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18F-FDG-PET and Neuropsychological Testing in Different Types of Neurodegenerative Dementias.

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Zusammenfassung

Demenz ist definiert als Syndrom, das durch einen Verlust der geistigen Funktionen wie Denken, Erinnern, Orientierung und Verknüpfen von Denkinhalten sowie eine Beeinträchtigung der Alltagsrelevanz charakterisiert ist. Patienten mit einer Demenz zeigen ein regionales Defizit des Glucosemetabolismus im Gehirn. Das Ziel dieser Studie ist, einen Zusammenhang zwischen der neuropsychologischen Untersuchung und des regionalen Glucosemetabolismus des Gehirns bei Demenz-Patienten zu finden. In dieser Studie wurden 24 Patienten mit einer Demenz im Alter 69.2 $\pm$ 7.5 Jahren, die nach den Kriterien der ICD-10 und der DSM-IV diagnosziert wurden, eingeschlossen. Die kognitiven Leistungen wurden mit Hilfe der CERAD-NP Testbatterie, des Uhrentests nach Shulman und des Stroop-Paradigmas nach dem Nürnberger-Alters-Inventar (NAI) getestet. Die MRT- und FDG-PET Untersuchungen wurden bei allen Patienten durchgeführt. Die Bildgebungsdatensätze wurden mit Hilfe der *Medical Image Processing, Analysis and Visualisation software* (MIPAV) nach der *Region of Interest* (ROI) – Methode in neun Gehirnregionen (die rechten und linken Hemisphären, der rechte und linke Gyrus frontalis inferior, der rechte und linke Hippocampus, der rechte und linke Parietallappen) ausgewertet. Die Daten wurden mittels des Spearman-Koeffizierten korreliert. In dieser Studie wurde eine signifikante Korrelation zwischen dem MMSE–Wert und dem Hypometabolismus im linken und rechten Parietallappen ermittelt. Beeinträchtigungen in der verbalen Lernleistung (Wortliste Lernen im CERAD-NP) korrelierten mit einem Hypometabolismus in der linken Hemisphäre, dem linken und rechten Hippocampus und dem linken Parietallappen. Zusätzlich wurde eine signifikante Korrelation zwischen der Wortliste Wiedererkennen (CERAD-NP) und einem reduzierten zerebralen Metabolismus des linken Gyrus frontalis inferior gefunden. Die konstruktive Praxis (CERAD-NP) korrelierte mit einem verringerten Glukosemetabolismus in der rechten Hemisphäre. Die visuokonstruktive Praxis (Uhrentest) konnte nicht signifikant mit spezifischen Gehirnregionen in Verbindung gebracht werden. Auffälligkeiten im Stroop-Paradigma korrelierten mit einem Hypometabolismus im rechten Gyrus frontalis inferior. Die Ergebnisse dieser Studie zeigen, dass spezifische kognitive Defizite Aufschluss über die entsprechende Lokalisation der neurodegenerativen Erkrankung im Gehirn geben können.

Contents

1 Introduction 1

1.1 Alzheimer's Dementia 2

1.2 Fronto-temporal Lobar Degeneration 3

1.3 Corticobasal Degeneration 5

1.4 Posterior cortical atrophy 6

1.5 Dementia with Lewy bodies 7

1.6 Neuroimaging in Dementia 9

2 Aims of Study 13

3 Materials and Methods 14

3.1 Patients 14

3.2 Neuropsychological Tests 14

3.3 Neuroimaging 16

3.4 Image analysis 20

3.5 Statistical analysis 21

4 Results 22

4.1 Neuropsychological and FDG-PET data 22

4.2 Correlation between neuropsychological testing and FDG-PET 22

5 Discussion 26

5.1 MMSE 27

5.2 Memory 28

5.3 Language 28

5.4 Attention 29

5.5 Visuo-constructional abilities 29

6 Summary 31

7 References 32

8 Acknowledgements 42

9 Appendix 43
9.1 Tables 43
9.2 Figures 54
9.3 Image standardization 66
9.4 Regions of interests 68
10 Curriculum Vitae 72

1 Introduction

Dementia is a syndrome of acquired impairment in multiple areas of intellectual function not due to delirium. “Dementia is a compromise in three or more of the following spheres of mental activity: memory, language, praxis, conceptual or semantic knowledge, executive functions, personality or social behaviour, and emotional awareness or expression.” (1). Conditions lasting hours to days are regarded as delirium, whereas those lasting weeks to months are considered dementias. The criterion of intellectual impairment rather than a simple decline in intellectual function aims at objective documentation of the dementia. The criterion that the intellectual impairment includes multiple mental deficits excludes patients with isolated neuropsychological disturbances such as amnesia or aphasia from focal brain lesions (1).

