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ORIGINAL ARTICLE

Impact of plasma glucose level on the pattern of brain FDG uptake and the predictive power of FDG PET in mild cognitive impairment

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Abstract

Purpose Increased blood glucose level (BGL) has been reported to cause alterations of FDG uptake in the brain that mimic Alzheimer's disease (AD), even within the "acceptable" range ≤ 160 mg/dl. The aim of this study was (i) to confirm this in a large sample of well-characterized normal control (NC) subjects, and (ii) to analyze its impact on the prediction of AD dementia (ADD) in mild cognitive impairment (MCI).

Methods The study included NCs from the Alzheimer's Disease Neuroimaging Initiative (ADNI) that were cognitively stable for ≥36 months after PET ($n = 87$, 74.2 ± 5.3 y), and ADNI MCIs with ≥36 months follow-up if not progressed to ADD earlier ($n = 323$, 71.1 ± 7.1 y). Seventy-three of the MCIs had progressed to ADD within 36 months. In the NCs, parenchyma-scaled FDG uptake was tested for clusters of correlation with BGL on the family-wise, error-corrected 5% level. In the MCIs, ROC analysis was used to assess the power of FDG uptake in a predefined AD-typical region for prediction of ADD. ROC analysis was repeated after correcting mean FDG uptake in the AD-typical region for BGL based on linear regression in the NCs.

Results In the NCs, BGL (59–149 mg/dl) was negatively correlated with FDG uptake in a cluster comprising the occipital cortex and precuneus but sparing the posterior cingulate, independent of amyloid-β and ApoE4 status. In the MCIs, FDG uptake in the AD-typical region provided an area of 0.804 under the ROC curve for prediction of ADD. Correcting FDG uptake in the AD-typical region for BGL (55–189 mg/dl) did not change predictive performance (area = 0.808, $p = 0.311$).

Conclusions Increasing BGL is associated with relative reduction of FDG uptake in the posterior cortex even in the "acceptable" range ≤ 160 mg/dl. The BGL-associated pattern is similar to the typical AD pattern, but not identical. BGL-associated variability of regional FDG uptake has no relevant impact on the power of FDG PET for prediction of MCI-to-ADD progression.

Keywords Plasma glucose · F-18-fluorodesoxyglucose · Healthy controls · MCI

Introduction

FDG PET is a promising biomarker to support the diagnostic process in patients with suspicion of Alzheimer's disease (AD), although its validity and utility in real-world patients has not yet been fully demonstrated [1]. Neuronal dysfunction and loss of synapses in AD are reflected by a characteristic pattern of reduced brain FDG uptake comprising the precuneus/posterior cingulate area and parietotemporal association cortices [2]. This pattern can be detected in FDG PET before cognitive decline is recognized [3, 4].

Strongly elevated blood glucose levels (BGLs) compromise statistical image quality and gray-to-white matter contrast in brain FDG PET due to competition of FDG with endogenous glucose for transport by glucose transporters and for phosphorylation by hexokinase. Procedure guidelines,

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu). The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis/writing of this report. A complete list of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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therefore, recommend fasting condition with BGL ≤ 160 mg/dl for brain FDG PET [5].

Yet, recent studies reported increased BGL to cause not only global reduction of brain FDG uptake but also alteration of the regional pattern of brain FDG uptake that mimics AD-characteristic hypometabolism, even when BGL is still within the acceptable range ≤ 160 mg/dl [6–10]. In a study of 9 young healthy volunteers, Ishibashi and colleagues found that glucose loading prior to PET (resulting in a mean BGL of 112 mg/dl) caused decreased FDG uptake in AD-characteristic brain regions including the precuneus/posterior cingulate as well as the lateral parietal and frontal cortex [6]. Another study by the same group performing dynamic FDG PET with arterial blood sampling for quantitative assessment of the metabolic rate of glucose in 12 young healthy volunteers confirmed these findings [9]. In 51 cognitively normal elderly subjects, the same group found a mildly increased fasting BGL of 100–110 mg/dl to be associated with significantly decreased FDG uptake in the precuneus [7]. Repeat FDG PET in four cognitively normal elderly subjects with diabetes revealed an AD-like pattern of hypometabolism when BGL was increased [8].

