Brain glucose metabolism and its relation to amyloid load in middle-aged adults with childhood-onset epilepsy

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Abstract

Uncomplicated childhood-onset epilepsy is associated with increased brain amyloid load at late middle age, but its possible association with Alzheimer-type neurodegenerative processes is unclear. After 50-year follow-up, 42 childhood onset epilepsy subjects and 45 matched controls were investigated with [^{18}F]fluorodeoxyglucose PET. There were no significant differences between the subjects and controls, but higher [^{18}F]fluorodeoxyglucose uptake was associated with a higher local amyloid load (as measured with [^{11}C]PIB PET) in the prefrontal cortex, parietal cortex, and posterior cingulate/precuneus in subjects but not in controls. These findings parallel reported observations in cognitively normal individuals with increased brain amyloid accumulation who are at risk for future Alzheimer's disease.

1. Introduction

Epilepsy is frequently associated with cognitive impairment and epidemiological studies have demonstrated overlap between epilepsy and Alzheimer's disease (AD).(Hermann et al. 2008) In addition, post-mortem human and translational studies have provided evidence linking epileptic seizures with brain amyloid pathology.(Hermann et al. 2008) Furthermore, a higher brain amyloid accumulation in subjects with a history of epilepsy was very recently confirmed in humans *in vivo*.(Joutsa et al. 2017) Brain amyloid retention was localized mainly to the prefrontal cortex, posterior cingulate cortex and precuneus, resembling the findings reported in patients with preclinical AD.(Kemppainen et al. 2007, Rowe et al. 2007)

According to the hypothetical dynamic model of the temporal unveiling of biomarkers in AD, amyloid retention is among the first events, which is later followed by neurodegeneration as evidenced by tau-pathology and reduced brain glucose metabolism.(Jack et al. 2013) Brain structural damage and clinical cognitive impairment become evident only later on along with progressive neurodegeneration which are considered as relatively late events in the disease process.(Jack et al. 2013) Although epilepsy is associated with increased amyloid load, it is not known if it reflects a static benign condition or a progressive neurodegenerative process leading to dementia.(Joutsa et al. 2017)

The aim of the present study was to investigate if subjects with childhood-onset epilepsy show signs of early neurodegeneration, reflected as altered brain metabolism. The study was conducted with a population-based cohort of subjects with childhood-onset epilepsy prospectively followed for more than half a century since the early 1960s. This study builds on the previous study that demonstrated the increase in brain amyloid accumulation in childhood-onset epilepsy. (Joutsa et al. 2017)

2. Methods

The study protocol received approval from the local Institutional Review Board (Diary No. 120/2008/26.1.2009 §454). Written informed consent was obtained and the study was conducted according to the Declaration of Helsinki.

2.1 Participants

The recruitment of the participants and the follow-up setting has been described in detail previously.(Sillanpää et al. 1998, Sillanpää 1973, Sillanpää et al. 2015) Briefly, the subjects with childhood onset epilepsy were enrolled at age 0 to 15 years in 1961-1964 at an average age of 4.3 years and followed through their lives until late middle age (average 56 years). Overall 51 subjects and 52 controls participated in the Turku Adult Childhood-Onset Epilepsy (TACOE) study for follow-up.(Sillanpää et al. 2015) Of the 103 participants, 13 (7 subjects, 6 controls) declined PET imaging, two subjects were excluded due to structural brain lesions and one control discontinued due to a panic attack in the scanner, leaving 87 participants (42 subjects and 45 controls) in the final sample with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET imaging. Of these subjects, [^{11}C]Pittsburgh compound B ([^{11}C]PIB) imaging data were available from 86 participants (41 subjects, 45 controls) except for failure of quantitative analyses in one subject.(Joutsa et al. 2017) Neuropsychological examination included ten validated tests examining memory, language, executive and visuomotor functions. Three or more test scores at least 1.5 SD below the mean of the control group was defined as cognitive impairment (for more details, please see Karrasch et al.(Karrasch et al. 2017)).

2.2 Imaging

All but one subject and one control that had a contraindication to MRI, were scanned with 3T brain MRI (Siemens AG, München, Germany) and 3D T1-weighted images with 1x1x1mm voxels were obtained for structural reference. MR images were clinically evaluated by a consultant neuroradiologist.