All definitions of dementia emphasize both memory impairment and functional impairments. The American Psychiatric Association’s Diagnostic and Statistical Manual, fourth edition (DSM-IV, 1994) criteria for dementia require the presence of memory loss plus an aphasia, agnosia, apraxia or a disturbance in executive functions (2) (see also Table 1). The core feature of this definition is a loss of at least two cognitive abilities, one of which must be memory.

The diagnostic criteria of the ICD-10 (3) definition of dementia require: a) impairment in short- and long-term memory; b) impairment in abstract thinking, judgement, higher cortical function, or personality changes; c) memory and intellectual impairment, which cause significant social impairments; and d) the occurrence of these traits when patients are not in a state of delirium (see details in Table 2).

From this perspective, dementia implies involvement of multiple neural systems, supported by multiple anatomic structures. Classical examples include memory loss, which is due to involvement of mesial temporal lobe structures; aphasia, which is due to impairment of the left perisylvian cerebral cortex; ideomotor apraxia, which is due to impairment of the left parietal lobe; agnosia, due to involvement of the dorsal occipital and parietal lobes. It is

clear, that the clinical manifestation of degenerative processes depend in part on which neural anatomical structures are affected earliest and most extensively.

Alzheimer's dementia (AD) is the leading type of dementias and accounts for approximately two thirds of cases of dementia (4). Dementia with Lewy bodies (DLB) is a relatively recently identified entity, with about half the number of cases of AD pathology (5). Fronto-temporal dementias (FTLD) are the third most common cause of cortical dementias, following AD and DLB (6).

These different dementias are associated with distinctive characteristic neuropsychological syndromes.

1.1 Alzheimer's Dementia

1.1.1 Definition

In 1906, the German neuropsychiatrist Alois Alzheimer described a 51-year-old woman with the dementia that came to bear his name (7). The path to accurate diagnosis of AD, however, is paved with difficulties, particularly at the very onset of clinical symptoms of the disease. The clinical diagnosis of AD is complicated by heterogeneity of the cognitive and other symptoms. Various clinical, biochemical, pharmacological, and genetic factors have consistently failed to be valid diagnostic instruments, and no early, or even ante mortem, marker for AD has yet been identified. Thus, the diagnosis of definite AD can be made only by invasive methods, either by biopsy, or more commonly, in autopsy (8). Current clinical diagnosis is made on the basis of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (8) (see Table 3) for possible and probable AD.

1.1.2 Neuropathology and Etiology

The major histopathologic hallmarks of AD are:

- Neurofibrillary tangles (NFTs)
- β-Amyloid peptide deposition in senile plaques and blood vessels
- Neuronal death

Neurofibrillary tangles are masses of abnormal filaments within the cytoplasm of neurons that are made up of paired helical filaments. The major protein abnormality in NFTs is the presence of a highly insoluble, hyperphosphorylated microtubule-associated protein called tau. Its disruption of the normal cytoskeletal architecture may be an important factor in the death of neurons (9;10).

Amyloid deposition appears to play a critical role in the pathology of AD. The amyloid precursor protein (APP) molecule is a transmembrane protein of unknown function. In humans, the predominant metabolism of APP involves an enzyme, termed alpha secretase, that cuts the extracellular portion of the molecule at a site close to the membrane surface, producing a long protein comprised entirely of the extracellular portion of the molecule (11). Subsequent studies of familial AD led to the discovery of mutations in the amyloid precursor protein (APP) on chromosome 21 (12).

Senile plaques are spherical structures averaging about 100 microns in diameter, composed of degenerating neuronal processes, extracellular ß-amyloid, microglia and astrocytes (11).

