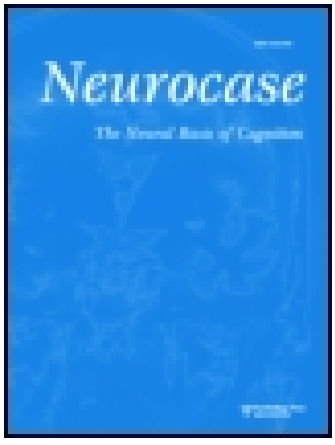

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Degree of abnormality is associated with rate of change in measures of beta-amyloid, glucose metabolism and cognition in an autopsy-verified Alzheimer's disease case

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Degree of abnormality is associated with rate of change in measures of beta-amyloid, glucose metabolism and cognition in an autopsy-verified Alzheimer's disease case

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The degree of abnormality and rate of change in cognitive functions, positron emission tomography Pittsburg compound B (PET PIB), and fluorodeoxyglucose (FDG) measures were studied for 8 years in an autopsy-confirmed Alzheimer's disease (AD) patient, who died 61 years old (Mini-Mental State Examination (MMSE) score 7). At first encounter with medical care, the patient was very mildly demented (MMSE score 27). She had four cognitive assessments and two examinations with PET PIB and FDG in 23 bilateral brain regions. The onset of cognitive decline was retrospectively estimated to have started in the early forties. The degree of impairment was inversely related to the rate of decline. A similar relationship was seen between the rate of change and the level of abnormality in both PIB and FDG. To conclude, rate of change in cognition, PIB, and FDG was associated with the degree of abnormality.

Keywords: Alzheimer's disease; cognition; PET; PIB; FDG

The cascade hypothesis in Alzheimer's disease (AD; Hardy & Selkoe, 2002) postulates that there is an unbalance between production and clearance of beta-amyloid (Aβ) in the brain, which results in aggregation of Aβ and formation of neuritic plaques (NPs), which are the cardinal neuropathological hallmarks of AD. The ultimate definition of AD is based on the presence of NPs as well as neurofibrillary tangles (NFTs) in the brain. Aβ is abundant in NPs and vessel walls in the brain (Thal, Griffin, & Braak, 2008), and NPs are first found in the neocortex followed by allocortical regions (e.g., enthorhinal region) later in third stage in subcortical regions and finally in basal nuclei as well as cerebellum. NFTs may be indicated by tau-proteins, and NFTs are first found in transentorhinal cortex, followed by hippocampus and later they spread to neocortex (Braak & Braak, 1991).

At present, the level of Aβ may be indicated by measuring Aβ in cerebrospinal fluid (CSF) as Aβ is secreted into CSF or by brain imaging using positron emission tomography (PET) and measurement of a ligand that binds to Aβ in the brain (Nordberg, 2008). The most commonly used ligand is the Pittsburg compound B (PIB). In vitro, levels of Aβ may be evaluated by various histochemical markers (Mirra et al., 1991). The cascade hypothesis also states that there is a progressive course of disease severity as indicated by degree of cognitive decline and decreased level of glucose metabolism as measured by PET fluorodeoxyglucose (FDG). Most frequently, the level of each parameter (cognition, PIB, and FDG) is used in clinical examination and in research. Less often the rate of change is used.

In the current study, three measures of AD (PET PIB and FDG as well as cognition) were investigated focusing on absolute values of abnormality and annual rate of change in a case of sporadic AD that has been followed by clinical examinations several times during a period of 8 years starting by clinical diagnosis of AD and continuing until death occurred. Previously, data on brain histopathology, nicotine receptor binding, neuroinflammatory processes, and some information on clinical examinations in this case have been published (Kadir et al., 2011). In this study, the description is expanded regarding cognitive functioning and in terms of patterns of cognitive change.

Methods

Case description

The subject was a married woman working fulltime as a midwife, who was referred to an open ward examination at a nearby hospital (baseline examination at 52 years of age) from occupational health service because of memory difficulties at work. Memory difficulties had been noticed since at least 2 years prior to the referral (at 50 years of age) as reported by colleagues at work. At home, memory difficulties occurred before the diagnosis as reported by a daughter at first examination. The patient was diagnosed with AD at the nearby hospital and later referred to Karolinska university hospital at Huddinge for a second opinion, and she was then followed by repeated examinations spanning almost 8 years.

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Finally, the patient died at the age of 60.8 years due to pneumonia and came to neuropathological examination.

Clinical examinations

The baseline examination showed a lack of heredity for dementia, no history of previous brain-affecting diseases or events, no current medication, a normal computerized tomography (CT), a bilateral reduction of parietal perfusion on single photon emission computed tomography (SPECT) examination, a pronounced delta-theta activity in bilateral frontotemporal regions and changed amplitude of alfa-activity as well as impaired episodic memory (retention of a story), visuospatial ability (copying, constructional praxis) in contrast to a verbal knowledge (vocabulary) which was better than normal. The Mini-Mental State Examination (MMSE) score (Folstein, Folstein, & McHugh, 1975) varied between 24 and 27. Home duties were performed without any remarks according to her husband. The diagnosis of AD was confirmed and treatment with a cholinesterase inhibitor was initiated at age close to 53. An overview of all examinations is presented in Table 1.