These findings suggest that mildly elevated BGL within the acceptable range ≤ 160 mg/dl might impact the performance of FDG PET in the diagnosis of AD, in particular by increasing the risk of false positive results. This has not yet been investigated. The present study, therefore, first tested for BGL-associated occurrence of an AD-like FDG PET pattern in a large sample of normal control (NC) subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) that was well-characterized not only with respect to cognition during at least 3 years following PET but also with respect to amyloid-ß and ApoE4 status. The primary aim, however, was to assess the impact of BGL on the utility of brain FDG PET for prediction of AD dementia (ADD) in patients with mild cognitive impairment (MCI). A large sample of well-characterized ADNI MCI subjects was used for this task.

Materials and methods

Subjects

The study included all ADNI NCs with baseline FDG PET (including BGL measurement) that were cognitively stable for ≥36 months. These criteria were fulfilled by 87 NC subjects (40 females) with a mean age of 74.2 ± 5.3 years. Furthermore, the study included all ADNI MCI subjects with baseline FDG PET (including BGL measurement), baseline T1- and FLAIR-MRI at 3 T, and ≥36 months follow-up if not progressed to ADD earlier. These criteria were fulfilled by 326 MCI subjects. Three subjects were excluded because of implausible low BGLs of 13–15 mg/dl (participant roster ID (RID) 4138, 4631, 4919). This resulted in inclusion of 323 subjects (146 females) aged 71.1 ± 7.1 years. Seventy-three of the MCIs had progressed to ADD within 36 months, and the remaining 250 subjects had been cognitively stable for at least 36 months. Data were obtained from the ADNI (adni.loni.usc.edu) launched in 2003 as a public-private partnership and led by Michael W. Weiner. ADNI aims at testing MRI, PET, other markers, and clinical and neuropsychological assessment to measure progression of MCI and early AD (up-to-date information at www.adni-info.org).

Amyloid-ß and ApoE4 status of normal controls

Baseline cerebrospinal fluid (CSF) data of NC subjects was obtained from the master table provided at the ADNI homepage by the University of Pennsylvania ("UPENNBIOMK_MASTER.csv"). Re-sampled baseline CSF data anchored to CSF data from ADNI1 was used. Amyloid-$ß_{1–42}$ (CSF-Aβ) was available for 51 of the 87 NC subjects. Dichotomization into AD-positive or AD-negative with respect to CSF-Aβ was based on the cut-off value 192 pg/ml recommended by ADNI (33 AD-negative, i.e., CSF-Aβ ≥ 192 pg/ml; 18 AD-positive, i.e., CSF-Aβ < 192 pg/mL) [11]. For NC subjects from ADNIGO/2, florbetapir PET standard uptake value ratio (SUVR) was downloaded ("UCBERKELEYAV45_10_17_16.csv") and dichotomized using the recommended cut-off value 1.11 [12]. Florbetapir PET was available for 51 subjects (36 AD-negative, i.e. SUVR ≤ 1.11; 15 AD-positive, i.e., SUVR > 1.11).

NC subjects that were AD-negative on both CSF-Aβ and florbetapir SUVR or on one of both Aβ markers when the other was not available, were categorized as 'Aβ-negative' ($n = 44$). All other NC subjects were categorized as "Aβ-other" ($n = 43$). The Aβ-other category comprised all subjects that were AD-positive on CSF-Aβ and/or florbetapir SUVR ($n = 24$, including 5 cases with conflicting Aβ markers) and all subjects without an Aβ marker ($n = 19$).

The number of ApoE4 alleles was obtained from "ApoE-Results[ADNI1,GO,2].csv" ($n = 63/22/2$ with 0/1/2 ApoE4 alleles, respectively). NC subjects with at least one ApoE4 allele were categorized as "ApoE4-positive" (n = 24), and subjects without the ApoE4 allele as "ApoE4-negative" (n = 63).