PET imaging was performed using Siemens High Resolution Research Tomograph (Siemens Medical Solutions, Knoxville, TN, USA). Antecubital vein was cannulated for the tracer injection. Mean (SD) 202 (19) MBq bolus of [^{18}F]FDG was administered at the beginning of scan. In case [^{11}C]PIB and [^{18}F]FDG scanning were performed on the same day, [^{11}C]PIB was performed first allowing at least five ^{11}C half-lifes in between the injections to prevent carry-on effects of the signal. To ensure normoglycemia, plasma glucose levels were controlled before [^{18}F]FDG injection. The duration of the scan was 55 minutes. The participants were required to stay awake and keep their eyes open during the scanning. Head motion was measured using Polaris tracking device with infrared light detectors attached to a plastic cap positioned on top of the thermoplastic mask, which was used to reduce head motion. None of the participant reported epileptic seizures during the imaging or preceding days.

Preprocessing of the images was conducted using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), as described earlier. Regions-of-interest (ROIs) were created in the anterior cingulate (ACC), cerebellar cortex (CER), occipital cortex (OCC), parietal cortex (PAR), posterior cingulate and precuneus (PCP), prefrontal cortex (PFC) and temporal cortex (TEM) using the Anatomical Automatic Labelling (AAL) atlas (Tzourio-Mazoyer et al. 2002) excluding the white matter regions. Pons was designated as the reference region for quantification of the tracer uptake.(Mosconi et al. 2010) Regional [^{18}F]FDG uptake was calculated as the region-to-pons uptake ratio from 35 to 55 minutes from the injection. The ratio images were smoothed using 10 mm full-width-at-half-maximum (FWHM) Gaussian kernel for SPM analyses to improve the signal-to-noise ratio.

The [^{11}C]PIB imaging protocol and results have been published previously.(Joutsa et al. 2017) Briefly, preprocessing was conducted similarly as [^{18}]FDG and [^{11}C]PIB uptake was analyzed using data from 60 to 90 minutes from the injection by calculating region-to-cerebellar cortex uptake ratios. [^{11}C]PIB images were visually evaluated as abnormal if the tracer uptake in the frontal

cortex, posterior cingulate / precuneus, parietal cortex or temporal cortex was higher or equal to white matter.

2.3 Statistical analysis

Demographic variables were compared between subjects and controls using Student's t-Test or Fisher's Exact Test, as appropriate. The primary outcome measure, regional [^{11}C]PIB uptake, was compared between subjects and controls using general linear model with and without adjusting for apolipoprotein E4 allele (ApoE4) genotype and age. Corresponding voxel-by-voxel analyses were run in SPM with and without the covariates searching over the entire brain with average [^{18}F]FDG uptake ratio threshold of ≥1.0 using family-wise error (FWE) correction for multiple comparisons. Furthermore, brain regional [^{18}F]FDG uptake in subjects with active epilepsy (not in remission), abnormal [^{11}C]PIB scan, ApoE4 genotype or cognitive impairment were compared to other subjects using Student's t-Test. The interrelationship between regional [^{11}C]PIB and [^{18}F]FDG uptakes were investigated using Spearman's rank order correlation coefficient using the ROI data. The analyses, apart from voxel-by-voxel analyses, were run in SPSS Statistics 23 (IBM Corp., Armonk, NY) and P values less than 0.05 were considered significant.

3. Results

The demographics and quality control imaging parameters are described in Table 1. Of the subjects, 24 had idiopathic and 18 cryptogenic etiologies. The most common syndromes were temporal lobe epilepsy (n=10), epilepsy with common generalized tonic-clonic seizures (n=9) and rolandic epilepsy (n=8). The most commonly used medications were barbiturates (n=33, 79%), hydantin (n=23, 55%) and carbamazepine (n=9, 21%). Only three (7%) of the subjects had not received any antiepileptic medication. None of the subjects had underwent epilepsy surgery. Subjects and controls did not differ in regional brain [^{18}F]FDG uptake in any of the examined ROIs (Figure 1), which was confirmed with the

whole-brain SPM analysis. Correcting for age and ApoE4 genotype did not change the results and there was no group x ApoE4 interaction effect in any of the studied regions. Subjects with or without abnormal brain amyloid retention (n=9 vs n=32) did not significantly differ in [^{18}F]FDG uptake ($p>0.05$). However, there was a significant positive association between [^{11}C]PIB and [^{18}F]FDG uptake in the PFC ($r_{40}=0.40$, $p=0.01$), PAR ($r_{40}=0.40$, $p=0.01$) and PCP ($r_{40}=0.40$, $p=0.01$) in subjects, but not in controls ($r_{45}=0.15$, $p=0.33$, $r_{45}=0.01$, $p=0.95$ and $r_{45}=0.09$, $p=0.56$, respectively) (Figure 2).