The first follow-up examination (second examination) was performed 1 year later (age 53.6 years). Minor white matter hyperintensities but no atrophy was found on MRI, apolipoprotein E was e4/e4, routine laboratory analyses on blood and urine showed normal values, CSF total tau and $A\beta_{42}$ was abnormal, and there was a slight BBB leakage, MMSE was 24 and a first comprehensive neuropsychological examination was performed.

The next follow-up (third examination) at age 55.3 years included clinical status, cognitive screening using MMSE, neuropsychological assessment. Later, PET PIB and FDG evaluations were performed twice at 56 and 58 years of age (fourth and fifth examinations). At the same time, neuropsychological assessments were made. Now, MMSE had declined to 13. From now on the patient was supported in her activities of daily life (ADL) by a personal assistant because she did not manage to perform basic ADL sufficiently.

The last follow-up at 60.0 years of age (sixth examination) was performed about 8 months prior to death. MMSE was 7 and a comprehensive neuropsychological assessment was not appropriate at this time. A couple of months later the patient became anxious, and she was moved from her home to a nursing home where she died calmly at 60.8 years of age. During the last weeks in life, the patients had a urinary infection, cramps with falls and difficulties to swallow.

Neuropsychological assessment

A comprehensive assessment of cognitive functions was carried out by an experienced neuropsychologist four times (second, third, fourth, and fifth clinical examinations) using the following tests that covered six cognitive domains: measuring global cognitive status (Full-Scale Intelligence Quotient, FSIQ; Bartfai, Nyman, & Stegman, 1992; Wechsler, 1981), as well as specific cognitive functions, such as verbal abilities (Similarities, Bartfai et al., 1992; Wechsler, 1981; Information, Bartfai et al., 1992; Wechsler, 1981), visuospatial ability (Block Design, Bartfai et al., 1992; Wechsler, 1981; Rey–Osterrieth copying, Lezak, 1995), short-memory (Digit Span performed both as a WAIS-R test, Bartfai et al., 1992; Wechsler, 1981, and according to Smith & Langolf, 1983; Corsi Block Tapping, Lezak, 1995), episodic memory (Rey Auditory Verbal Learning and Retention after 30 minutes, Lezak, 1995; and Rey–Osterrieth Retention, Lezak, 1995), and attention/executive function (Digit Symbol, Bartfai et al., 1992; Wechsler, 1981; and Trailmaking A & B, Lezak, 1995).

Raw scores were transformed to *z*-scores using a reference group of healthy adults (Bergman, Blomberg, & Almkvist, 2007). The premorbid global cognitive function was assessed once (at the fourth clinical examination when the patient was 58 years of age and MMSE score was 13) using two tests, one National Adult Reading Test-type

Table 1. Specific clinical examinations performed during the study period.

		Examinations						
No.	Age (years)	MMSE[1]	NP	PET[2]	CSF	MR/CT/SPECT	EEG	blood & urine
1	52.6	27	Brief	–	–	CT & SPECT	Yes	Yes
2	53.8	24	Full	–	Yes	MR	–	Yes
3	54.9	26	Full	–	–	–	–	–
4	56.4	21	Full	Yes	–	–	–	–
5	57.8	13	Full	Yes	–	–	–	–
6	59.7	7	Brief	–	–	–	–	–

Notes: [1] MMSE examinations were performed both at all clinical examinations (see earlier) and at short visits between comprehensive examinations (range: 24–27, 22–27 and 25–27; at first, second, and third examinations, respectively).
[2] The PET examination included both measuring PIB retention and FDG.

based on reading (Tallberg, Wenneborg, & Almkvist, 2006) and a lexical decision test (Almkvist, Adveen, Henning, & Tallberg, 2007). The patient was still relatively competent in verbal thinking at that time, see later.

PET examination of amyloid and glucose metabolism

Twice (in close connection to the third and fourth clinical examinations), the patient underwent PET examination at Uppsala PET center/Uppsala Imanet AB in Uppsala, Sweden, using a Siemens ECAT EXACT HR+ scanner (CTI PET-systems Inc., Knoxville, TN, USA). The present case was included in a group of AD patients, and data from these examinations have been reported previously (Engler et al., 2006; Kadir et al., 2011; Klunk et al., 2004).

The production of PIB was carried out according to good manufacturing standards at Uppsala Imanet, and the synthesis of PIB was performed using an established method (Klunk et al., 2004; Mathis et al., 2003). A detailed description of tracer dose of PIB, the scanner protocol for transmissions, emissions, and reconstructions have been described in detail previously (Klunk et al., 2004), as well as the set of 47 regions of interest (ROIs) used in the statistical analysis (Forsberg et al., 2008; Klunk et al., 2004).

The examination of glucose metabolism in 47 brain ROIs was performed twice and in close connection to clinical as well as PIB examinations as described in previous studies (Forsberg et al., 2008).

Neuropathological markers of amyloid

A routine macroscopic examination was performed according to the consortium to establish a registry for Alzheimer's disease (CERAD) criteria (Mirra et al., 1991). Microscopic neuropathological examination was performed with right-hemisphere material. Markers of NP (Aβ6 F/3D, Aβ40, Aβ42, extracellular Aβ4G8, Aβ6E10, and GFAP) and NFT (AT8 and intracellular Aβ4G8) were analyzed in the neuropathological examination (for a detailed description of methods and results, see Kadir et al., 2011).