1.2 Fronto-temporal Lobar Degeneration

1.2.1 Definition

Over a century ago, in 1862, Arnold Pick (13) described several elderly patients with progressive aphasia; later he augmented the study with additional patient reports and post-mortem correlations. A unique histopathology with globose intraneuronal inclusion and achromatic ballooned

neurons, called “Pick bodies” and “Pick cells”, was reported and Pick’s disease was established. Then later the Lund and Manchester group renamed Pick’s disease as fronto-temporal lobar degeneration (FTLD) (14), because of pronounced frontotemporal atrophy with loss of neuronal cells, grey and white matter gliosis and superficial cortical spongiform changes. Neary et al. established three prototypic neurobehavioral syndromes of FTLD: Frontotemporal Degeneration (FTD), Progressive Nonfluent Aphasia or Primary Progressive Aphasia (PPA) and Semantic Dementia (SD), see Table 4. FTLD is the third most common cause of cortical dementia, following AD and Lewy body disease.

1.2.2 Clinical symptoms

Three prototypic neurobehavioral syndromes can be produced by FTLD. The most common clinical manifestation of FTLD is a profound alteration in personality and social conduct, characterized by inertia and loss of volition or social disinhibition and distractibility, with relative preservation of memory function (14-17). There is emotional blunting and loss of insight. Behavior may be stereotyped and perseverative. Speech output is typically economical, leading ultimately to mutism, although a press of speech may be present in some overactive, disinhibited patients.

PPA is a disorder of expressive language, characterized by effortful speech production, phonologic and grammatical errors, and word retrieval difficulties (15). Difficulties in reading and writing can also occur. Understanding of word meaning is relatively well preserved. The disorder of language occurs in the absence of impairment in other cognitive domains, although behavioral changes of FTD may emerge late in the disease course. In patients with PPA, core features like nonfluent spontaneous speech and phonological paraphasias with preserved (single) word comprehension were observed (18).

Patients with a diagnosis of SD were characterized by fluent and grammatically correct spontaneous speech, but empty of content words, semantic paraphasias, impaired (single) word comprehension, and frontal behavioral features. Also there is an inability to recognize the meaning of visual percepts (associative agnosia) (15;18).

1.3 Corticobasal Degeneration

1.3.1 Definition

Corticobasal degeneration (CBD) is an extrapyramidal syndrome characterized by progressive asymmetric rigidity, involuntary movements, and localized cortical signs, particularly apraxia or cortical sensory loss. Proposed criteria for the diagnosis of the corticobasal syndrome are presented in Table 5.

1.3.2 Neuropathology

CBD was first described by Rebeiz et al. in 1968 based on the pathological findings in 3 patients of “corticodendatonigral degeneration with neuronal achromasia” (19). CBD has disease-specific tau protein isoform profiles and hence, is one of the disorders associated with tau pathology (20;21).
Some authors reported that typical pathological findings in CBD comprise cortical atrophy, especially in the frontal and anterior parietal lobes, with degeneration of the substantia nigra (22;23). The medial temporal lobe may be involved in some cases of CBD (24).

1.3.3 Clinical symptoms

Clinically, patients typically have onset of symptoms in one arm, although a leg, gait or speech may more rarely be affected first. The patients often initially describe ‘clumsiness’ in the affected limb (25;26). Dementia may occur later in the disease.

1.4 Posterior cortical atrophy

1.4.1 Definition

Posterior cortical atrophy (PCA) is a syndrome with cognitive manifestation of visual deficits which are more prominent than the memory and language abnormalities. The term PCA was first applied by Benson et al. in 1988 (27). They described a group of patients with progressive dementia and disorders of higher visual function, including alexia and visual object and topographic agnosia. The clinical syndrome is most frequently dominated by elements of Balint's syndrome (simultanagnosia, oculomotor apraxia, optic ataxia) and Gerstmann's syndrome (agraphia, acalculia, right-left disorientation, finger agnosia) and ideomotor apraxia (27;28). The visual cognitive deficits may remain more prominent than memory, language and other cognitive abnormalities.

