi-square tests (sex, APOE genotype), Kruskal-Wallis analyses (education, duration of complaints, MMSE, CDR, and NPI), or analysis of variance (ANOVA) with post hoc Bonferroni analyses (SUVr, age, age at onset of complaints, CSF biomarkers, neuropsychological compound z-scores). When group differences were observed with chi-squared tests or Kruskal-Wallis analyses, ANOVA with Tamhane's T2 post hoc analyses was used, in which equal variances are not assumed.

For assessment of PCC hypometabolism prevalence in AD, bvFTD and CN, first visual reading was performed. Inter-reader agreement was assessed using Cohen's kappa (κ). Agreement was considered poor if $\kappa < 0.20$, satisfactory if $0.21 < \kappa < 0.40$, moderate if $0.41 < \kappa < 0.60$, good if $0.61 < \kappa < 0.80$, and excellent if $\kappa > 0.81$ (Zwan et al., 2014).

Second, the presence of PCC hypometabolism in bvFTD was verified using a SUVr cut-off, which was defined based on the Receiver Operating Characteristic (ROC) separating AD from CN. Findings were validated using the split-half approach, in which the sample was randomly split in half, resulting in a training sample and test sample. In addition, ROC analyses were performed separating AD from bvFTD, and separating bvFTD from CN. Since we aimed to explore specificity of PCC hypometabolism, we chose cut-offs corresponding with a minimum specificity of 90%. Furthermore, ROC curves of cerebellum-normalised SUVr were compared with ROC curves of pons-normalised SUVr with the method by Hanley and McNeil (1983) using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

Relationships between PCC [^{18}F]FDG SUVr (dependent variable) and all clinical characteristics shown in Table 1 (independent variables) were explored using linear regression analyses. Age, sex, diagnostic group and scanner type were included as covariates. In addition, the interaction between diagnosis and clinical variable of interest was introduced into the model.

Within the bvFTD group we compared characteristics of patients having normal PCC metabolism with patients having PCC hypometabolism based on visual reading (reader A). First, clinical characteristics were compared between these two subgroups using chi-squared tests,

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