Asymmetries of amyloid-β burden and neuronal dysfunction are positively correlated in Alzheimer’s disease

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Clinical Alzheimer’s disease affects both cerebral hemispheres to a similar degree in clinically typical cases. However, in atypical variants like logopenic progressive aphasia, neurodegeneration often presents asymmetrically. Yet, no in vivo imaging study has investigated whether lateralized neurodegeneration corresponds to lateralized amyloid-β burden. Therefore, using combined 11C-Pittsburgh compound B and 18F-fluorodeoxyglucose positron emission tomography, we explored whether asymmetric amyloid-β deposition in Alzheimer’s disease is associated with asymmetric hypometabolism and clinical symptoms. From our database of patients who underwent positron emission tomography with both 11C-Pittsburgh compound B and 18F-fluorodeoxyglucose (n = 132), we included all amyloid-positive patients with prodromal or mild-to-moderate Alzheimer’s disease (n = 69). The relationship between 11C-Pittsburgh compound B binding potential and 18F-fluorodeoxyglucose uptake was assessed in atlas-based regions of interest covering the entire cerebral cortex. Lateralizations of amyloid-β and hypometabolism were tested for associations with each other and with type and severity of cognitive symptoms. Positive correlations between asymmetries of Pittsburgh compound B binding potential and hypometabolism were detected in 6 of 25 regions (angular gyrus, middle frontal gyrus, middle occipital gyrus, superior parietal gyrus, inferior and middle temporal gyrus), i.e. hypometabolism was more pronounced on the side of greater amyloid-β deposition (range: r = 0.41 to 0.53, all P < 0.001). Stronger leftward asymmetry of amyloid-β deposition was associated with more severe language impairment (P < 0.05), and stronger rightward asymmetry with more severe visuospatial impairment (at trend level, P = 0.073). Similarly, patients with predominance of language deficits showed more left-lateralized amyloid-β burden and hypometabolism than patients with predominant visuospatial impairment and vice versa in several cortical regions. Associations between amyloid-β deposition and hypometabolism or cognitive impairment were predominantly observed in brain regions with high amyloid-β load. The relationship between asymmetries of amyloid-β deposition and hypometabolism in cortical regions with high amyloid-β load is in line with the detrimental effect of amyloid-β burden on neuronal function. Asymmetries were also concordant with lateralized cognitive symptoms, indicating their clinical relevance.

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**Introduction**

In clinical Alzheimer’s disease it is widely agreed that cerebral amyloid-β pathology is followed by neurodegeneration which ultimately leads to the typical cognitive decline (Jack et al., 2010, 2013a). Amyloid-β pathology is not benign (Zetterberg and Blennow, 2013) and is the presumed starting point of Alzheimer’s disease in most cases (Jack et al., 2013b).

Typical Alzheimer’s disease is regarded as a disease that affects both cerebral hemispheres in a fairly symmetric fashion (Raji et al., 2008). In contrast, in atypical variants of Alzheimer’s disease like logopenic progressive aphasia, neurodegenerative features, such as reduced metabolism on fluorodeoxyglucose (FDG) PET (Rabinovici et al., 2008; Madhavan et al., 2013) and atrophy on MRI (Gorno-Tempini et al., 2004; Migliaccio et al., 2009), show a remarkable hemispheric asymmetry concordant with lateralized cognitive symptoms. Recently, asymmetries of atrophy in patients with primary progressive aphasia and underlying Alzheimer’s pathology have been demonstrated to reflect asymmetric distributions of neurofibrillary tangles (Gefen et al., 2012; Mesulam et al., 2014).

The spatial distribution of amyloid-β deposition frequently appears asymmetric on clinical amyloid PET scans. Thus, it is an intriguing hypothesis that asymmetric amyloid-β distribution may be associated with an ‘asymmetric’ phenotype. However, to date no in vivo imaging study has systematically investigated the relationship between asymmetries of amyloid-β deposition and biomarkers of neurodegeneration.