Statistical analyses

Pre-processed FDG PET images ("Coreg_Avg_Std_Img_and_Vox_Siz_Uniform_Resolution") in NIFTI format were downloaded from the ADNI homepage. The images were stereotactically normalized to Montreal Neurological Institute (MNI) space and smoothed with a Gaussian kernel (12 mm) using Statistical Parametric Mapping 8 (SPM8). The mean voxel intensity in the brain parenchyma was used for intensity scaling [13].

Voxel-wise multiple regression was employed to test for correlation between BGL and scaled FDG uptake in the NC sample using a cluster-defining voxel-level threshold of uncorrected $p = 0.05$. Resulting clusters were considered statistically significant if the family-wise, error-corrected p value of the cluster was ≤0.05.

In order to test for potential impact of age, gender, overall cognitive performance (ADAS-13), as well as Aβ and ApoE4 status, mean FDG uptake was computed in the region of interest (ROI) delineating the cluster of negative correlation between BGL and FDG uptake revealed by voxel-based testing. The impact of the potential confounders was tested by analysis of the partial correlation between FDG uptake and BGL corrected for confounders and/or by restricting Pearson's correlation analysis to subsamples of the NC subjects, for example the Aß-negative NC subjects. To assess the risk of false positive AD diagnosis, FDG PET of each NC subject was inspected visually by two experienced readers. Visual interpretation was based on FDG uptake images and statistical parametric maps from voxel-based, single-subject analysis as described in [13].

In ADNI MCI subjects, mean FDG uptake in AD-characteristic brain regions was computed using an AD-meta ROI obtained previously by voxel-based group comparison of ADNI AD versus ADNI NC subjects [13] (Fig. 1). FDG uptake in the AD-meta ROI was scaled to mean voxel intensity in brain parenchyma. Receiver operating characteristic (ROC) analysis was used to assess the power of mean FDG uptake in the AD-meta ROI to identify the MCI subjects who progressed to ADD within 36 months amongst all MCI subjects.

ROC analysis in the MCI sample was repeated after correcting mean FDG uptake in the AD-meta ROI for BGL based on linear regression of mean FDG uptake in the AD-meta ROI versus BGL in the NC subjects.

Results

In the ADNI NCs, BGL was 98.4 ± 15.8 mg/dl (range 59–149). There was a significant cluster of negative correlation between scaled FDG uptake and BGL comprising the

