Psychopharmacology (2006) 188:509–520
DOI 10.1007/s00213-006-0447-7

ORIGINAL INVESTIGATION

PET imaging of cortical ^{11}C-nicotine binding correlates with the cognitive function of attention in Alzheimer's disease

Ahmadul Kadir · Ove Almkvist · Anders Wall · Bengt Långström · Agneta Nordberg

Received: 10 February 2006 / Accepted: 24 May 2006 / Published online: 11 July 2006

Abstract
Rationale Patients suffering from Alzheimer's disease (AD) experience a marked reduction in cortical nicotinic acetylcholine receptors (nAChRs). In particular, selective loss of the $\alpha_4\beta_2$ nAChR subtype was observed in postmortem AD brain tissue. The α_4 and α_7 nAChR subunits were suggested to play an important role in cognitive function. Positron emission tomography (PET) has so far been used to visualize neuronal nAChRs in vivo by ^{11}C-nicotine binding.

Objectives To investigate the relationship between measures of cognitive function and in vivo ^{11}C-nicotine binding in mild AD brain as assessed by PET.
Materials and methods Twenty-seven patients with mild AD were recruited in this study. A dual tracer model with administration of ^{15}O-water for regional cerebral blood flow and (*S*)(−)^{11}C-nicotine was used to assess nicotine binding sites in the brain by PET. Cognitive function was assessed using neuropsychological tests of global cognition, episodic memory, attention, and visuospatial ability.
Results Mean cortical ^{11}C-nicotine binding significantly correlated with the results of attention tests [Digit Symbol test (r=−0.44 and p=0.02) and Trail Making Test A (TMT-A) (r=0.42 and p=0.03)]. No significant correlation was observed between ^{11}C-nicotine binding and the results of tests of episodic memory or visuospatial ability. Regional analysis showed that ^{11}C-nicotine binding in the frontal and parietal cortex, which are the main areas for attention, correlated significantly with the Digit Symbol test and TMT-A results.
Conclusion Cortical nicotinic receptors in vivo in mild AD patients are robustly associated with the cognitive function of attention.

Keywords Alzheimer's disease (AD) · Nicotinic acetylcholine receptors (nAChRs) · Positron emission tomography (PET) · ^{11}C-nicotine binding · Cognition · Attention

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Introduction

Alzheimer's disease (AD) is a common form of dementia, characterized by degeneration of basal forebrain cholinergic neurons innervating the cortex, amygdala, and hippocam-

pus, which manifests itself through difficulties in maintaining and sustaining attention and profound cognitive impairments, such as loss of memory and learning ability (Aubert et al. 1992; Coyle et al. 1983). A major loss of cholinergic neurons in the nucleus basalis of Meynert suggested the possible involvement of cholinergic receptors in AD. Numerous preclinical and clinical studies provided evidence implicating the nicotinic system in AD (Aubert et al. 1992; Paterson and Nordberg 2000).

Patients suffering from AD experience a marked reduction in cortical nicotinic acetylcholine receptor (nAChR) binding (Nordberg and Winblad 1986; Perry et al. 2000). Selective loss of the $\alpha_4\beta_2$ nAChR subtype was observed in vitro in postmortem brain tissue from patients suffering from AD (Warpman and Nordberg 1995). Although reduction of α_7 nAChR subtype levels was observed in the frontal cortex (Wevers et al. 1999), no significant loss was detected in the temporal cortex of patients with AD (Guan et al. 2000). A significant increase in the total number of astrocytes and of astrocytes expressing the α_7 nAChR subunit, along with significant decreases in the level of α_7 and α_4 nAChR subunits on neurons was observed in the hippocampus and temporal cortex in vitro in AD brain tissue (Yu et al. 2005).

The use of positron emission tomography (PET) for assessing the longitudinal progression in the brains of AD patients is known to be a sensitive method (Nordberg 1999). Use of PET to visualize neuronal nAChRs in vivo has so far been used by ^{11}C-nicotine binding. An earlier PET study has demonstrated that the uptake of ^{11}C-nicotine binding is lower in the brains of patients with AD compared with that in control subjects, reflecting losses in high and low affinity nicotinic receptor sites (Nordberg et al. 1990). In addition, significantly lower ^{11}C-nicotine binding was observed in the frontal cortex, temporal cortex, and hippocampus of AD patients compared with controls (Nordberg et al. 1995). Neuronal nAChRs are involved in cognitive processes in the brain where both α_4 and α_7 subunits were suggested to play an important role in cognitive function (Nordberg 2001). A significant correlation between the reduction of ^{11}C-nicotine binding and cognitive impairment of AD patients was reported (Nordberg et al. 1995). When nicotinic receptors were blocked with antagonist drugs in healthy humans, the most prominent effect on cognition was concerned with attention rather than memory (Lawrence and Sahakian 1995; Robbins et al. 1997). Attention may thus be associated with nAChRs, which represent one of the main targets in cholinergic replacement therapy (Nordberg 1999). Outcomes of treatment with the cholinesterase inhibitor (ChEI) tacrine in AD patients showed that the cognitive parameters of attention and executive functions improved more after treatment than did mnemonic functions (Alhainen et al. 1993; Almkvist et al. 2001; Sahakian et al. 1993). In a recent study, it was shown that galantamine especially improved attention in patients with AD and this effect may be a consequence of the potentiating action of galantamine at nicotinic receptors (Vellas et al. 2005). In the present study, we wanted to investigate the relationship between measures of cognitive function and ^{11}C-nicotine binding in vivo as assessed by PET to better understand the effect of nicotinic receptors as regards cognitive syndrome in mild AD. Scores of global cognition [mini-mental state examination (MMSE)], episodic memory, attention, and visuospatial ability were chosen in this study as a standardized cognitive battery in the diagnosis of AD.