Using combined $^{11}$C Pittsburgh compound B (PiB) and $^{18}$F FDG PET, we explored the relationship between asymmetries of amyloid-β deposition and hypometabolism in amyloid-β-positive, clinically diagnosed Alzheimer’s disease and prodromal Alzheimer’s disease patients, i.e. mild cognitive impairment due to Alzheimer’s disease. Specifically, we hypothesized that lateralization of amyloid-β deposition as assessed by PiB PET correlates with the lateralization of hypometabolism as measured with FDG PET. Moreover, to assess the clinical relevance of lateralized amyloid-β deposition, we tested for associations with language and visuospatial test scores as well as predominance of verbal or visuospatial cognitive deficits.

**Materials and methods**

**Patients**

From our clinical registry we identified all 132 patients who underwent both PET scanning with FDG and PiB for dementia diagnostics in clinical routine between May 2009 and September 2013. In a standardized procedure and blinded to clinical symptoms, two expert PET readers (P.T.M. and R.B.) rated 77 of 132 patients as amyloid-β-positive. As associations of amyloid-β with hypometabolism were the focus of the present study, only amyloid-β-positive patients were included.

According to currently established criteria (Albert et al., 2011; McKhann et al., 2011), 69 of 77 patients were diagnosed as Alzheimer’s disease or mild cognitive impairment due to Alzheimer’s disease in multidisciplinary consensus taking into account all available information (neuropsychology, PET, MRI and CSF markers if available). Given that the current study did not focus on diagnostic accuracy, PET imaging data served as supplementary information for final clinical diagnoses. Most of the patients were right-handed ($n=61/69$), six were left-handed, and information on handedness was unavailable in two patients. Patients mild cognitive impairment are referred to as prodromal Alzheimer’s disease patients, as incorporation of biomarkers for amyloid-β and neuronal injury provided high certainty for mild cognitive impairment due to Alzheimer’s disease diagnoses (Albert et al., 2011). All patients gave written informed consent as approved by the local ethics committee.

**PET acquisition and preprocessing**

All patients underwent PiB and FDG PET examinations on the same PET scanner, either an ECAT EXACT 922/47 PET system (Siemens-CTI) ($n=37$) or a Philips Gemini TrueFlight 64 integrated PET/CT system (TF64, Philips) ($n=32$). PiB and FDG PET scans were acquired on the same day in 34 patients, within 1 week in 26 patients, and within 1 month in five patients; the time gaps in the remaining four patients were 47, 50, 83, and 198 days. PiB PET data sets were acquired over 60 min (frames: $3 \times 20$ s, $3 \times 30$ s, $2 \times 60$ s, $2 \times 90$ s, $3 \times 150$ s, and $9 \times 300$ s) after intravenous bolus injection of $480.2 \pm 96.9$ MBq (ECAT) or $392.3 \pm 51.7$ MBq (TF64) PiB. Data sets were reconstructed by filtered back-projection (Shepp filter, 5 mm full-width at half-maximum) for the ECAT scanner or 3D-RAMLA algorithm for the TF64 scanner. FDG PET scans were performed 40 min after intravenous injection of $306.9 \pm 14.8$ MBq on the ECAT (10-min scan) or 50 min after intravenous injection of $211.5 \pm 13.9$ MBq on the TF64 scanner (10-min scan). FDG images were reconstructed with...
the same reconstruction parameters as the PiB images. All patients had fasted for >6 h beforehand, with plasma glucose levels within the normal range. PiB radiochemical synthesis was performed as previously described (Solbach et al., 2005); the precursor was provided by ABX. Both scans were performed under resting conditions with eyes open, ambient noise levels, and dimmed light. For each acquisition, the patient’s head was gently restrained with an elastic tape; the position of the head was carefully monitored and, if necessary, manually corrected. In cases of head movements, additional software-based motion correction was performed by using the PMOD Software package (V 3.2, PMOD Technologies Ltd).