There were no significant correlations between [^{11}C]PIB and [^{18}F]FDG uptake in any other brain region in subjects or controls ($p>0.05$). Regional [^{18}F]FDG uptake in subjects with active epilepsy, abnormal [^{11}C]PIB scan, ApoE4 presence or cognitive impairment did not differ significantly from other subjects ($p>0.05$).

4. Discussion

The results of the present study show that although uncomplicated childhood-onset epilepsy is associated with increased brain amyloid at late middle age,(Joutsa et al. 2017) it is not yet associated with signs of neurodegeneration. However, higher prefrontal, parietal and precuneus amyloid showed moderate to low positive correlation with local cortical metabolism paralleling the findings in presymptomatic individuals with brain amyloid pathology,(Oh et al. 2014) providing further evidence that these individuals are at heightened risk for developing neurodegenerative dementia at older age.

AD is associated with widespread progressive brain amyloid pathology and decreased regional glucose metabolism that is most prominent in the parietal and temporal cortices.(Li et al. 2008) However, at preclinical and early stages of the disease, the amyloid accumulation is associated with increased local brain glucose metabolism. (Cohen et al. 2009, Johnson et al. 2014, Oh et al. 2014, Kemppainen et al. 2015) Increased glucose metabolism is thought to reflect compensatory or reactive metabolic upregulation,(Cohen et al. 2009, Johnson et

al. 2014, Oh et al. 2014) but disturbed glucose metabolism can also be an independent process contributing to the development of clinical AD.(Jagust 2016) Nevertheless, compensatory/reactive hypermetabolism is present only in preclinical AD later reverts to hypometabolism along with progressive neuronal damage and conversion to clinical AD.(Cohen et al. 2009, Johnson et al. 2014, Li et al. 2008) Therefore, increased brain amyloid load with increased glucose metabolism in adults with childhood-onset could be interpreted as an early sign of an AD-type neurodegenerative process.(Joutsa et al. 2017) In the present study, the association between brain amyloid load and glucose metabolism was not seen in controls, which is probably caused by a floor-effect as only very few of the controls had abnormal [^{11}C]PIB scans (i.e. most of the controls had very low [^{11}C]PIB uptake) reducing the sensitivity to detect significant correlations.

The main limitation of the present study is the relatively modest number of subjects with abnormal brain amyloid load, which might decrease the sensitivity to detect subtle group differences. In addition, the study population was heterogeneous in terms of epilepsy syndromes and clinical outcome, possibly further masking changes in the brain metabolism in group-level analyses. However, the very long-term consequences of childhood-onset epilepsy are extremely hard to study, and the present study sample provided a unique opportunity to address these questions considering the exceptionally long prospective follow-up of a population-based cohort.

4.1 Conclusions

In conclusion, adults with childhood-onset epilepsy have, at late middle age, an increased brain amyloid accumulation associated with a higher local metabolic activity, but no manifest neurodegeneration. The finding parallels previous observations with individuals at-risk or at preclinical stages of AD. Further follow-up of the cohort will determine if these subjects will indeed develop AD.

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Author contribution statement

Dr Joutsa contributed to the concept and design, acquisition and analysis of data, interpretation of data, wrote the first draft of the manuscript. Dr Rinne, Dr Karrasch, Dr Hermann and Dr Shinnar contributed to the concept and design and interpretation of data. Dr Johansson contributed to the analysis of the data. Dr Anttinen contributed to the concept and design and acquisition of data. Dr Eskola and Dr Helin contributed to the acquisition of data. Dr Sillanpää was the principal investigator, and contributed to the concept and design, acquisition of data and interpretation of data. All authors critically revised the draft of the manuscript and approved the final version to be published.

Conflicts of interest

Dr Joutsa has received research grants from Lundbeck and Orion Research Foundation, and travel grants from Abbvie and Orion. Dr. Rinne reports grants from Sigrid Juselius Foundation, grants from Turku University Hospital, during the conduct of the study; and Dr. Rinne serves as a consultant for CRST Ltd (Clinical Research Services Turku). Dr. Karrasch serves as Associate Editor for Nordic Psychology. Dr. Hermann reports grants from Citizens United for Epilepsy Research (Co-PI), during the conduct of the study. Dr. Shinnar reports personal fees from Accorda, personal fees from AstraZenica, personal fees from Malinckrodt, personalfees from Neurelis, personal fees from Upsher-Smith, personal fees from UCB Pharma, and personal fees from Xeris outside the submitted work; In addition, Dr. Shinnar is Co-Editor of Book "Febrile Seizures" by Elsevier 2002 with royalties paid. Dr Anttinen, Dr Helin, Dr Eskola and Dr Sillanpää have nothing to disclose.