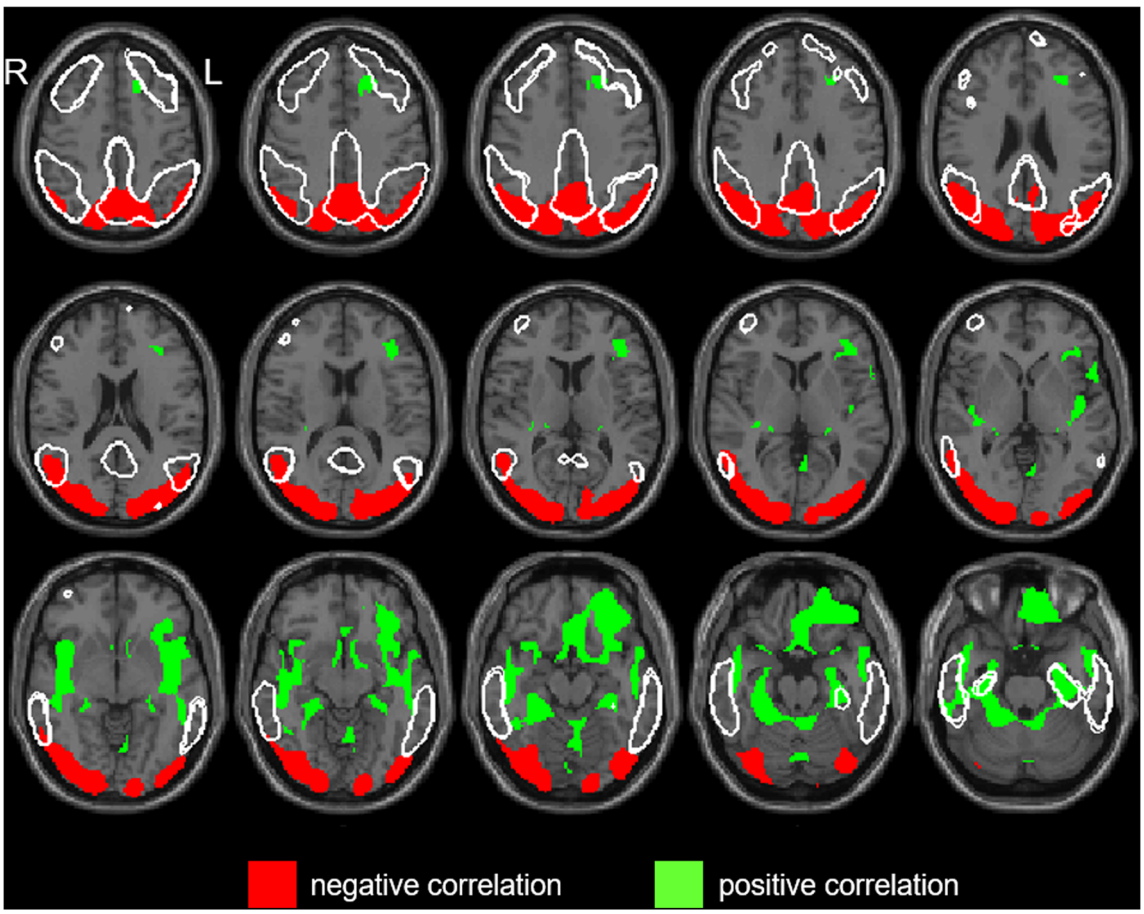

Fig. 1 The significant cluster of negative correlation between scaled FDG uptake and BGL revealed by voxel-based testing is shown in *red* (128.5 ml, $p = 0.022$). The area of positive correlation at the voxel level (*green*) did not reach statistical significance at a cluster level (100.5 ml, $p = 0.061$). The AD-meta ROI is shown as the *white contour*

occipital cortex (including the cuneus and precuneus, but not the posterior cingulate gyrus) and slightly extending bilaterally to the parieto-occipital cortex (cluster volume 128.5 ml, $p = 0.022$, Fig. 1). Positive correlation at a voxel level was detected in a cluster mainly comprising white matter in the centrum semiovale, which however did not reach the level of statistical significance at a cluster level (100.5 ml, $p = 0.061$, Fig. 1). Including amyloid-ß status as fixed factor in the voxel-by-voxel regression analysis resulted in a cluster of significant negative correlation between scaled FDG uptake and BGL that was very similar to the one without correction of amyloid-ß status (with correction: cluster volume 132.6 ml, $p = 0.021$; without correction: 128.5 ml, $p = 0.022$; Sørensen-Dice similarity index 0.97).

A scatter plot of FDG uptake in the negative correlation cluster versus BGL is shown in Fig. 2. The negative correlation between scaled FDG uptake and BGL was confirmed by partial correlation analyses that corrected for age (partial correlation coefficient between scaled FDG uptake and BGL $r = -0.382$, $p < 0.0005$), gender ($r = -0.392$, $p < 0.0005$), ADAS-13 ($r = -0.377$, $p < 0.0005$) or for the presence of ApoE4 alleles ($r = -0.366$, $p = 0.001$). Furthermore, the correlation between FDG uptake in the negative correlation cluster and BGL was confirmed in the Aβ-negative NC subsample ($r = -0.423$, $p = 0.004$) as well as in the Aβ-other subsample ($r = -0.362$, $p = 0.017$; Fig. 2). Similarly, the correlation was present in both ApoE4-negative ($r = -0.326$, $p = 0.009$) and ApoE4-positive ($r = -0.473$, $p = 0.020$) NC subjects.

On visual inspection, only one of the 87 NCs showed an FDG PET pattern suggestive of AD (RID 845). The BGL of this subject was not increased (106 mg/dl, amyloid status not available, ApoE 3/4).