PET data preprocessing was performed with the PMOD Software package, as previously described (Meyer et al., 2011; Frings et al., 2013). Parametric images of regional amyloid load [i.e. non-displaceable binding potential (BP_{ND}) images] were generated with the simplified reference tissue model (SRTM2) (Wu and Carson, 2002). The cerebellar cortex was chosen as the reference region devoid of specific PiB binding (Klunk et al., 2004). For further analysis, PiB BP_{ND} and FDG data sets were spatially normalized to the Montreal Neurological Institute (MNI) PET template provided by PMOD. For spatial normalization of individual PiB BP_{ND} images, respective R_{1} images were normalized to the PET template, and normalization parameters were then applied to the PiB BP_{ND} images. Regional FDG uptake was proportionally scaled to FDG uptake of the whole brain. To assess regional FDG uptake and BP_{ND} values, all normalized data sets were analysed by use of the LPBA40 template, an established set of 56 cortical and subcortical brain regions (LONI Probabilistic Brain Atlas, LPBA40) (Shattuck et al., 2008). We analysed all cortical regions (25 for each hemisphere). For each region of interest, the hemispheric asymmetry index (AI) was calculated for PiB BP_{ND} using the formula:

$$\text{PiB - AI[\%]} = 200 \times (R - L)/(R + L)$$

For FDG uptake, the following formula was used to represent relative hypometabolism (defined as lower metabolism compared with the contralateral region) and thus to reflect lateralized neuronal injury:

$$\text{FDG - AI[\%]} = -200 \times (R - L)/(R + L)$$

**Cognitive symptoms**

The German version of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropsychological assessment battery (Morris et al., 1989) was used as part of the clinical work-up in most cases (n = 63/69). A few patients performed only selected subtests of the battery. The median interval between neuropsychological assessments and PET imaging was 44 days (mean ± SD: 3.1 ± 5.5 months). Each patient was categorized into one of three clinical presentation groups: predominant memory, language, or visuospatial impairment. Categorizations were performed according to CERAD subtest performance (based on normative data). Average z-scores were computed separately for each of the three domains (memory: verbal learning, verbal recall, figure recall; language: verbal fluency, Boston Naming Test; visuospatial: figure drawing), and the most impaired domain was determined. The predominant cognitive deficit was categorized as memory in 26, language in 12, and visuospatial impairment in 18 cases. Thirteen patients remained unclassified due to incomplete available data that prevented a comparison between domains. See Table 1 for patient characteristics of the entire group as well as the clinical presentation subgroups.

**Statistics**

Statistical analyses were performed with MATLAB and the Statistics Toolbox (http://www.mathworks.com). Controlling for scanner type, sex, age, and Mini-Mental State Examination (MMSE) score, partial correlations were calculated between (i) AI of PiB BP_{ND} (PiB-AI) and AI of FDG hypometabolism (FDG-AI); and (ii) PiB BP_{ND} and normalized FDG uptake (separately for each hemisphere).

For correlation analyses between PiB-AI and FDG-AI as well as PiB BP_{ND} and normalized FDG uptake, results were regarded as significant if P < 0.002, in accordance with applying the Bonferroni correction to take into account that 25 regions were analysed.

PiB-AI and FDG-AI have furthermore been explored for differences between clinical presentation groups (categorization based on CERAD subtest performance). Kruskal-Wallis tests were applied to test for significant group effects in each of the 25 cortical regions plus the composite region.

Relationships between cognitive performance on one side and PiB-AI or FDG-AI on the other were assessed within a composite region of interest comprising all regions which showed a significant relationship between PiB-AI and FDG-AI. Partial correlations between PiB-AI and z-scores of CERAD subtests that assess lateralized cognitive functions were calculated, with verbal fluency and Boston Naming Test as language tests (left hemisphere) and figure drawing as a visuospatial test (right hemisphere). The same was performed for FDG-AI (partial correlations, controlling for sex and age; one-tailed tests). Results of the exploratory tests of associations between AI and cognition were regarded as significant if P < 0.05 (not corrected for multiple tests).