1.4.2 Neuropathology

Amongst cases of PCA coming to autopsy, there has been a predominance of AD pathology (29-32). In comparison with typical Alzheimer's disease, patients with PCA have a much higher incidence of senile plaques and neurofibrillary tangles in Brodmann areas (BA) 17, 18 and 19 of the occipital cortex as well as in the posterior parietal cortex (BA 7b/7m), the inferior temporal-occipital junction (area MT) and the posterior cingulated gyrus (BA 23). The difference from AD is most marked in the posterior occipital cortex, and less marked, though still significant, in the posterior parietal cortex. In addition, areas 9, 45 and 46 in the prefrontal cortex, show much less pathology than the posterior cortical areas in these patients and much less than is typical in AD (27;31;33;34).

1.4.3 Clinical symptoms

Insofar as PCA is a disorder most often associated with AD pathology, it is still unclear whether it is best characterised as part of the spectrum of presentations constituting typical AD (27;33), or as a distinct entity. Some studies have demonstrated a subgroup with prominent visual problems among patients meeting standard criteria for diagnosis of probable AD (35). Mendez *et al*. (36) have argued that PCA patients differ from AD patients in having, in addition to greater visual problems, greater insight, more depression, better verbal fluency and memory, earlier age of onset, and, in general, focal posterior but not mesiotemporal atrophy on magnetic resonance imaging (MRI). Mendez *et al*. suggested criteria for the clinical diagnosis of PCA (see Table 6).

1.5 Dementia with Lewy bodies

The current consensus criteria by McKeith et al. (see Table 7) for probable dementia with Lewy bodies (DLB) are the presence of the core features: fluctuating sensorium/cognition, parkinsonism and visual hallucinations. A definite diagnosis of DLB rests on the histopathological examination, which shows the presence of Lewy bodies in brain tissue.

DLB is acknowledged as the second most common degenerative dementia, trailing only Alzheimer's disease. Lewy bodies are found in substantia nigra, locus ceruleus and basal nucleus of Meynert (37).

1.5.1 Clinical symptoms

Disease progression usually occurs over years, and it can be more rapid than in AD (38). The cognitive decline associated with DLB can precede the onset of parkinsonian symptoms and is associated with prominent impairment in visuospatial and executive function. Visuospatial deficits can be manifested

clinically as a loss of the ability to cope with familiar surroundings. Formal neuropsychological testing shows impaired executive function and working memory (39). Individuals are slow to perform tasks of set-shifting and spatial working memory. In contrast to AD, short-term memory is relatively intact in DLB.

Recurrent, well-formed, detailed visual hallucinations are a core feature of DLB (40;41); one study found delusions in 27.8% of cases (42). Delusional misidentification is surprisingly common, and patients often complain that their spouse or child has been replaced by an impostor (Capgras syndrome) (42). Selective degeneration of the amygdala, a brain region involved in identifying familiar faces, appears to be the anatomic substrate of this syndrome. The delusions and visual hallucinations seen in DLB have been associated with upregulation of cholinergic muscarinic receptors caused by decreased cholinergic levels (43).

1.6 Neuroimaging in Dementia

1.6.1 Magnetic resonance imaging (MRI)

Structural magnetic resonance imaging (MRI) is an important method in identification of dementia. The use of MRI in the practical assessment helps to distinguish different types of dementia, particularly in their early stages. The different pathological processes that produce cerebral dysfunction at a cellular level also produce macroscopic effects that can be detected *in vivo* with imaging. For these reasons, neuroimaging in general, and MRI in particular, is an essential part of the investigation of a patient with dementia.

Medial temporal lobe atrophy

Neuropathological studies have implicated the medial temporal lobe as an early site of pathological involvement in AD and many imaging studies have therefore focused on this part of the brain (44-49). The availability of MRI enabled the study of specific structures within the medial temporal lobe, such as the hippocampus, the parahippocampal gyrus, subiculum, entorhinal cortex and amygdala. Scheltens *et al.* (50) reported that in patients with AD the degree of medial temporal lobe atrophy correlated significantly with scores on the mini-mental state examination and memory tests. O'Brien *et al* (48) showed a significant temporal lobe atrophy in AD in contrast to normal ageing, depression, vascular dementia and other causes of cognitive impairments. Thus, several studies conclude that atrophy of the medial temporal lobe is quite sensitive for AD (45-51).