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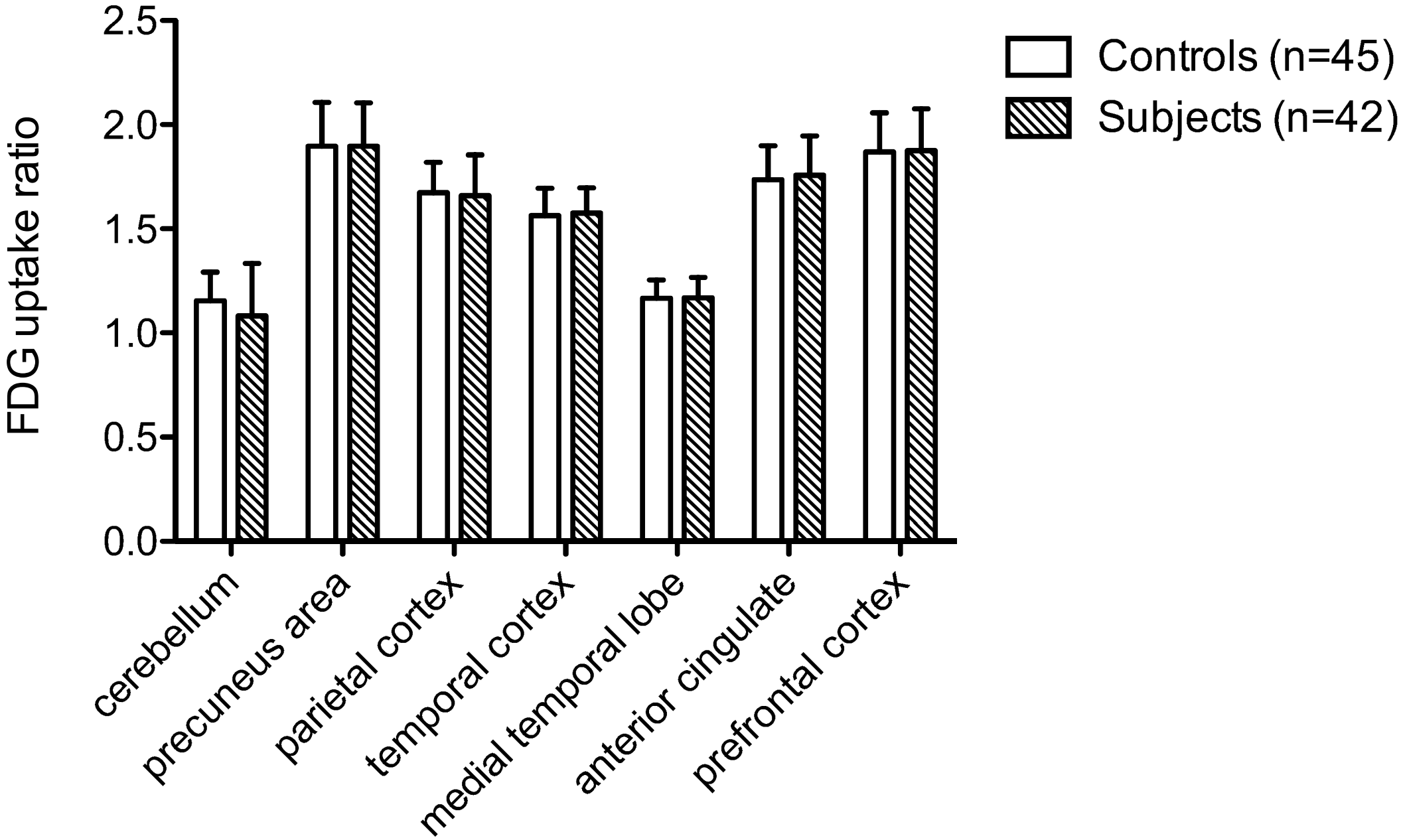
Figure legends

Figure 1. Brain regional uptake in adult controls and subjects with childhood-onset epilepsy.
All group comparisons in all brain regions are non-significant.

Figure 2. Correlation between prefrontal cortex amyloid load and glucose metabolism in adult controls and subjects with childhood-onset epilepsy.