**Results**

PiB-AI was significantly positively correlated with FDG-AI in 6/25 regions, i.e. more right-lateralized amyloid-β deposition was associated with more right-lateralized hypometabolism (Fig. 1). Regions that showed this significant relationship were the angular gyrus, inferior temporal gyrus, middle temporal gyrus, middle frontal gyrus, middle occipital gyrus, and superior parietal gyrus. Partial correlation coefficients in these regions ranged from r = 0.41 to 0.53 (all P < 0.001). This was essentially replicated in the subgroup of patients with predominant memory deficits (n = 26). Notably, significant associations were mainly detected in regions with an amyloid-β load that was comparable to or above global average amyloid-β deposition (Figs 3 and 4; see also Supplementary material for distribution of PiB BP_{ND} and normalized FDG uptake in example patients).
Within the left hemisphere, PiB $BP_{ND}$ showed a significant negative correlation with normalized FDG uptake only in the middle occipital gyrus (partial correlation, $r = -0.48$, $P < 0.001$; Fig. 1). A significant positive correlation between PiB $BP_{ND}$ and normalized FDG uptake was observed in the hippocampus ($r = 0.42$, $P < 0.001$).

Within the right hemisphere, a significant negative correlation between PiB $BP_{ND}$ and normalized FDG uptake was observed also in the middle occipital gyrus ($r = -0.48$; Fig. 1). A significant positive correlation was observed in the right superior frontal gyrus ($r = 0.42$, $P < 0.001$).

Within the composite region of interest of regions that showed a significant association between asymmetries of amyloid-β deposition and hypometabolism, PiB-AI was significantly positively correlated with verbal fluency (partial correlation, $r = 0.27$, $P < 0.05$), i.e. stronger leftward amyloid-β deposition was associated with more severe language impairment. PiB-AI showed a tendency towards a significant negative correlation with figure drawing performance ($r = -0.2$, $P = 0.073$), i.e. stronger rightward amyloid-β deposition was associated with more severe visuospatial impairment. FDG-AI showed a tendency towards a significant positive correlation with verbal fluency ($r = 0.19$, $P = 0.080$). Neither PiB-AI nor FDG-AI were correlated with Boston Naming Test performance.

PiB-AI differed between clinical presentation groups in 4/25 regions: angular gyrus, insular cortex, inferior and middle temporal gyrus ($P < 0.05$). In each of the regions showing a significant group difference, PiB was more left-lateralized in patients with language than patients with visuospatial deficits, while memory-type patients were intermediate (see boxplot medians in Fig. 2). This general pattern was observed in 11/25 regions.

FDG-AI showed a main effect of the clinical presentation group in 13/25 regions (cuneus, fusiform gyrus, hippocampus, inferior, middle, and superior occipital gyrus, inferior, middle, and superior temporal gyrus, middle orbitofrontal gyrus, parahippocampal gyrus, superior frontal gyrus, supramarginal gyrus), as well as the composite region. In each of the regions showing a significant group difference, hypometabolism was more left-lateralized in language than visuospatial deficit patients, while patients with predominant memory deficits were intermediate. This general pattern was observed in 20/25 regions. Figure 2 displays data from the six regions that showed a significant relationship between PiB-AI and FDG-AI as well as the composite region.

Neither sex, age, nor MMSE score, as a measure for dementia severity, had a significant effect on PiB-AI or FDG-AI (all $P > 0.1$; independent-samples $t$-tests or linear regressions).

### Discussion

We observed a significant positive correlation between asymmetries of both amyloid deposition and hypometabolism in amyloid-positive Alzheimer’s disease and prodromal...
Alzheimer’s disease patients. Importantly, these asymmetries were reflected by concordant cognitive deficits, indicating that differential spatial distribution of amyloid-β pathology may also have a differential effect on neurodegeneration and cognitive decline. We observed associations between amyloid-β deposition and hypometabolism or cognitive deficits predominantly in regions with high amyloid-β burden, which might indicate that amyloid-β pathology exerts its detrimental effect only after a critical threshold has been exceeded.