Materials and methods

Patients and HCs

Twenty-seven patients (11 women and 16 men) with mild AD (MMSE score ≥21) were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. All subjects for memory disorder assessments had undergone a thorough clinical investigation, including medical history, cognitive (MMSE score), physical, and neurological examination, laboratory blood tests, apolipoprotein E genotyping, psychometric investigation, lumbar puncture to analyze the level of tau and beta amyloid, and magnetic resonance imaging/computed tomography scans. The diagnosis of mild AD was made by exclusion of other dementia diseases, in accordance with guidelines from the National Institute of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984). In the present study, no subjects were taking any anticholinesterase drugs. The patients later participated in a PET study involving treatment with rivastigmine and galantamine. The results of these treatment studies are reported elsewhere (Kadir et al. 2006a,b, in preparation).

In this study, we also used neuropsychology data from 36 healthy controls (HCs). These subjects had no history of neurological, psychiatric or major medical disease, and had normal neurological examination results at the time of the study.

The present study was conducted according to the declaration of Helsinki and subsequent revisions and was approved by the Ethics Committee of Karolinska University Hospital Huddinge, Stockholm and the Faculty of Medicine and Isotope Committee of Uppsala University, Sweden.

PET studies

PET studies were performed on all mild AD patients at the Uppsala PET Centre, Uppsala. The tracers ^{15}O-water for

regional cerebral blood flow (rCBF) and (*S*)-[^{11}C]methyl nicotine (^{11}C-nicotine) were synthesized according to a standard manufacturing procedure for each tracer, following the guidelines in radiopharmaceutical preparations (D125) and local QC procedures.

PET was performed using one of the two Siemens ECAT HR^{+} cameras with an axial field of view of 155 mm, providing 63 contiguous 2.46 mm slices with 5.6 mm transaxial and 5.4 mm axial resolution. The orbitomeatal line was used to center the subjects so that the first slice corresponded to the lowest level of the cerebellum.

Tracers were given as intravenous bolus injections. With PET the time course of the regional radioactivity concentration was measured in the brain. The following tracer doses and predetermined scanning protocols were used: 22 MBq/kg of bodyweight of [^{15}O]water (frames of 17×5 and 2×20 s during 125 s in 2D mode); and approximately 5 MBq/kg of [^{11}C]nicotine (frames of 20×6, 6×30, and 1×120 s during 7 min in 3D mode).

Attenuation correction was based on a 10-min windowed transmission scan with rotating ^{68}Ge rod sources before administration of the tracer. The emission data were normalized and corrected for random coincidences, dead time, and for scatter using a method devised by Watson et al. (1997). Images were reconstructed with the standard software supplied with the scanner (ECAT 7.1 CTI PET systems, Knoxville TN, USA) using Fourier rebinning followed by two-dimensional filtered back projection applying a 5-mm Hanning filter. In a subsequent step, image data were converted from Siemens/CTI format to Scanditronix/General Electric format with in-house developed software. The 63 slices were resampled to 30 slices with a slice thickness of 5 mm because the local procedures for PET image analysis utilize tools based on the image analysis software IDA from Scanditronix/General Electric. A computerized reorientation procedure was used to align consecutive PET studies for accurate intra- and interindividual comparisons, and to correct for movements within the PET scans (Anderson 1995).

Continuous blood sampling with online registration of radioactivity in blood from the arteria radialis, report rate of 1 sample/s, was used during the [^{15}O]water and [^{11}C] nicotine scans. Blood sampling was started simultaneously with the tracer injection; 3 ml/min were withdrawn during 145 and 300 s for the [^{15}O]water and the [^{11}C]nicotine scans, respectively. Discrete arterial samples (4 ml/sample) were withdrawn at 6 and 7 min after [^{11}C]nicotine injection.

Analysis of the PET data

Regions of interest (ROIs) were drawn on a ^{11}C-nicotine image where the brain anatomy was seen most clearly. Most of the ROIs were delineated in several consecutive slices and were linked, i.e., summed up to a volume of interest (VOI). The defined regions were checked to ensure that they were inside the realigned volume for every PET scan. The regions delineated were putamen, thalamus, parietotemporal cortex, and the whole brain at the level of basal ganglia in one slice per region; pons, sensorimotor cortex, primary visual cortex, cerebellum, and frontal association cortex were drawn in two consecutive slices; frontal cortex and anterior cingulate cortex in four consecutive slices; and the parietal cortex in six consecutive slices. The regions for the temporal cortex were drawn in six consecutive coronal slices and the medial temporal lobe in two coronal slices with a slice thickness of 8 mm. The VOIs were subsequently used to generate time activity (TACT) data or for measurements of rCBF. Mean cortical value was calculated as a composite score from anterior cingulate cortex, frontal cortex, frontal association cortex, parietal cortex, parietotemporal cortex, and temporal cortex, considering the areas most susceptible to disease progression (Herholz et al. 1990). Because we did not have the complete data from the medial temporal lobe of all patients (18 out of 27 patients were available), we could not include the medial temporal lobe in the mean cortical value. Figure 1 illustrates ROIs placement in PET images.