FDG uptake ratio
2.5
2.0
1.5
1.0
0.5
0.0
Controls (n=45)
Subjects (n=42)
cerebellum
precuneus area
parietal cortex
temporal cortex
medial temporal lobe
anterior cingulate
prefrontal cortex

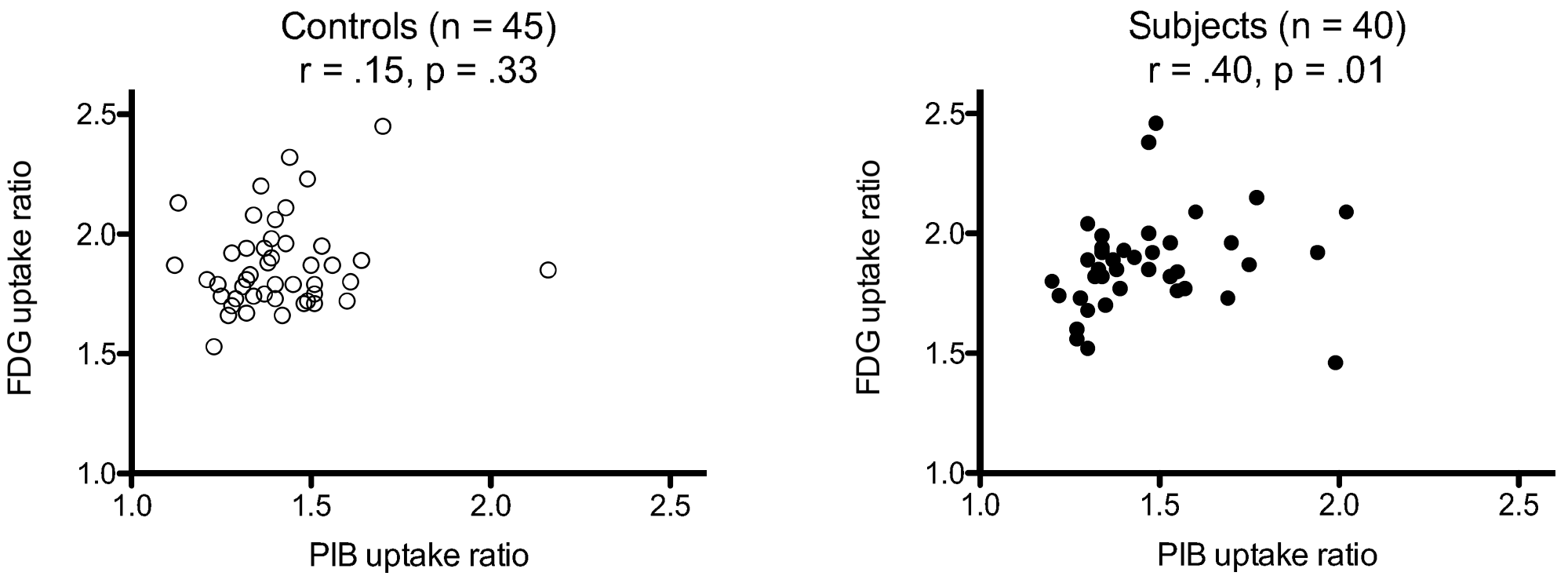

Controls (n = 45)
r = .15, p = .33
FDG uptake ratio
PIB uptake ratio
2.5
2.0
1.5
1.0
1.0
1.5
2.0
2.5
Subjects (n = 40)
r = .40, p = .01
FDG uptake ratio
PIB uptake ratio
2.5
2.0
1.5
1.0
1.0
1.5
2.0
2.5

Table 1. Demographics.

	Subjects (n=42)	Controls (n=45)	P
Age (y)	56.0 (4.3, 48-63)	56.0 (4.3, 49-64)	1.0
Sex (males)	16 (38%)	16 (36%)	1.0
BMI (kg/m^2)	27.5 (5.9)	29.0 (5.0)	0.20
APOE ε4 allele	11 (27%)	13 (29%)	1.0
Cognitively impaired[1]	18 (43%)	6 (13%)	0.002
Abnormal PIB scan[2]	9 (22%)	3 (6.7%)	0.04
Cumulative years with seizures	8.3 (10.4, 1-41)	-	-
Duration of antiepileptic therapy	20.2 (18.6, 0-55)	-	-
Active epilepsy (not in remission)	9 (21%)	-	-
FDG dose (MBq)	205 (25)	199 (10)	0.15
FDG dose per weight (MBq/kg)	2.6 (0.5)	2.6 (0.6)	0.58
Between-frame transposition (mm)[3]	1.2 (0.8-1.8)	0.9 (0.5-1.7)	0.20
Within-frame amplitude (mm)[3]	0.5 (0.3-0.8)	0.3 (0.2-0.5)	0.10

The values represent, mean (SD, range) or number (percent) with t-test or Fisher exact test, as appropriate.
[1]Three or more out of 10 test scores at least 1.5 SD below normal (Karrasch et al., 2017)
[2]PIB scan available from 41 subjects. 1-sided Fisher exact test.
[3]Motion data available from 34 subjects and 34 controls. Median (IQR) values with Mann-Whitney U-test p-values are presented.