Ethics

The study was approved by the Ethics Committee, Karolinska University Hospital, Huddinge, the Isotope Committee at Uppsala University, and it was performed in accordance with the Declaration of Helsinki. The subject gave her written informed consent to participate in the clinical part of the study and relatives gave consent to neuropathological examination of the brain.

Results

Cognitive functions

The first neuropsychological assessment demonstrated cognitive deficits in multiple domains typical for AD in relatively early clinical stage. The second and third neuropsychological assessment showed a progressive decline in cognitive functions, although the patient was still able to communicate verbally relatively well in contrast to the severely impaired visuospatial ability. The results in neuropsychological tests at the second assessment are presented in Table 2. At this time, visuospatial construction (Block Design) was most impaired followed by episodic memory (RAVL learning and retention) and attention/executive function (Digit Symbol and trail making test (TMT) A) in contrast to relatively intact verbal abilities (Similarities, Information and Digit Span forward).

The fourth neuropsychological assessment showed that verbal functions (Vocabulary and Phonemic fluency (using letters F, A and S)) had begun to deteriorate and that copying of geometrical designs (Rey–Osterrieth copy) was not possible and that the patient was not able to solve a task with heavy demands on executive function (TMT B).

Considering the four comprehensive neuropsychological assessments, the rate of decline was most pronounced in verbal information processes (Information, Similarities, and Digit Span forward) and least pronounced in visuospatial information processes (Block Design, Corsi Block Tapping, and Rey–Osterrieth retention) as indicated by beta-weights on each neuropsychological test with age as predictor (see Table 2). By using decline estimates and the constant in

Table 2. Predicted age of onset (PAO) of decline, annual rate of decline (ARD, change in *z*-score/year), and performance (*z*-score) at the second assessment (at 55 years of age).

Test	PAO, year	ARD, *z*-score/year	Test results at second assessment, *z*-score
FSIQ	51.1	−.687	−2.65
Information	54.1	−.687	−0.21
Similarities	52.9	−.451	−0.79
Digit Span, forward	53.6	−.459	+0.91
Block Design	42.6	−.087	−3.84
Rey–Osterrieth copying	NA	NA	−1.93
Corsi Block Tapping, forward	45.7	−.377	−2.32
RAVL total learning	49.1	−.385	−2.14
RAVL retention	42.2	−.190	−2.63
Rey–Osterrieth retention	48.0	−.380	−2.88
Digit Symbol	48.2	−.417	−2.65
TMT A	49.3	−.373	−2.09

Note: NA = not assessable.

regression equations, the onset of decline was possible to calculate (see Table 2). Interestingly, the decline was predicted to have started in the early 40s in some tests (Block Design, Corsi Block Tapping, and RAVL retention), that is, at a time long before any cognitive symptoms were observed as calculated by regression analyses of empirical data and estimation of premorbid level (see Table 2). The decline in verbal information processes (Information, Similarities, and Digit Span forward) was predicted to have started about 10 years later, approximately at the time when cognitive symptoms were first observed.

When annual rate of decline (ARD) was related to the degree of impairment at the third assessment at 55 years of age, significant negative relation was obtained between ARD and degree of impairment across 10 neuropsychological tests ($r = -.74$, df = 9, $p < .05$). This relation indicated that the larger the impairment the smaller was ARD (see Table 2 and Figure 1).

The global cognitive decline as assessed by MMSE and FSIQ demonstrated a similar course of decline, slowly in the beginning followed by a more rapid decline as the disease became more advanced. For MMSE, the whole clinical stage of disease was assessed (11 observations during about 8 years), and the decline was strongly time-related and best and strongly fitted to a curve linear model using a quadratic function, $r = .97$, as previously reported (Kadir et al., 2011). The first MMSE score was 27 (52 years) and the last MMSE score was obtained about half a year prior to death (60.0 years).

For parts of the clinical stage, global cognitive decline could be visualized by means of the FSIQ score (53.4, 54.9, and 56.4 years of age). By including estimated premorbid status and three FSIQ values, the decline during the whole disease (preclinical and clinical) could be mapped, see Figure 2. The association between age and FSIQ, including both premorbid estimate and current performance, was strongly significant ($r = .99$, $F = 215.9$, df = 2/2, $p < .005$) using a quadratic model and premorbid level as maximum level of FSIQ. The premorbid function was estimated to have been retained until the age of 46. Other hypotheses regarding onset time of decline (both earlier and later onset) resulted into less good fit. These results indicate that the decline in cognition started in the mid-40s and continued for a number of years without being noticed as symptoms or diagnosed as a disease. Thus, the total part of the disease course is estimated to have continued for about 15 years, half as a preclinical stage and half as a clinical stage.