k_2^* model for ^{11}C-nicotine binding

A dual tracer model with administration of ^{15}O-water and ^{11}C-nicotine in close succession was used to assess nicotine binding sites in the brain. The parameter k_2 for ^{11}C-nicotine is highly flow-dependent, hence, a flow-compensated parameter (k_2^*) was calculated as k_2 for nicotine divided by rCBF (Lundqvist et al. 1998). In this model, a low (k_2^*) value corresponds to high ^{11}C-nicotine binding in the brain. The TACT data for VOIs and the blood TACT data were the input functions in the two-compartment model used to calculate k_2 for ^{11}C-nicotine. Five parameters were included in the model: k_1=rate constant of radioactivity transport from blood to tissue, k_2=rate constant of radioactivity transport from tissue to blood, t_d=time delay in the input function due to the transport time in the arterial catheter, k (min^{-1})=blood dispersion constant, and ε=blood volume. During the modeling, k_1 and k_2 were fitted independently. Radioactivity in the whole brain was fitted with the parameter-free dispersion. Dispersion for the whole brain region was subsequently used as a fixed constant to model k_2 for the other VOIs. Data from the first 5 min of the investigation were used for the calculation of k_2. For a full description of the compartment model, see (Lundqvist et al. 1998).

Regional CBF was measured from parametric blood flow images generated according to the method described by Herscovitch et al. (1983) and Raichle et al. (1983). The

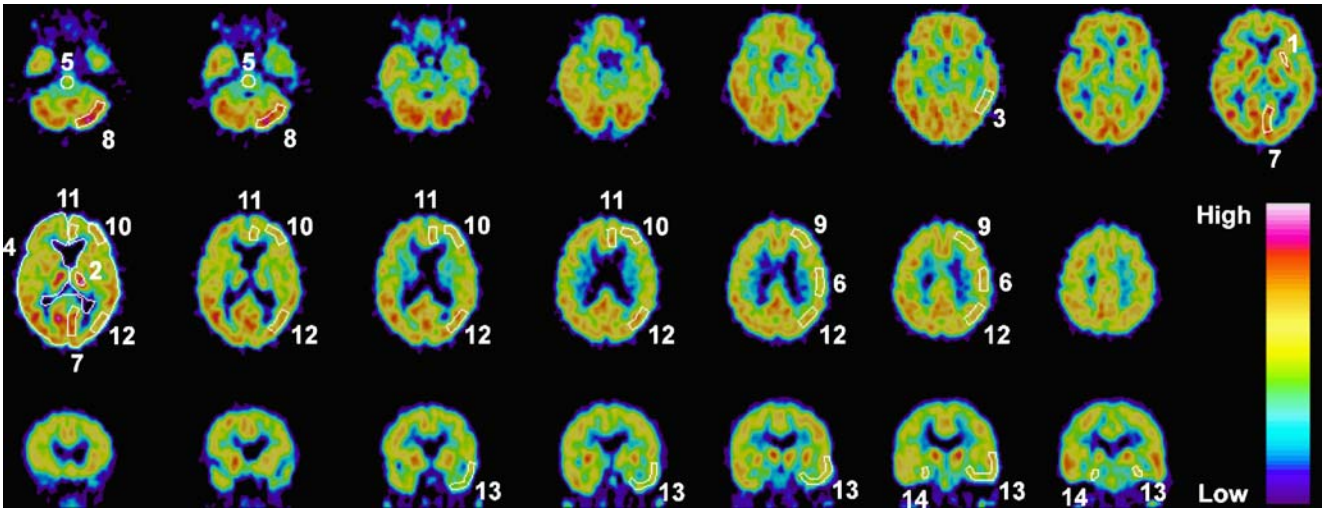

Fig. 1 Illustration of the ROIs placement in PET images. *1* Putamen, *2* thalamus, *3* parietotemporal cortex, *4* whole brain, *5* pons, *6* sensorimotor cortex, *7* primary visual cortex, *8* cerebellum, *9* frontal association cortex, *10* frontal cortex *11* anterior cingulate cortex, *12* parietal cortex, *13* temporal cortex, and *14* medial temporal lobe. The *vertical bar* indicates ^{11}C-nicotine uptake

integration time used was 0–60 s after the bolus appeared in the brain; blood density was set to 1.05 g/cc and the distribution volume was set to 0.95.

Neuropsychology tests

Global cognition was assessed using the MMSE score (Folstein et al. 1975). Episodic memory was evaluated using two measures from the Stockholm Gerontology Research Center test (Backman and Forsell 1994) of memory for words: (1) the number of correct responses in free recall of words (word recall); and (2) the *d*-prime value (an integration of correct responses and false alarms following decision theory) in recognition of words (word recognition-d). The test procedure was as follows:

- Twelve common and unrelated words were presented in written format and also orally by the instructor; one word at a time (1 word/5 s) with the instruction to remember the words presented. The subject had to recall as many words as possible.
- For word recognition, the subject had to respond yes/no as to whether a word had been presented previously (12 target words mixed with 12 distractor words). These words were also presented one at a time and in random order.

It is believed that these measures of memory are related to medial temporal brain activity in particular (Cabeza and Nyberg 2000).

Attention was assessed using two measures: (1) the number of correct responses in the Digit Symbol test from the revised Wechsler Adult Intelligence Scale (Wechsler 1981); and (2) the time needed to complete the Trail Making Test A (TMT-A) (Lezak 1995). These measures are thought to be associated with the frontal and parietal network of brain activity (Cabeza and Nyberg 2000).

Visuospatial ability was judged on the basis of the number of correct responses in drawing and recognizing the clock time (Luria 1966). The latter tests were chosen to reflect parietal lobe function (Cahn-Weiner et al. 1999).

Statistical analysis

Data are expressed as mean±SD. Student's unpaired *t* test was used to evaluate the difference of cognitive function between the AD and HC groups. Two-tailed Pearson's correlation coefficients were used in correlation analysis between ^{11}C-nicotine binding and cognitive function of patients with mild AD, and the data were then visualized graphically using simple regression plots. In all instances statistical significance was defined as $p<0.05$.