Linear regression of FDG uptake in the AD-meta ROI in the NC subjects resulted in: FDG uptake = 1.022 – 0.176*BGL (mg/dl)/1000 (one-sided $p = 0.059$). This regression equation was used to correct FDG uptake in the AD-meta ROI in the MCI patients to mean BGL in the NC subjects (98.4 mg/dl) according to the formula: corrected FDG uptake = uncorrected FDG uptake +0.176/1000*[BGL (mg/dl) – 98.4].

In the ADNI MCI subjects, BGL was 101.2 ± 16.9 mg/dl (55–189). FDG uptake in the AD-meta ROI provided an area under the ROC curve of 0.804 for identification of MCI-to-AD progressors (95% CI: 0.746–0.863). Correcting FDG uptake in the AD-meta ROI for BGL based on the linear regression in the NC group did not result in significant change (area = 0.808, 95% CI: 0.751–0.866, Delong test $p = 0.311$, Fig. 3).

Discussion/conclusion

A series of studies by Ishibashi and co-workers has demonstrated that a mildly increased BGL that is still within the acceptable range ≤ 160 mg/dl probably causes reversible alteration of brain FDG uptake in cognitively normal subjects that mimic AD-typical hypometabolism [6–10]. The present study confirmed this finding in a large sample of ADNI NC subjects who had remained cognitively stable for at least 3 years after FDG PET. The latter suggests that the reduction of FDG uptake in the occipital and parieto-occipital cortex observed in these subjects was not due to presymptomatic AD. This was confirmed by the negative correlation between occipital FDG

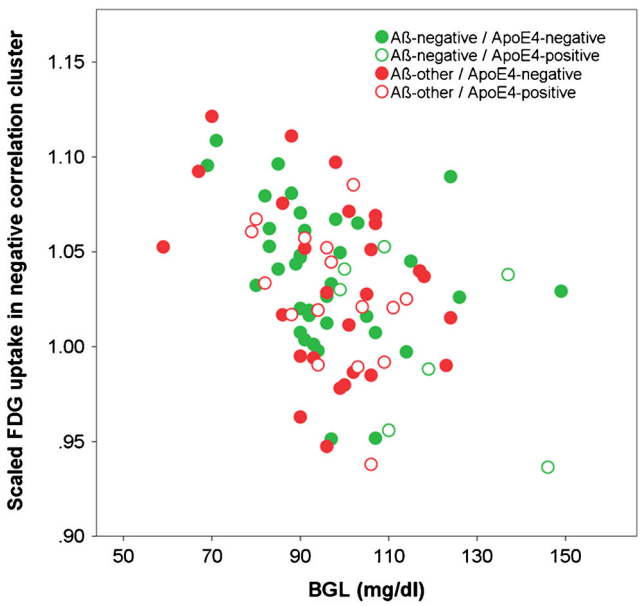

Fig. 2 Scaled FDG uptake in the negative correlation cluster versus blood glucose level (BGL) in the NC subjects

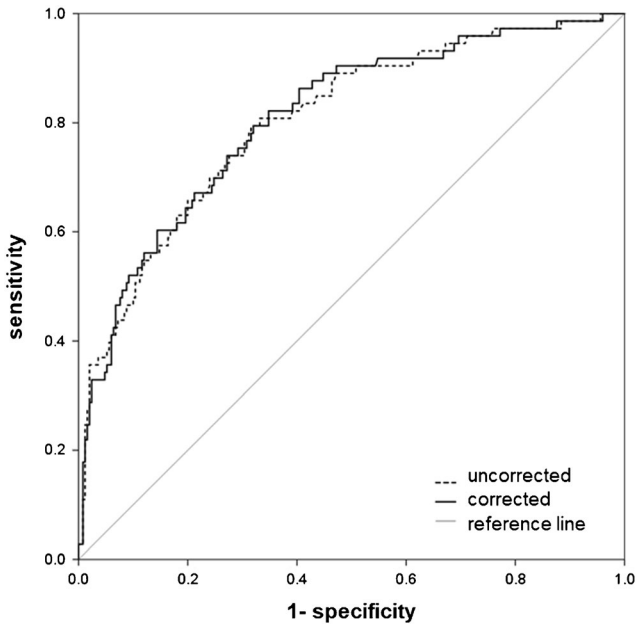

Fig. 3 ROC curve for identification of MCI-to-ADD progressors by FDG uptake in the AD meta-ROI with and without correction for BGL