Figure 1 Lateralization of amyloid-β deposition was positively correlated with lateralization of neuronal dysfunction, indicating reduced metabolism with increasing amyloid-β deposition, in 6/25 cortical regions. A composite region is also shown. When each hemisphere was assessed separately (i.e. local associations, not AI), the relationship between elevated amyloid-β load and metabolism was observed only in the middle occipital gyrus. Linear fit (only for significant correlations) determined by principal component major axis. Correlation coefficients and P-values refer to partial correlations controlling for scanner type, sex, age, and MMSE score (n = 62; MMSE scores were not available in seven patients). Note that PiB-AI and FDG-AI were calculated inversely to reflect asymmetries of amyloid-β deposition and hypometabolism. AD = Alzheimer’s disease; n.s. = not significant; ROI = region of interest.
Combined PET imaging has been performed with both PiB, an established marker of amyloid pathology, and FDG, an established marker for neurodegeneration (McKhann et al., 2011; Jack et al., 2013a; Dubois et al., 2014), in the same individuals, allowing for a direct comparison between the two and with cognition. For BPND estimation, we used the SRTM2, which was previously validated as the reference tissue model most suitable for PiB analyses (Yaqub et al., 2008). It has to be emphasized that dynamic data acquisition with subsequent pharmacokinetic analyses, as done in the present work, allows for an estimation of BPND that is least biased by non-specific effects like cerebral blood flow changes and peripheral tracer clearance, as opposed to frequently used standardized uptake value ratios (SUVR) derived from late static scans. Thus, in this first analysis using AI we sought to assure that PiB measures were not biased by cerebral blood flow, which like FDG uptake is a marker of neuronal dysfunction. Nevertheless, replication of our findings is warranted. Publicly available databases like those from the Alzheimer’s Disease Neuroimaging Initiative may be well suited for this purpose. Although these databases only contain static PET data, they offer the advantage of large data sets. Furthermore, we used a conventional region of interest-based analysis because region of interest analyses represent the most established and robust analysis approach, especially concerning the calculation of AI. The main findings were also replicated with voxel-wise correlational analyses of PiB BPND with FDG uptake and PiB-AI with FDG-AI using the biological parametric mapping approach (Casanova et al., 2007) in combination with voxel-wise AI calculations (Kurth et al., 2015) (Supplementary material).

To our knowledge, this is the first study to use asymmetry indices to investigate the association between amyloid-β, glucose metabolism, and cognitive deficits.
Notably, asymmetry indices revealed effects that were largely concealed using classical measures of amyloid-β deposition and hypometabolism, indicating increased sensitivity. Previous studies, which investigated the relationship between amyloid-β deposition and glucose metabolism in the same individual, yielded inconclusive results: in cohorts of Alzheimer’s disease patients, the majority of previous studies did not find this association (Furst and Lal, 2011; Yokokura et al., 2011; Forster et al., 2012; Furst et al., 2012; La Joie et al., 2012; Landau et al., 2012; Ossenkoppele et al., 2012; Tauber et al., 2013). Only a few studies found an association between amyloid load and regional glucose metabolism (Engler et al., 2006; Edison et al., 2007; Cohen et al., 2009; Kadir et al., 2012; Frings et al., 2013). The reported associations were mainly located in posterior cortical regions. Similarly, an association between elevated amyloid-β deposition and hypometabolism in the occipital cortex was observed in the present study, which was presumably driven by patients with predominant visuospatial impairment. In patients with mild cognitive impairment, some studies found a significant negative correlation between amyloid-β load and metabolism (Drzezga et al., 2011; Landau et al., 2012; Zhou et al., 2015), whereas at least one other did not (Hata and Yamasaki, 2013). In healthy controls, several studies indicated no significant correlation between regional glucose metabolism and amyloid load uptake (Jagust and Landau, 2012; Mosconi et al., 2013; Wirth et al., 2013a, b, c; Hedden et al., 2014). In contrast, a large, recent study (n = 600 healthy controls) reported a significant association between elevated PiB levels and hypometabolism posterior cortical regions (Lowe et al., 2014). Taken together, this suggests that the correlation between amyloid-β deposition and cerebral metabolism is probably only weak, which prevents its detection in small samples. Furthermore, according to the hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade (Jack et al., 2010), this correlation presumably depends on the actual disease stage (i.e., most noticeable at preclinical and prodromal stages) and possible factors modulating the temporal relationship between these biomarkers (e.g., anatomical order and interindividual variations of amyloid-β processing, susceptibility to amyloid-β-promoted neuronal dysfunction, additional pathologies, brain resilience, or cognitive reserve).