Results

Patients and HCs

There were no significant differences in age between the groups: mild AD (69.8±8.2 years) and HCs (68.8±7.8 years; $t=0.50$ and p=ns). Global cognitive functions measured by MMSE scores were significantly decreased in mild AD (25.6±3.0) compared with the HC group (28.7±1.0; $t=-5.6$ and $p<0.00001$).

Table 1 Neuropsychological test results in the mild AD and HC groups

	AD (n=27)	HC (n=36)	t value	Significance (p value)
Word recall (0–12)	3.7±1.9	6.0±2.3	–4.2	<0.0001
Word recognition-d (0–4.64)	1.6±0.9	3.2±1.2	–5.8	<0.00001
Digit Symbol (0–93)	23.5±12.9	41.8±10.3	–6.2	<0.00001
TMT-A (0–300 s)	100.3±67.8	37.4±8.5	5.5	<0.00001
Clock drawing (0–15)	8.3±4.7	12.3±2.7	–4.3	<0.0001
Clock recognition (0–15)	11.3±4.6	14.8±1.1	–4.4	<0.0001

Values are mean±SD
AD Alzheimer's disease, *HC* healthy Control, and *TMT A* Trail Making Test A (a high score indicated more cognitive impairment)

Cognitive tests

The cognitive data are summarized in Table 1. Patients with mild AD showed significantly worse performance in all cognitive measures compared with HC subjects. The relative differences in cognitive performance between the two groups were greatest as regards the Digit Symbol attention test (t=−6.2 and p<0.00001).

Correlation between ^{11}C-nicotine binding (k_2^*) and cognitive function

For correlation between cognitive function and (*S*)(−)^{11}C-nicotine binding, k_2^* values were used. Correlation coefficients between mean cortical ^{11}C-nicotine binding (k_2^*) and test results of cognitive function in patients with mild AD are shown in Table 2. The attention tests Digit Symbol and TMT-A were the only cognitive tests that showed significant correlations with mean cortical ^{11}C-nicotine binding. The correlations between mean cortical ^{11}C-nicotine binding and cognitive measures were further checked by using partial correlation coefficients, i.e., the influence of MMSE score on the relationship between specific cognitive tests and ^{11}C-nicotine binding was sorted out. After correction for the influence of MMSE score, the results of the Digit Symbol test (r=−0.40 and p=0.04) and TMT-A (r=0.37 and p=0.03, one-tailed) were also significantly associated with ^{11}C-nicotine binding.

Table 2 Correlation coefficients between cognitive function test results and mean cortical ^{11}C-nicotine binding (k_2^*) measured by using (*S*)(−)^{11}C-nicotine adjusted for rCBF in patients with mild AD

Cognitive test	Pearson's correlation coefficient (r)	p value
MMSE	–0.22	ns
Word recall	–0.04	ns
Word recognition-d	–0.09	ns
Digit Symbol	–0.44	0.02
Trail Making Test A (s)	0.42	0.03
Clock drawing	–0.36	ns
Clock recognition	–0.31	ns

Visual plots of mean cortical ^{11}C-nicotine binding (k_2^*) and attention test data (Digit Symbol and TMT-A) from patients with mild AD are presented in (Fig. 2a,b). The correlation analyses demonstrated that patients with mild AD and high cortical ^{11}C-nicotine binding (i.e., low k_2^* value) performed better in attention tests than patients with lower ^{11}C-nicotine binding.

When the regional k_2^* values of individual patients were plotted against the Digit Symbol test results, significant negative correlations were observed in the right frontal association cortex (r=−0.49 and p=0.009), right parietal cortex (r=−0.47 and p=0.01), left parietal cortex (r=−0.47 and p=0.01), right parietotemporal cortex (r=−0.52 and p=0.005), and left thalamus (r=−0.37 and p=0.03, one tailed) (Fig. 3a–d). On the other hand, when regional k_2^* values of individual mild AD patients and the results of the attention test TMT-A were compared, significant positive correlations were observed in the right anterior cingulate cortex (r=0.37 and p=0.03, one-tailed), right parietal cortex (r=0.44 and p=0.02), left parietal cortex (r=0.53 and p=0.005), right parietotemporal cortex (r=0.55 and p=0.003), left temporal cortex (r=0.43 and p=0.03), and left thalamus (r=0.44 and p=0.02) (Fig. 4a–d).

The correlation between regional ^{11}C-nicotine binding and visuospatial ability test data (clock drawing and clock recognition) was as follows: There was significant correlation between the clock drawing test results and ^{11}C-nicotine binding in the left parietal cortex (r=−0.51 and p=0.007), right temporal cortex (r=−0.40 and p=0.04), and left temporal cortex (r=−0.39 and p=0.05). ^{11}C-nicotine binding in the right parietal cortex (r=−0.50 and p=0.008) and left parietal cortex (r=−0.51 and p=0.007) significantly correlated with clock recognition test results (Fig. 5a–d).

No significant correlation was observed between ^{11}C-nicotine binding in any of the brain regions and the episodic memory test data. Episodic memory is a function of the medial temporal lobe, but in this study, we found no correlation between ^{11}C-nicotine binding in the medial temporal lobe and episodic memory results (word recall and word recognition-d). When we analyzed cognitive data and rCBF as measured by ^{15}O-water, we found no significant correlation (data not shown).