Frontotemporal atrophy

Neary *et al.* (15) listed frontal and temporal atrophy as supportive diagnostic features for frontotemporal lobar dementia, but absence of these features does not rule out this diagnosis. Asymmetrical, predominantly left-sided perisylvian atrophy characterises progressive non-fluent aphasia and asymmetrical anterior temporal lobe atrophy – semantic aphasia (15). In both

disorders atrophy becomes more widespread but generally remains asymmetrical. In Galton and colleagues' study (52) of 30 patients with Alzheimer's disease, 17 with semantic dementia, 13 with the frontal variant of frontotemporal dementia and 18 controls, a new visual scale was used; it was based on atrophy of the temporal pole, parahippocampal gyrus, and lateral temporal gyrus, and it could be helpful in distinguishing Alzheimer's disease from semantic dementia, because the latter disorder shows significantly more atrophy in all these regions in both hemispheres.

Occipital lobe atrophy

Dementia with Lewy bodies (DLB) is associated with occipital changes in blood flow and metabolism. But Middelkoop *et al.* (53) performed volumetric MRI measurement of the occipital lobe blind to the diagnosis in 23 subjects with DLB, 25 with AD, and 24 age-matched control subjects and found no significant differences between groups in occipital lobe volume. The authors conclude that gross structural changes in the occipital lobe do not occur in patients with mild to moderate DLB or AD.

Parieto-occipital atrophy on brain MRI was also reported in patients with the posterior cortical atrophy variant of AD (31;33).

1.6.2 Positron emission tomography with [^{18}F] fluorodeoxyglucose (^{18}F-FDG-PET)

Positron emission tomography is a diagnostic examination that involves the acquisition of images based on the detection of radiation from the emission of positrons. Positrons are tiny particles emitted from a radioactive substance administered to the patient.

FDG-PET is a useful instrument for the detection of brain regions with reduced metabolic activity in the early stages of progressive neurodegenerative diseases, even at a stage before atrophic brain changes become apparent on structural imaging. ^{18}F-FDG-PET has become important also in differentiation between different types of dementia.

1.6.2.1 FDG-PET in Alzheimer's dementia (AD)

FDG-PET in patients with AD shows a typical hypometabolism in neocortical structures, mainly the parietal, frontal, and posterior temporal association cortices, i.e. the same areas where neuronal as well as synaptic degeneration is most severe in post-mortem studies (54;55); further to the regional abnormalities, AD also exhibits a global reduction of cerebral glucose metabolism. Decrease of the cerebral metabolic rate of glucose (CMRglc) in the parietotemporal association cortex has been recognised as potentially diagnostic for AD and the use of PET in clinical settings to evaluate patients with dementia has been facilitated by this recognition (56).

Demetriades *et al.* (57) suggested the following criteria for AD:

- bilateral metabolic reduction in the parietotemporal association cortex,
- glucose metabolism reduction in the frontal association cortex, mainly in advanced disease,
- relative preservation of primary neocortical structures, such as the sensorimotor and primary visual cortex, and also of subcortical structures, like the basal ganglia, brainstem, and thalamus,
- metabolic reduction in the mesial temporal cortex.

An interesting study of Minoshima *et al.* showed a close correlation between progressive metabolic reduction in the posterior cingulate cortex and cinguloparietal transitional area and Mini-Mental State Examination score (58). Matsuda also reported that in very early AD metabolism is reduced first in the posterior cingulate gyrus and precuneus (59). This reduction may arise from neural degeneration in the entorhinal cortex that is the first to be pathologically affected in AD.

1.6.2.2 FDG-PET in fronto-temporal lobar degeneration (FTLD)

A study of patients with FTLD showed significant metabolic deficits primarily in frontal cortical areas including the gyrus frontalis superior, medius and inferior and subcortical structures, particularly the caudate nuclei and the thalami (60;61). In comparison with follow-up (after 17.1 $\pm$ 6.0 months) patients showed a significant progression of metabolic deficits in the orbitofrontal parts

of the frontal lobe. A metabolic decrease was also observed in the dorsal parts of the frontal lobes and in the left inferior parietal lobule (61).

Another interesting study by Ibach *et al.* (18) highlights metabolic group differences between patients with FTLD and early onset of Alzheimer's disease (EOAD). These regions comprised the bilateral medial frontal gyrus (BA 10), the left insula (BA 13), and inferior frontal gyrus (BA 45) with a relative metabolic decrease in the FTLD group and the right middle temporal gyrus (BA 39) with a relative decrease in the EOAD group.