We suggest that the use of asymmetry indices enhances the sensitivity to detect the association between amyloid-β burden and hypometabolism possibly by accounting for interindividually different susceptibility to amyloid-β-promoted neuronal dysfunction. It is widely accepted that amyloid-β deposition has a detrimental effect on neuronal function across the entire spectrum of the disease—in healthy individuals, patients with mild cognitive impairment, and patients with mild-to-moderate Alzheimer’s disease (Sperling et al., 2013; Mitsis et al., 2014). However, two findings call the neurotoxic effects of an increased amyloid-β load into question: (i) amyloid-β-positivity has been detected in cognitively healthy elderly persons; and (ii) even within clinically homogeneous groups of amyloid-β-positive Alzheimer’s disease patients, PiB BPND shows a considerable variability. Both observations might be explained by interindividually different susceptibility to amyloid-β pathology. Lower vulnerability to pathology in some individuals than in others has been associated with cognitive reserve (Jagust and Mormino, 2011), which has been suggested to comprise both brain structural health and active compensation for pathology (Braskie and Thompson, 2013). The analysis of asymmetries of

![Figure 3](https://academic.oup.com/brain/article-abstract/138/10/3089/2468716)
Amyloid-β burden and neuronal dysfunction in the current study had the effect of a within-subject ‘normalization’ for susceptibility and enabled us to detect that increased amyloid-β load was associated with decreased neuronal function in Alzheimer’s disease-typical regions. In line with this, a previous study used asymmetry indices to demonstrate that in logopenic progressive aphasia both amyloid-β deposition and hypometabolism were lateralized to the left hemisphere (Rabinovici et al., 2008). This study, however, did not test for a significant correlation between the two.

In the present study, associations between asymmetries of amyloid-β load and hypometabolism have not been observed in some candidate regions that are known to be involved in Alzheimer’s disease, such as precuneus or cingulate gyrus (Fig. 3). We assume that AI calculated in midline regions are confounded by the imperfect separation of the hemispheres by PET due to its limited spatial resolution. Furthermore, positive correlations between amyloid-β load and metabolism have been found in the right frontal gyrus and the left hippocampus, similar to a previous report (Cohen et al., 2009). These might reflect compensatory upregulation of metabolism in the presence of local pathology. However, given that the hippocampus on one hand has only very little PiB binding (Fig. 3) and on the other hand is one of the most atrophied regions in Alzheimer’s disease, it is especially prone to partial volume effects.

Cognitive deficits reflect PET asymmetries

As expected, impaired metabolism within the left hemisphere was associated with predominant verbal deficits, whereas decreased metabolism within the right hemisphere was related to non-verbal deficits. This corroborates similar findings regarding atrophy patterns in logopenic progressive aphasia and posterior cortical atrophy (Migliaccio et al., 2009). Remarkably, a significant association between amyloid-β and cognition has rarely been found and remains a matter of debate (Jagust et al., 2009). Post-mortem studies revealed a relationship between amyloid-β pathology and tau deposition in the form of neurofibrillary tangles related to neuronal loss in Alzheimer’s disease (Thal et al., 2002). Further studies demonstrated that the distribution of neurofibrillary tangles corresponds to clinical symptoms and severity in Alzheimer’s disease (Bennett et al., 2004). In dementia with predominant language impairment, tau pathology is lateralized to the language-dominant hemisphere (Mesulam et al., 2014), but a relationship between amyloid-β pathology and cognition has not been observed. The inability to detect this relationship has often been ascribed to a plateau of amyloid-β deposition that has been reached while degeneration and concomitant cognitive deficits progress. This certainly holds true for previous studies that failed to detect a...
relationship between post-mortem amyloid-β pathology and in vivo cognition, as they merely analysed final stages of the disease. In contrast, the current study investigated prodromal and mild-to-moderate Alzheimer’s disease stages, highlighting the extraordinary value of in vivo studies in this field.