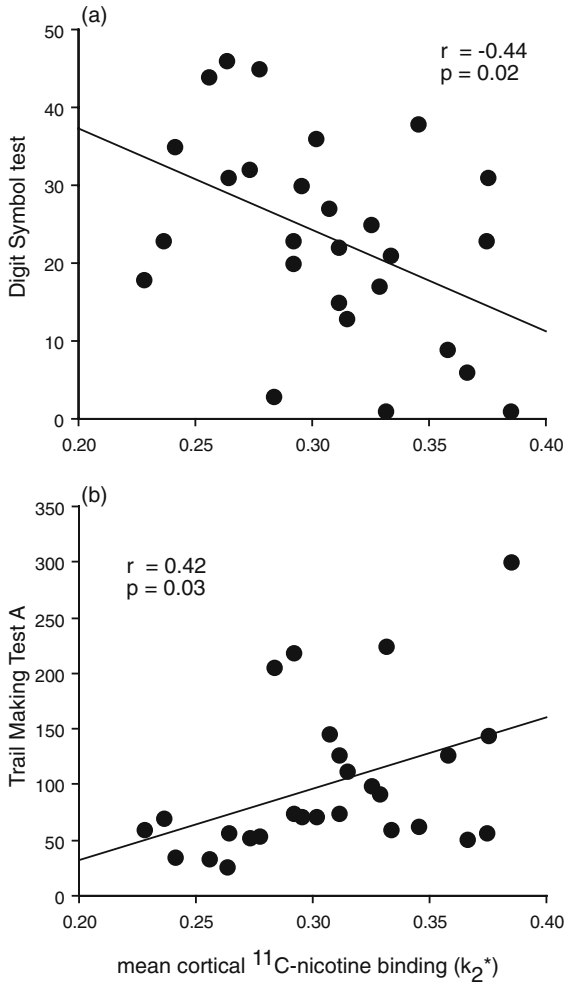

Fig. 2 Correlation between mean cortical ^{11}C-nicotine binding (k_2^*) and attention test results in patients with mild AD. **a** Digit Symbol test: Higher scores indicate better cognitive function. **b** TMT-A (s): Lower scores indicate better cognitive function. Lower (k_2^*) values indicate more ^{11}C-nicotine binding. All values are absolute

Discussion

The first PET ligand applied in monkeys and humans for visualizing nAChRs in the brain was ^{11}C-nicotine. Because ^{11}C-nicotine is an agonist of nicotinic receptors, it is not an ideal PET ligand, owing to a relatively high level of nonspecific binding, short receptor interaction, and strong dependence on cerebral blood flow (Maziere and Delforge 1995). These problems can be overcome by applying a dual tracer method (Lundqvist et al. 1998). In several studies (Nordberg et al. 1998; Nordberg et al. 1997; Nordberg et al. 1995), we have applied a kinetic model approach where the rate constant k_2^* expresses ^{11}C-nicotine binding and is independent of cerebral blood flow. A low k_2^* rate constant corresponds to high ^{11}C-nicotine binding in the brain. To demonstrate the use of this kinetic model, we performed a study in monkeys and confirmed that the calculated k_2^* rate constant was blood flow-independent (Lundqvist et al. 1998). A significant increase in k_2^* values was observed in the temporal and frontal cortices and hippocampus of AD patients compared with age-matched HCs (Nordberg et al. 1997; Nordberg et al. 1995).

Recently, several other compounds were developed as PET ligand candidates for visualizing nAChRs (Nordberg 2006). So far, only ^{11}C-nicotine was applied in clinical studies in AD patients while 2-[^{18}F]fluoro-A-85380 and 6-[^{18}F]fluoro-A-85380 were tested in healthy subjects (Ding et al. 2004; Gallezot et al. 2005). It is evident from in vitro binding studies that various PET ligands such as [^{76}Br]Br-A-85380 (Sihver et al. 1999), 6-[^{18}F]fluoro-A-85380 (Gundisch et al. 2005), and 2-[^{18}F]fluoro-A-85380 (Chefer et al. 2003), show a very high affinity for α_4 nAChR subunits, whereas ^{11}C-nicotine also shows a high affinity for non-α_4 nAChR subtypes. However, it seems plausible that A-85380 also binds to the $\alpha_6\beta_2$ nAChR subtype (Mogg et al. 2004). A drawback of 2-[^{18}F]fluoro-A-85380 and 6-[^{18}F]fluoro-A-85380 as PET ligands is the very long scanning time (hours) that is needed, while the scanning time with ^{11}C-nicotine is 1 h or less.

In the current study, we found that the patients with mild AD differed from HC subjects most strongly in all measures of cognitive function. Furthermore, we observed that mean cortical ^{11}C-nicotine binding in AD patients significantly correlated with the results of tests of attention (Digit Symbol test and TMT-A). It is interesting to note that we did not find any significant correlation between cortical ^{11}C-nicotine binding and memory function in our patients. Cholinergic deficits probably do not account for the full severity of memory loss seen in AD. Our findings are in accordance with the results of a recent study on AD patients showing that cortical acetylcholinesterase (AChE) activity measured by ^{11}C-PMP PET was more robustly associated with the cognitive functions of attention and working memory compared with performance in primary memory (Bohnen et al. 2005). Studies on experimental lesions in the basal forebrain in monkeys suggest that attention, rather than memory function, is disrupted when cortical cholinergic neurons are eliminated (Voytko et al. 1994). A previous study with non-human primates also failed to show a significant correlation between reduced cholinergic innervation and memory impairment (Calhoun et al. 2004). It is plausible that primary memory deficits in AD may be related to microstructural changes, such as the deposition of neurofibrillary tangles in the medial temporal lobe, causing disruption of hippocampal pathways (Guillozet et al. 2003; Ikonomovic et al. 2003). A different explanation for the memory deficits in AD was described in a previous study in which it was suggested that soluble oligomers of the amyloid beta protein may directly interfere with synaptic