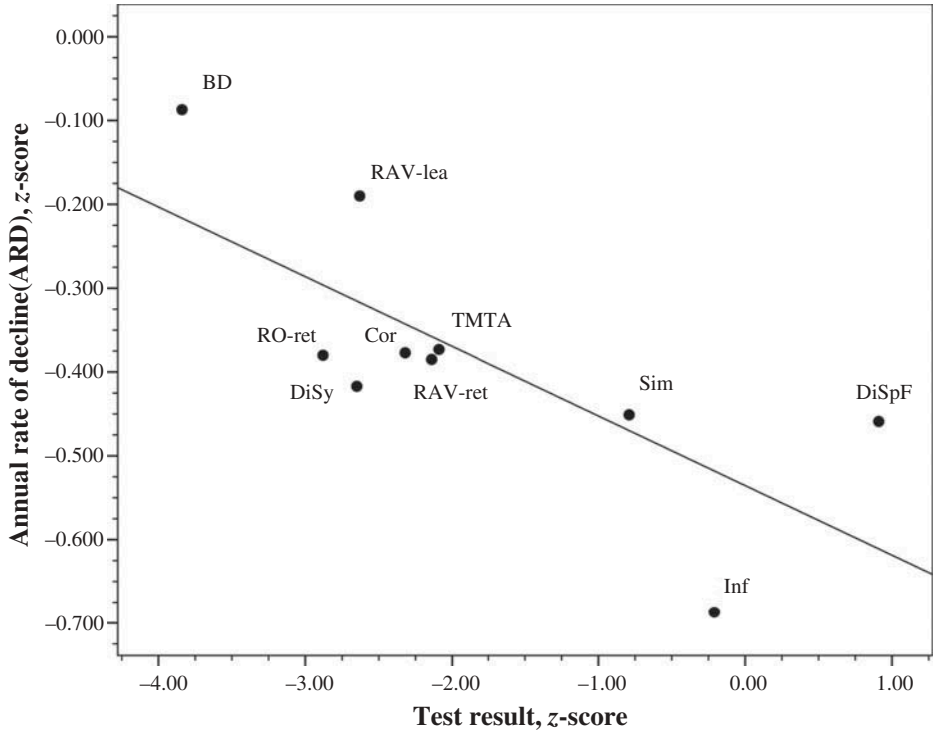

Figure 1. A scatter plot of ARD in relation to z-scores of cognitive impairment at the third assessment.

Notes: BD = Block Design, Cor = Corsi Block Tapping, DiSpF = Digit Span Forwaed, DiSy = Digit Symbol, Inf = Information, RAV-lea = Rey Auditory Verbal Learing total learning, RAV-ret = Rey Auditory Verbal Learing retention, RO-ret = Rey–Osterrieth retention, Sim = Similarities, TMTA = Trailmaking A.

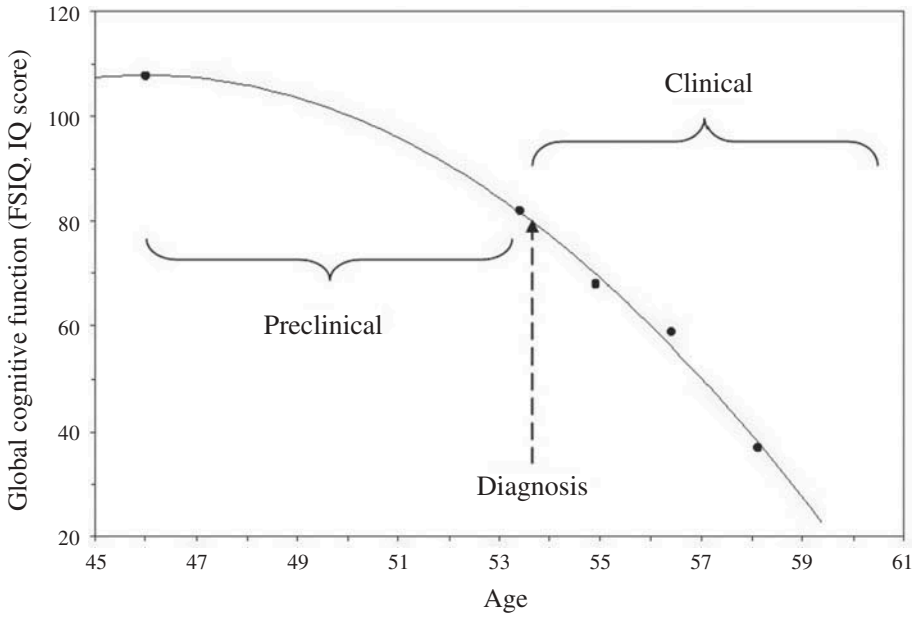

Figure 2. ARD for global cognitive function (FSIQ) in relation to current performance in neuropsychological tests when the patient was 55 years of age.

PIB and FDG measures

First, a composite score was calculated for PIB retention and FDG metabolism as the mean across all brain regions. There was no statistically significant difference between right and left hemisphere values neither for PIB ($t = -0.44$, df = 22, $p > .1$) nor for FDG ($t = 1.10$, df = 22, $p > .1$), so mean values across hemispheres for 23 ROIs were calculated. The mean for both PIB and FDG was clearly abnormal compared to values from previous studies (Engler et al., 2006).

Next, the change in PIB retention and FDG metabolism across 23 ROIs is presented for the present case in Figure 3, when the clinical stage was moderate/severe (MMSE 13). The changes were significantly correlated ($r = .76$, df = 22, $p < .001$). Three patterns were seen, possibly reflecting the selective spread of disease across brain regions. First, a pattern of decreasing values in both PIB and FDG (increasing pathology) was observed, possibly indicating an advanced stage, which was seen primarily in frontal regions. Second, a pattern of increase in PIB retention (increasing pathology) and decrease in FDG metabolism (increasing pathology) was seen in parietal regions as well as anterior and posterior gyrus cinguli, possibly indicating a less advanced stage. A third pattern of increase in PIB retention (increasing pathology) and increase in FDG metabolism was observed in lateral and inferior temporal anterior regions as well as visual cortex, hypothetically indicating a compensatory effort in these regions and representing the least advanced pathology. No areas demonstrated decrease in PIB retention and increase in FDG metabolism.