uptake and BGL when the analysis was restricted to amyloid-negative control subjects. Furthermore, the BGL-associated pattern was similar to the typical AD pattern, but it was not identical: it comprised the occipital cortex including the cuneus and precuneus but not the posterior cingulate, and it extended towards the parieto-occipital rather than parieto-temporal cortex. Thus, the posterior cingulate, the brain region that first shows hypometabolism in AD [2], was relatively spared by the BGL effect. The negative correlation between occipital FDG uptake and BGL was also present in ApoE4-negative NC subjects, suggesting that it was not driven by ApoE4 status independent of AD pathology [14].

The sample of ADNI NCs included in the present study comprised data from 14 different PET models from 3 different vendors. The most frequently used PET model was the Siemens ECAT HR+ (28 of 87 subjects, 32.2%). This causes additional variability compared to a single-scanner setting. However, all ADNI sites had been qualified by an image center qualification process including a technical set-up visit with imaging of a 3D Hoffman brain phantom to optimize the acquisition and reconstruction protocol for the specific PET system to be used in ADNI participants [15]. Furthermore, ADNI provides not only original "raw" PET images uploaded by the imaging sites to the central image repository. ADNI also provides preprocessed PET images [16]. Preprocessing includes interpolation onto an uniform image grid (1.5-mm^3 voxels) followed by smoothing with a scanner-specific filter derived from each site's Hoffman phantom measurement. This results in a common isotropic resolution of 8 mm full-width-at-half-maximum in preprocessed ADNI PET images. Harmonization of PET acquisition and reconstruction protocols combined with scanner-specific preprocessing in the imaging core lab strongly reduces scanner-dependent variability in preprocessed ADNI PET images [16]. This was the rationale for using pre-processed FDG PET images in this study ("Statistical analyses" in Materials and methods). However, residual scanner-dependent variability that might have driven the observed regional correlation between FDG uptake and BGL might not be ruled out a priori. In order to test this, we restricted the analysis of correlation between scaled FDG uptake in the negative correlation cluster and BGL to the 28 NC subjects scanned with a Siemens ECAT HR+ PET system. The negative correlation was statistically significant in this subsample, too (Pearson correlation coefficient = −0.379, $p = 0.047$). This suggests that the BGL-associated variability of regional FDG uptake observed in this study was not driven by PET scanner-specific variability.

Concerning the mechanism underlying BGL-associated reduction of relative FDG uptake in the occipital cortex, we hypothesize that it just reflects the well-known reduction of gray-to-white matter contrast due to reduced count statistics secondary to BGL increase. We hypothesize that the reduction of gray-to-white matter contrast is more pronounced in the occipital cortex compared to frontal and temporal cortex, because the occipital cortex is considerably thinner [17]. As a consequence, count statistics in FDG PET are lower in the occipital cortex already at low normal glucose levels. This makes the occipital cortex more sensitive to mild reduction of count statistics.

The main finding of this study is that the BGL-associated variability of FDG uptake has no relevant impact on the power of FDG PET for prediction of ADD in MCI. In particular, there is no increased risk of false positive AD diagnosis in healthy subjects (without presymptomatic AD) by visual interpretation of FDG PET, neither based on uptake images nor based on statistical parametric maps. This is valid for BGL within the acceptable range ≤ 160 mg/dl. The present study does not allow conclusions regarding the possible impact of BGL > 160 mg/dl.

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Compliance with ethical standards

Conflicts of interest P.S. and L.S. are employees of jung diagnostics GmbH, Hamburg, Germany. This did not bias their work, as they have no financial interest in the results of this study. All other authors declare that they do not have any potential conflict of interest concerning this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent As the present study was retrospective in nature, formal consent was not required.

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