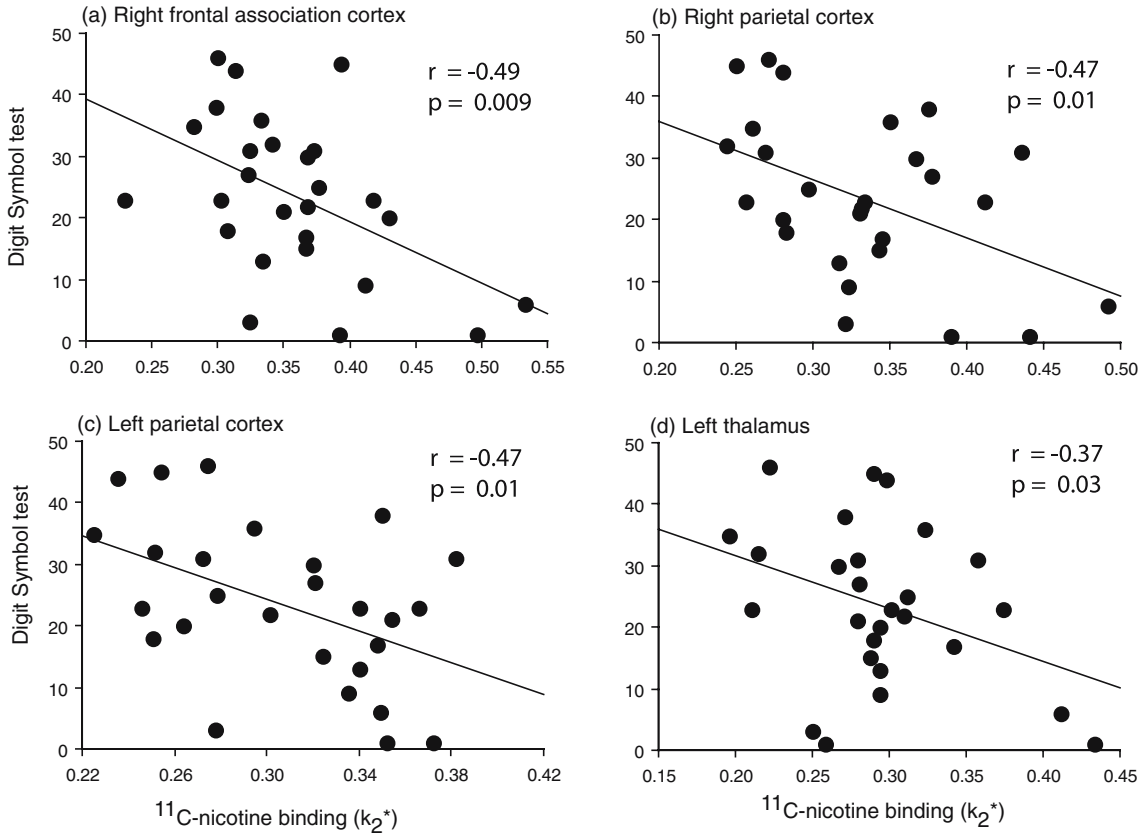

Fig. 3 Correlation between ^{11}C-nicotine binding and results of the Digit Symbol test, a measure of attention in patients with mild AD. **a** Right frontal association cortex, **b** right parietal cortex, **c** left parietal cortex, and **d** left thalamus. Lower (k_2^*) values indicate more ^{11}C-nicotine binding. All values are absolute

mechanisms mediating aspects of learning and memory, including long-term potentiation (Walsh and Selkoe 2004).

To our knowledge, this is the first study in which nAChRs visualized by PET in vivo in the brains of patients with mild AD were correlated with measurements of cognitive function of attention. Previous studies evaluating the effects of acute or chronic nicotinic receptor agonist administration on cognitive function in AD patients tend to support enhancement of attention but not memory function. In clinical studies, Newhouse et al. (1988) showed evidence of improvement in cognitive function after intravenous injection of nicotine in AD subjects. Nicotine administration by subcutaneous injection was shown to improve attention-related task performance in AD (Jones et al. 1992; Sahakian and Jones 1991). In AD patients, a 4-week trial of transdermal nicotine treatment was shown to lead to significant improvement in attention (White and Levin 1999). Furthermore, these findings are consistent with data showing improvements of attention by means of chronic nicotine administration in individuals with age-associated memory impairment (White and Levin 2004). In contrast to nicotine-induced improvements in attention, in at least three studies no evidence was found on the improvement of memory function by nicotine administration in AD patients (Snaedal et al. 1996; White and Levin 1999; Wilson et al. 1995). However, despite these negative findings regarding memory function, transdermal nicotine was shown to improve acquisition of information in AD patients (Wilson et al. 1995) and the nicotinic agonist ABT-418 was also shown to improve components of both learning and memory in AD patients (Potter et al. 1999). Rusted et al. (1998) have suggested that nicotine might selectively modulate processes concerned with associative memory, either through encoding or via a consolidation advantage. Careful separation of the cognitive domains affected by nicotinic stimulation has led to identification of attentional performance as the most likely candidate to be positively influenced by nicotinic receptor activation. Positive effects of nicotine on learning and memory might be mediated by its effect on attentional function (Rusted et al. 2000). Learning and memory require acquisition, encoding, storage, and retrieval; however, attention is the "front end" of this process and adequate attentional function is a primary requirement.

Attention may reflect frontal and parietal cortical function (Cabeza and Nyberg 2000). In the current study,

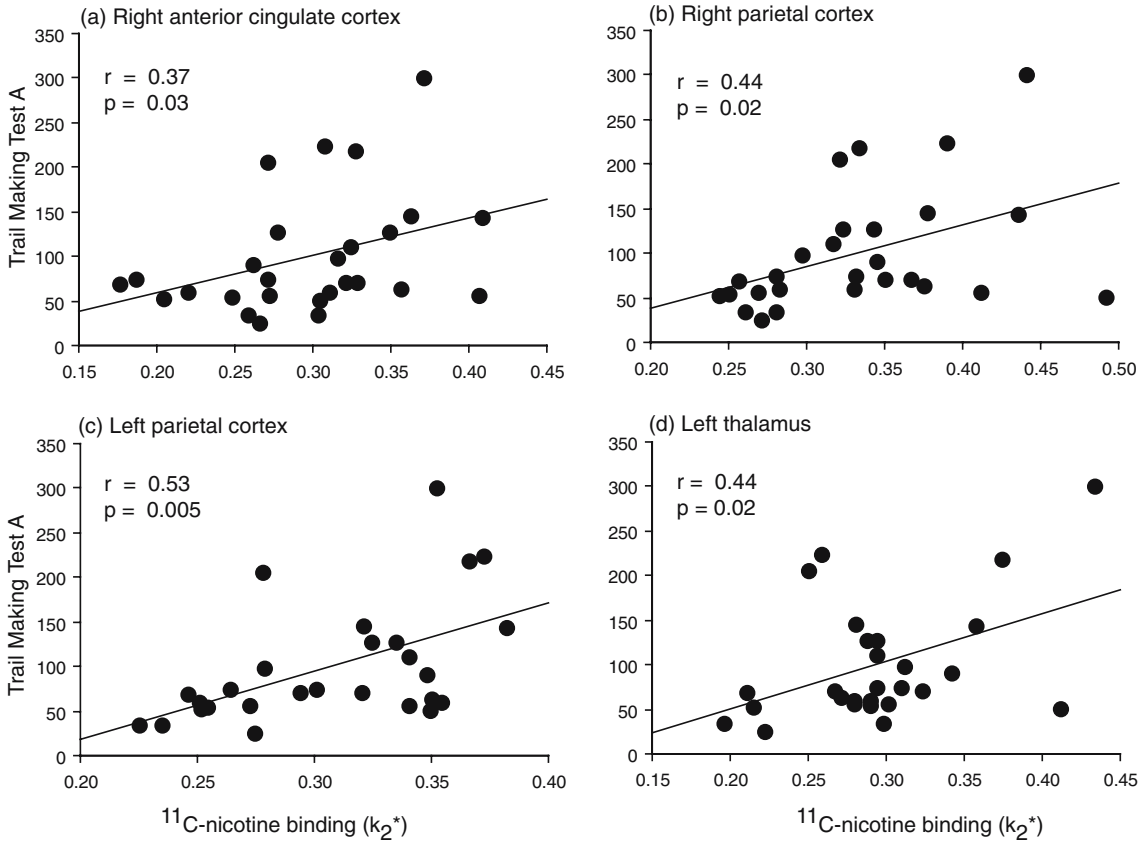

Fig. 4 Correlation between ^{11}C-nicotine binding and results of TMT-A, a measure of attention in patients with mild AD. **a** Right anterior cingulate cortex, **b** right parietal cortex, **c** left parietal cortex, and **d** left thalamus. Lower TMT A scores indicate better performance and lower (k_2^*) values indicate more ^{11}C-nicotine binding. All values are absolute

we observed that ^{11}C-nicotine binding in the right frontal association cortex and the right/left parietal cortex significantly correlated with the results of the Digit Symbol test. With the TMT-A (time) data, significant correlation with ^{11}C-nicotine binding was found in the right anterior cingulate cortex and the right/left parietal cortex. Significant correlations between ^{11}C-nicotine binding in the frontal-parietal cortex and attentional performance were also found in patients with mild AD treated with the ChEIs galantamine and rivastigmine (Kadir et. al 2006a,b, in preparation). In this study, we found that ^{11}C-nicotine binding in the left thalamus significantly correlated with attention test results. Previous studies showed that the thalamus is one of the brain regions containing a high density of nicotinic receptors (Nordberg et al. 1992). The $\alpha_4\beta_2$ receptors are predominant on the thalamocortical glutaminergic efferent pathway (Flores et al. 1992; Pabreza et al. 1991) that composes parts of the frontal subcortical circuits. As a nicotinic receptor modulator, galantamine was shown to increase glucose metabolism in the left anterior medial thalamus in cognitive and behavioral responders in a group of AD patients (Mega et al. 2005). Increased ^{11}C-nicotine binding was also found in the left thalamus of rivastigmine-treated patients with mild AD (Kadir et al., 2006b, in preparation). Studies indicate that the thalamus has an important effect on attention via nicotinic receptors. In this study, we also found that ^{11}C-nicotine binding in the parietotemporal cortex and temporal cortex significantly correlated with the results of attention tests. At least two previous studies also support our finding of involvement of the temporal cortex in attention tasks in patients with mild AD. Bohnen et al. (2005) showed that temporal cortical AChE activity measured by ^{11}C-PMP PET was significantly associated with attention and working memory test data (Digit Span). Another study with resting single photon emission computed tomography (SPECT) showed that perfusion of the superior temporal gyrus was significantly correlated with visually sustained attention (Nobili et al. 2005). These findings may be confounded by the fact that temporal changes are common early in the course of AD (Alexander et al. 2002; Herholz et al. 1999). The observed association between attentional performance and cortical