Next, a scatter plot of change in PIB versus initial PIB values is presented (see Figure 4). Considering all brain regions, there was close to significant association between level of PIB retention and annual change in PIB retention ($r = .39$, df = 22, $p = -.06$). However, the change was positive (decreasing PIB) for some regions and negative (increasing) for other regions. Separate analyses with positive and negative change in PIB retention resulted into significant correlation for both the subsets of data. When the analysis was performed for regions in which there was a positive change in PIB retention (decrease), for instance as seen in frontal regions, the association was clearly significant ($r = .74$, df = 12, $p < .01$) (see Figure 4). The larger the level of PIB retention, the larger was the annual positive change. When the analysis was performed for regions in which there was a negative change in PIB retention (increase), for instance as seen in some parietal, and temporal regions, as well as in uncus, visual cortex, and pons, the association was significant ($r = .64$, df = 8, $p < .05$) (see Figure 4). Again, the larger the level of PIB retention, the smaller was the annual change, or the smaller the level of PIB retention, the larger was the negative change. The subsets with positive and negative change in PIB retention will be discussed in terms of spread of pathology.

Considering all brain regions, a scatter plot of change in FDG versus level of FDG values is presented in Figure 5. It is obvious that the brain glucose metabolism was decreasing in the majority of regions and that this decrease was associated with the level of activity at this clinical stage as shown by a markedly significant association ($r = .63$, df = 22, $p < .001$). The higher the level of glucose

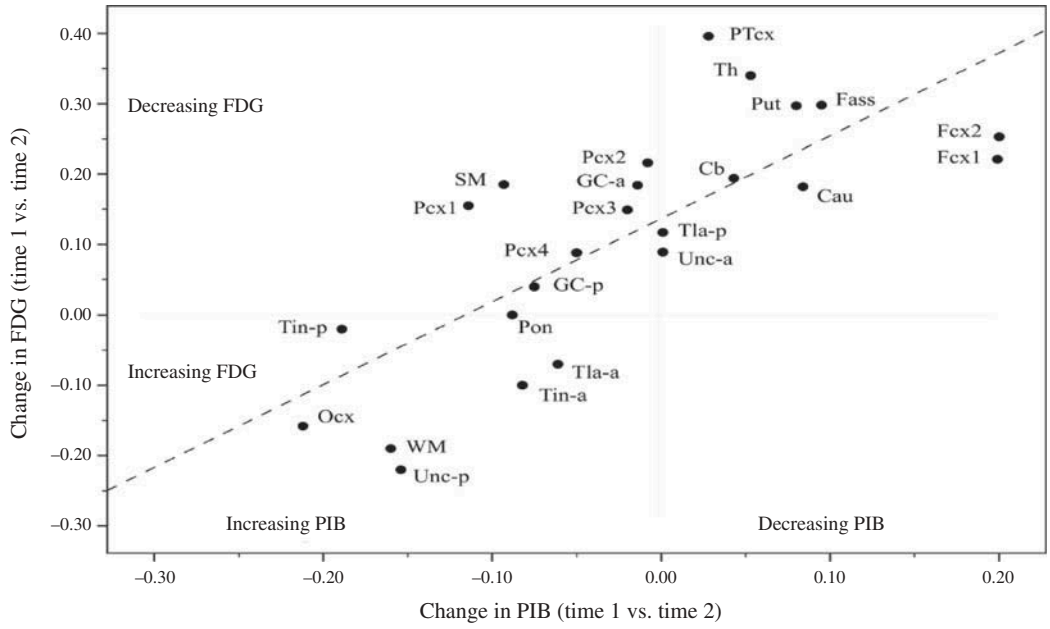

Figure 3. Change in PIB retention versus change in FDG (first − second examination).

Notes: Cau = caudate, Cb = cerebellum, Fass = frontal association cortex, Fcx = frontal cortex (digit represents various levels), GC-a = gyrus cinguli anterior, GC-p = gyrus cinguli posterior, Pcx = parietal cortex (digit represents various levels), Pon = pons, PTcx = parietotemporal cortex, Put = putamen, SM = sensorimotor cortex, Th = thalamus, Tin-a = temporal inferior ctx anterior, Tin-p = temporal inferior ctx posterior, Tla-a = temporal lateral ctx anterior, Tla-p = temporal lateral ctx posterior, Unc-a = uncus anterior, Unc-p = uncus posterior, WM = white matter.