The observed significant relationship does not necessarily imply that amyloid-β exerts a direct, detrimental effect on neuronal function. It is widely accepted that amyloid-β rather leads to neuronal dysfunction and neuron death via tau pathology (Jack et al., 2013a). In line with this notion, glucose hypometabolism has been demonstrated to be more strongly correlated with neurofibrillary tangles than amyloid-β plaque burden in vivo (Ossenkoppele et al., 2015) and post-mortem (Rapoport et al., 1991). Similar results have been reported for cognitive decline (Jack et al., 2008, 2009). In the present study, the direction of asymmetry of amyloid-β deposition was significantly different between clinical presentation groups, predominantly in regions with elevated amyloid-β load. Notably, asymmetries of hypometabolism differed between clinical groups in more regions than asymmetries of amyloid-β deposition (13/25 compared to 4/25 regions), including also regions with low amyloid-β burden. This is in line with the notion that cognition is more closely associated with metabolism than amyloid-β pathology.

Right lateralization of FDG uptake and PiB BPND

Both PiB BPND and FDG uptake were on average slightly higher within the right hemisphere (Fig. 1). To our knowledge, this has not been reported previously for amyloid PET. By contrast, it has been observed for FDG PET, especially in older subjects (Catafau et al., 1996; Brinkmann et al., 2012), as well as cerebral blood flow and oxygen utilization (Perlmutter et al., 1987). In our data, correction for this systematic right-sided shift (by using z-transformed AI; data not shown) even accentuated the results from 62% without correction to 83% of patients showing concordant lateralizations of amyloid-β deposition and hypometabolism.

Disease severity (indicated by MMSE score) was neither related to asymmetries of amyloid-β load nor to hypometabolism, suggesting that lateralization of pathology and neurodegeneration is not confined to disease onset, but rather persists to at least moderate stages. This is in line with the notion that lateralized neurodegeneration is a core feature throughout disease stages in primary progressive aphasia (Mesulam et al., 2014; Rogalski et al., 2014).

Limitations

The presence of the APOE4 allele has been linked to amyloid-β deposition as well as cognitive reserve. Its contribution to the relationship between amyloid-β pathology and neuronal function could not be assessed in the current study as the APOE4 status of the patients was unknown. However, a more recent study found no effect of APOE4 on amyloid distribution (Josephs et al., 2014).

Magnetic resonance images were not consistently available, and hence no partial volume correction has been performed. Atrophy might thus have contributed to decreased FDG uptake. However, both are established biomarkers for neurodegeneration, which leaves the validity of the observed amyloid-β effects on neurodegeneration uncompromised. Possible effects of partial volume correction on the results presented here are hard to predict and need to be assessed in future studies.

The focus of this study was on investigating regional relationships between amyloid-β load and hypometabolism. Contributions of amyloid-β pathology to neuronal dysfunction in remote but connected brain regions remain to be unravelled.

Only patients who have been referred for PET imaging due to clinical indication—and in most cases conforming with appropriate use criteria for amyloid PET (Johnson et al., 2013)—have been included, which might have biased the sample towards unclear, less typical cases. Furthermore, the retrospective study design led to missing or inhomogeneous cognitive test data, which made the classification and the diagnostic labelling according to current consensus criteria difficult. Patients have consequently been categorized under broader definitions and labels (predominantly language, memory, or visuospatial impairment). However, our sample selection provided us with a well-characterized group of patients with the clinical consensus diagnosis of Alzheimer’s disease or prodromal Alzheimer’s disease (achieved through multi-professional consensus) and confirmed amyloid-β positivity.

In summary, we demonstrate that asymmetric amyloid-β burden in Alzheimer’s disease is associated with asymmetric neurodegeneration, even in the typical Alzheimer’s disease variant with predominant memory impairment. The asymmetry of amyloid-β deposition also corresponds to lateralized cognitive deficits, indicating its clinical relevance.

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Supplementary material

Supplementary material is available at Brain online.

References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute