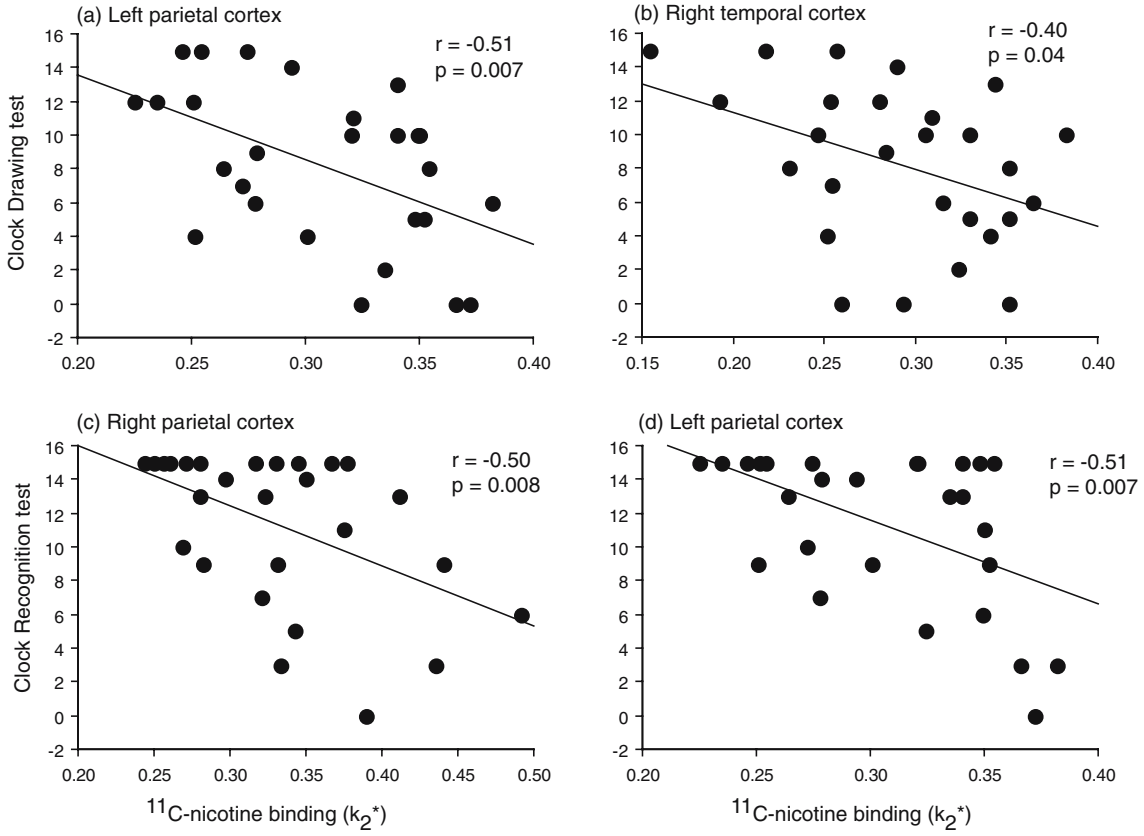

Fig. 5 Correlation between ^{11}C-nicotine binding and results of the visuospatial ability test in patients with mild AD. **a** Correlation between left parietal cortex and clock drawing, **b** correlation between right temporal cortex and clock drawing, **c** correlation between right parietal cortex and clock recognition, and **d** correlation between left parietal cortex and clock recognition. Higher scores indicate better visual spatial ability performance and lower k_2^* values indicate more ^{11}C-nicotine binding. All values are absolute

^{11}C-nicotine binding in various regions in the current study is consistent with a more topographically widespread appearance of cholinergic alteration in AD.

In this study, significant correlation was observed between ^{11}C-nicotine binding in the left parietal cortex and right/left temporal cortex and the results of the visuospatial ability test of clock drawing. ^{11}C-nicotine binding in the right/left parietal cortex in this study significantly correlated with the results of the clock recognition test, in spite of the fact that there was a ceiling effect in this test. However, this ceiling effect, or restriction of range, will result in an underestimation of the true association, given that there is an association. In a previous study, the results of visual–constructional function test in AD patients correlated with the left inferior parietal lobule as assessed by ^{18}F-FDG PET (Teipel et al. 2005). Impairment in copying of line drawings, which correlated with right parietal hypometabolism, was found in AD, as measured by PET (Foster et al. 1983; Haxby et al. 1985). In another study, visuoconstructive performance in AD patients showed correlation with left and right temporoparietal hypometabolism in resting state PET (Ober et al. 1991). A SPECT study of rCBF showed that in the left posterolateral temporal cortex, rCBF correlated with clock drawing test performance in AD patients (Nagahama et al. 2005). The strong correlation observed between ^{11}C-nicotine binding in the parietal cortex and visuospatial ability test data in our study may, thus, at least partly, reflect attentional deficits contributing to impaired performance in the visuospatial ability tests in AD patients. The left inferior parietal lobule subserves the allocation of attention to locations in the visual field (Robertson et al. 1988).

Attentional deficits are common in AD and are recognized as an important component of cognitive decline (Lawrence and Sahakian 1995; Perry and Hodges 2000). Loss of attention affects patients ability to respond to their surroundings and to interact with those around them (Foldi et al. 2002), and it also affects the ability to perform activities of daily living (Vitaliano et al. 1984) and specific skills (Duchek et al. 1997). Our study in patients with mild AD demonstrates that cortical nAChRs are robustly associated with the cognitive function of attention, suggest-

ing that nAChRs might be a promising target of drug treatment in AD.

Acknowledgements This research was supported by the Swedish Research Council (project no. 05817), Stiftelsen for Gamla Tjänarinnor, Stohne's Foundation, and Swedish Brain Power.

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