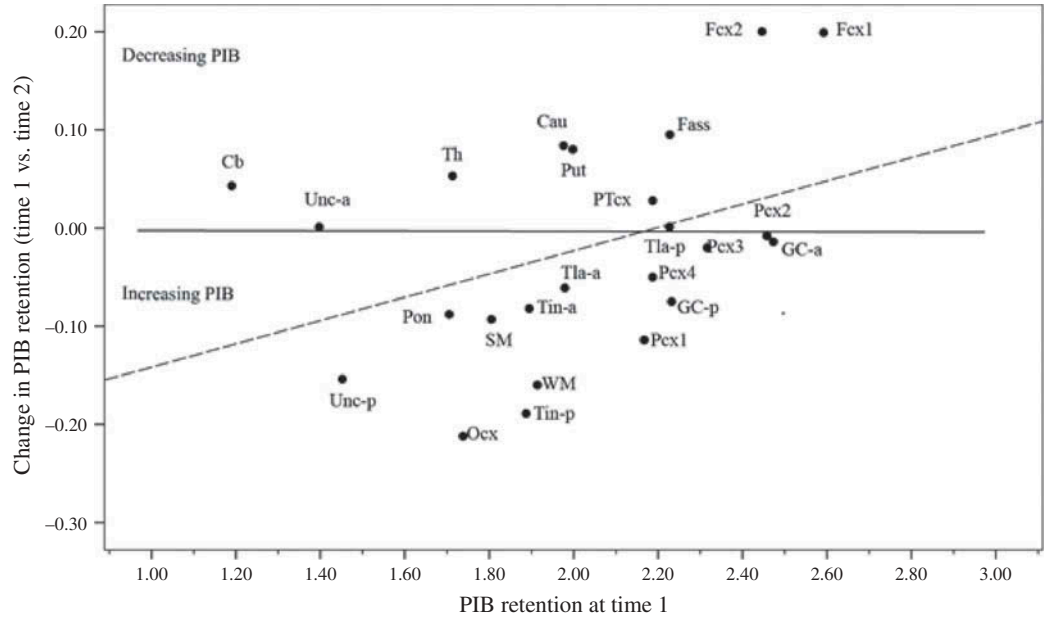

Figure 4. Scatter plot of change in PIB retention (first – second PET examination) versus PIB retention at first examination.

Notes: Cau = caudate, Cb = cerebellum, Fass = frontal association cortex, Fcx = frontal cortex (digit represents various levels), GC-a = gyrus cinguli anterior, GC-p = gyrus cinguli posterior, Pcx = parietal cortex (digit represents various levels), Pon = pons, PTcx = parietotemporal cortex, Put = putamen, SM = sensorimotor cortex, Th = thalamus, Tin-a = temporal inferior ctx anterior, Tin-p = temporal inferior ctx posterior, Tla-a = temporal lateral ctx anterior, Tla-p = temporal lateral ctx posterior, Unc-a = uncus anterior, Unc-p = uncus posterior, WM = white matter.

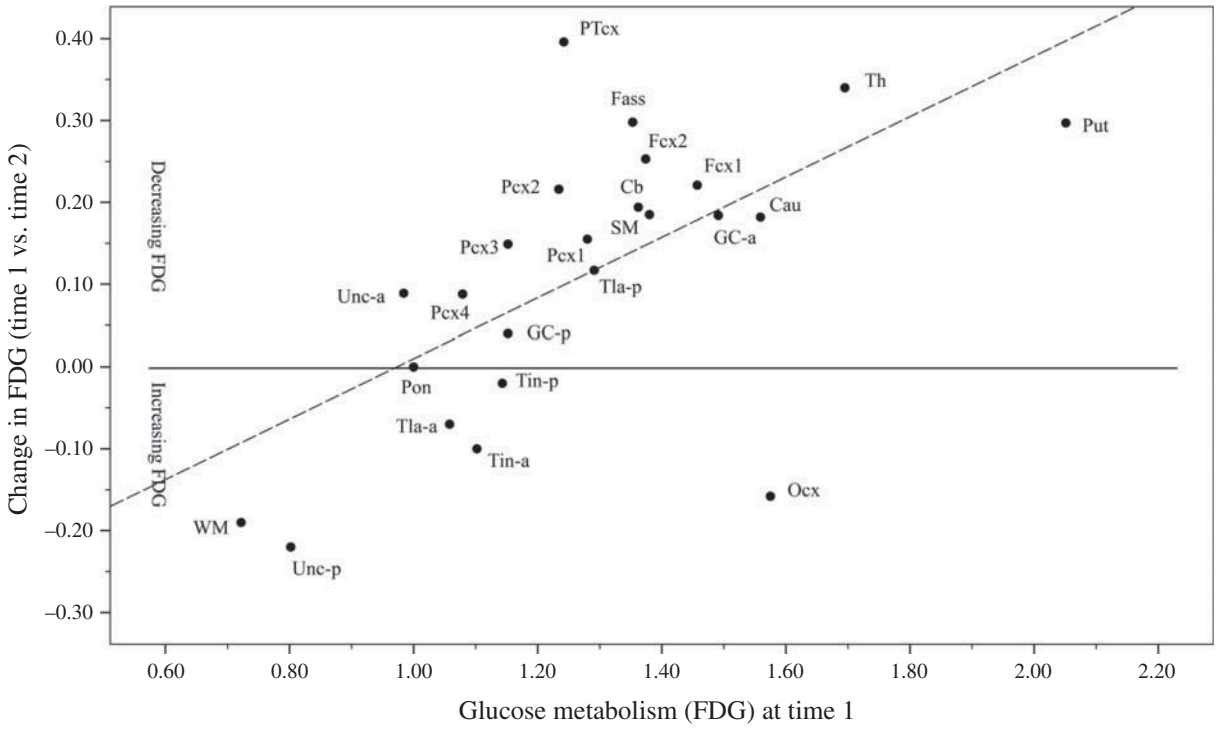

Figure 5. Scatter plot of change in FDG (first – second PET examination) versus FDG at first examination.

Notes: Cau = caudate, Cb = cerebellum, Fass = frontal association cortex, Fcx = frontal cortex (digit represents various levels), GC-a = gyrus cinguli anterior, GC-p = gyrus cinguli posterior, Pcx = parietal cortex (digit represents various levels), Pon = pons, PTcx = parietotemporal cortex, Put = putamen, SM = sensorimotor cortex, Th = thalamus, Tin-a = temporal inferior ctx anterior, Tin-p = temporal inferior ctx posterior, Tla-a = temporal lateral ctx anterior, Tla-p = temporal lateral ctx posterior, Unc-a = uncus anterior, Unc-p = uncus posterior, WM = white matter.

metabolism, the larger was the positive annual change (decrease). This association was significant also for positive FDG ARD ($r = .56$, df = 15, $p < .05$), but not for negative FDG ARD ($p > .1$).

Summary of results

A general pattern of results have emerged for cognitive functions, PET PIB and PET FDG measures. For cognition, the rate of change was related to level of performance, that is, the slower the rate of decline, the poorer was the observed level of performance at clinical examination. In addition, the slower the rate of decline, the earlier was the estimated onset of cognitive decline. For glucose metabolism and the majority of brain regions, the rate of decrease in glucose metabolism was positively related to level of metabolism, that is, the slower the rate of decrease, the poorer was the observed level of metabolism at clinical examination. A few brain regions with negative change across time (increasing values) did not show this kind of pattern. For PIB retention two clusters emerged with decreasing and increasing values, respectively. One cluster demonstrated decreasing PIB retention (diminished amyloid pathology), which was positively related to level of PIB retention (degree of amyloid pathology). This cluster included among other things frontal brain regions. The regions in this cluster were associated with decreasing glucose metabolism (see Figure 3). In contrast, another cluster demonstrated increasing PIB retention (worsening of amyloid pathology), and this change was positively related to level of PIB retention too. The regions in this cluster were associated with increasing glucose metabolism (see Figure 3).

Discussion

The present study focuses on details regarding changes in cognition, PIB and FDG in relation to degree of decline in the first AD patient with PIB measurement (Kadir et al., 2011; Klunk et al., 2004). Neuropathological examination confirmed that the patient had definite AD as shown by abundant presence of NPs and NFTs, and the severity of disease was compatible with stage VI using NFT stage identification (Braak & Braak, 1991). The verification of AD was further supported by microscopic neuropathological examination of Aβ and NFT across brain regions (Kadir et al., 2011). The regional distribution of Aβ and NFT in the current case was in agreement with the cascade hypothesis (Hardy & Selkoe, 2002) and staging of AD based on amyloid deposits (Bouras, Hof, Giannakopoulos, Michel, & Morrison, 1994; Thal, Rub, Orantes, & Braak,

2002; Thal et al., 2008) as well as NFT deposits (Bouras et al., 1994; Braak & Braak, 1991).

A second finding was that cognitive deficits were typical of AD (Almkvist, 1996; Lindeboom & Weinstein, 2004; Nestor, Scheltens, & Hodges, 2004). Furthermore, the onset of decline for various cognitive functions appeared to start at various times and many years prior to the clinical diagnosis according to retrospective prediction onset of cognitive decline. The observation saying that cognitive decline starts long before the clinical diagnosis is in agreement with previous epidemiological research on preclinical AD (e.g., see Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000). Here, the earliest estimated onset was predicted to have occurred about 10 years ahead of the clinical diagnosis in the Block Design test showing insidious start and then an accelerating decline. Interestingly, the time of onset appeared to vary a lot for various cognitive functions (tests) within the current case, which is in agreement with a previous study on mean values for elderly AD patients (Almkvist & Bäckman, 1993). It has also been reported previously in a hospital-based sample of AD patients that absolute values of cognitive impairment is associated with ARD (Almkvist & Bäckman, 1993). The explanation of this finding is not known.

To speculate, the spread of neuropathology is initially limited to certain brain areas for both NP (Thal et al., 2002) and NFT (Braak & Braak, 1991). This stage is followed by a next stage, when neuropathology is spread to neighboring brain areas (Nath et al., 2012; Thal et al., 2002) resulting in a larger and larger portion of affected brain, which may put increasing restriction on compensatory efforts and increasing rate of disease progression as observed in the current case. In this way increasing rate of decline may be caused by increasing portion of affected brain? This idea does not fit with ideas of an S-type course of disease progression as suggested in previous research (Bateman et al., 2012; Jack et al., 2010).

When rate of decline and degree of cognitive impairment were related to each other, a specific pattern was found. The slower the rate of decline the more advanced was the degree of impairment. The implication is that the earliest cognitive changes related to episodic memory may have an insidious onset in line with common knowledge in AD. At the same time, neuropathological changes occur in neocortical areas as documented by Aβ-deposits (Thal et al., 2008, 2002) and PET PIB retention (Klunk et al., 2004; Nordberg, 2008), whereas NFT are found in transenthorhinal cortex and hippocampus in the earliest stages of AD (Braak & Braak, 1991; Thal et al., 2002). So far, there is no explanation for this mismatch in brain regional distribution of the two cardinal neuropathological markers in AD and the mismatch between early cognitive change and Aβ-deposits in primarily frontal brain regions.

Compared to other cases of AD, PIB retention was widespread and extensive in the current patient indicating advanced stage of AD. The advanced stage of AD was further indicated by decreasing PIB retention as well as decreasing FDG values in many brain regions. The finding that there is a simultaneous significant change in PIB and FDG has not been reported previously according to our awareness. One pattern (decreasing PIB and decreasing FDG) was observed primarily in frontal regions, and it may represent an advanced stage in AD. In other brain regions (e.g., temporal), increasing PIB and decreasing FDG were observed, which may represent a later stage, when spread of neuropathology has reached temporal regions. Future studies using a large sample of AD patients will make it possible to evaluate these findings regarding differential patterns of change in PIB and FDG across brain regions.

Previously, two other single case studies has demonstrated that high values of PIB retention correspond to neuropathological findings in AD patients that have come to autopsy (Bacskai et al., 2007; Ikonomovic et al., 2008). The first case (Bacskai et al., 2007) was diagnosed with probable AD, and this case had abundant frequency of Aβ in brain vessels (indicated by Aβ6F3D) and relatively little Aβ in brain parenchyma, although PET PIB was clearly abnormal. The second case (Ikonomovic et al., 2008) showed that PIB binding was selective to Aβ and not related to NFT. Furthermore, there was a strong correlation between in vivo brain regional PIB retention and in vitro neuropathological findings of Aβ in corresponding brain regions. In addition, a biopsy study on patients with and without AD has shown that patients with abnormal PIB retention in frontal regions also had Aβ as indicated by neuropathological examination using the marker Aβ4G8 (Leinonen et al., 2008). However, it has recently been shown that single AD cases verified by typical cognitive decline and abnormal Aβ in CSF were not detected by PIB retention (Rosen, et al., 2010; Schöll et al., 2012).

The relationship between rate and degree of decline seen in cognitive function was also seen in PET FDG measures. In the majority of brain regions, there was a decrease in glucose metabolism during follow-up time interval, when the current case was in a moderate clinical stage of disease (MMSE sank from 21 to 13). Furthermore and across all brain regions, the rate of decrease was significantly associated with level of metabolism. Some regions showed a high glucose metabolism and high decreasing values, whereas other had a low metabolism and ARD. Thus, the lower the rate the poorer was the level of metabolism. This finding replicated the finding in cognitive functions. This finding is new as far as known.

Hypothetically, glucose metabolism and cognitive performance should have some connection as they are considered to reflect brain function in different ways. For instance, semantic knowledge as indicated by the Information test appeared to be relatively unaffected in the present case, and there was a minor change across time. This may be matched by glucose metabolism in lateral temporal regions of the

brain according to knowledge on brain behavior relationships showing that semantic memory/knowledge is linked to lateral temporal regions (Cabeza & Nyberg, 2000). This may exemplify the possible match between cognition and PET glucose metabolism.

In a similar vein, there were two clusters regarding rate and degree of PET PIB retention. One cluster showed decreasing PIB retention across time, that is, decrease of amyloid, which was positively associated with level of PIB retention, indicating that the higher the decrease the higher was the level of pathology. This pattern was observed in primarily frontal and parietal brain regions, which correspond to a very early stage of amyloid deposits (Thal et al., 2008, 2002). To speculate, this pattern is linked to the most early cognitive changes that were found in visuospatial performance in the present case. It is hard to include the early onset of episodic memory dysfunction in this explanation. The other cluster showed increasing PIB retention across time, that is, increase of amyloid, which was positively associated with level of PIB retention, indicating that decreasing pathology was linked to high level of pathology in other cortical regions. This pattern was obtained primarily in temporal, occipital, and subcortical brain regions, which may occur later than in frontal regions (Thal et al., 2008, 2002). The findings on PIB retention in the current case has to be regarded as preliminary and they need to be studied in the future.

Recently new research criteria for AD have been suggested (Albert et al., 2011; Dubois et al., 2007; Sperling & Jack, 2011). These criteria propose that in addition to early impairment of episodic memory, there should be at least one other abnormal finding indicating AD that could be found in CSF measures, structural MRI, or molecular brain imaging. In the present case, who was relatively young when symptoms emerged, it may be noted that routine MRI did not recognize AD, but routine neuropsychology and CSF as well as PET did. It is not known, whether this case could have been identified as AD prior to standard clinical examination close to onset of symptoms. Future longitudinal studies on MCI who develop AD are needed to identify the earliest marker or combination of markers that are most powerful in recognizing preclinical AD.

In conclusion, the present study concerns an autopsy-verified AD case with typical cognitive impairment and decline during 8 years showing considerable deficits in episodic memory and visuospatial function. In retrospect, these changes had started many years prior to the clinical diagnosis and onset of symptoms and developed slowly. Other cognitive functions had a much later onset and developed with higher rate of change. Rate and degree of change were correlated for cognition across functions and for glucose metabolism across the majority of brain regions. The slower the rate of change, the poorer was degree of cognitive impairment and glucose metabolism. For PET PIB retention two tentative clusters appeared presumably related to a very early stage and a somewhat later stage in terms of spatiotemporal pattern of disease process. Anyhow, these patterns showed an association between rate of change and degree of PIB retention, there was increasing pathology over time in one cluster and decreasing pathology in the other cluster.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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