1.6.2.3 FDG-PET in dementia with Lewy bodies (DLB)

Ishii *et al.* (62) found that in patients with DLB CMRglc was reduced in the cerebellum and in the occipital region compared to those with AD. Their comparison of patients with DLB and normal control subjects yielded differences in almost all parts of the brain except the sensomotor cortex, basal ganglia, thalamus and pons.

Minoshima *et al.* (63) found in DLB patients significant reductions in the occipital cortex, particularly in the primary visual cortex, which distinguished DLB from AD with 90% specificity and 80% sensitivity.

Previous FDG-PET studies (64;65) reported significant CMRglc decreases in patients with DLB (vs. those with AD) in the temporoparieto-occipital association cortices and cerebellar hemispheres. However, the medial temporal and cingulate CMRglc were significantly lower in the AD patients. The authors conclude that the different regional emphases of glucose hypometabolism might explain the different clinical features of the two diseases (64).

2 Aims of Study

This study investigates the quantitative correlation between local cerebral metabolic rate (CMRglc) determined with ^{18}Fluodeoxyglucose (^{18}F-FDG) and cognitive impairments in patients with dementia. As discussed in the introduction previous ^{18}F-FDG-PET studies (57;60;66) have localized significant metabolic reduction in different regions of the cortex in dementia.

The focus of this study is the correlation between local cerebral metabolic rate in selected regions of interest (ROI) and data derived from neuropsychological examinations (CERAD battery, clock-drawing test, Stroop paradigm) in patients with dementia.

The manually selected ROIs were: right and left hemispheres, right and left gyrus frontalis inferior, right and left hippocampus, right and left parietal lobe and occipital lobe. We hypothesize that:

- the selected ROIs of the hemisphere correlate with cognitive functions that are commonly attributed to the left and right hemisphere (left: verbal functions, right: non-verbal functions),
- decreased metabolism in the gyrus frontalis inferior correlates with decline in language processing,
- decreased metabolism in the hippocampus area correlates with decreased memory processing,
- hypometabolism in the parietal lobe correlates with visuospatial deficits,
- hypometabolism in the occipital lobe correlates with decline of visual perception.

3 Materials and Methods

3.1 Patients

Twenty-four patients with dementia aged 69.2 ± 7.5 years were examined (see Table 9). We examined 9 patients with Alzheimer's disease, 8 patients with fronto-temporal lobar degeneration, 2 with dementia with Lewy-bodies, 3 with a diagnosis of cortico-basal degeneration and 2 with posterior cortical atrophy. The patients fulfilled Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV) (2), (see Table 1) and ICD-10 (3), (see Table 2) criteria for dementia. Additionally we used the criteria of Neary *et al.*, 1998 (Table 4) to diagnose FTLD and the criteria of McKeith *et al.* for diagnosis of DLB (Table 7). Patients were recruited from the Cognitive Neurology Outpatient Clinic of the Neurologische Klinik und Poliklinik, Universität München – Grosshadern. The clinical assessment included detailed medical history, neurological and neuropsychological examination and laboratory studies (routine hematology and biochemistry screen, thyroid function tests), cerebralspinal fluid (CSF), magnetic resonance imaging and FDG-PET scans. The patients had no systemic or neurological disease apart from degenerative dementias that could account for their neurological deficits. The cognitive domains were assessed with neuropsychological testing.

3.2 Neuropsychological Tests

The German version of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD–NP) (67), which incorporates the Mini-Mental State Examination (MMSE), a clock-drawing test (68) and a Stroop-paradigm - Nürnberger-Alters-Inventar (NAI) Version (69) – were used for neuropsychological testing. In three patients MMSE values were available only from SIDAM testing (Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multiinfarct Dementia and Dementia of other Etiology) (70). Two patients were examined with a variant verbal fluency test (71).

Neuropsychological testing was administered within 0-6 weeks of MRI and PET scan.

3.2.1 CERAD

The following tests are included in the CERAD-NP battery to measure the principal cognitive changes of AD (i.e., memory, language, praxis and general intellectual status (67).

Verbal Fluency: “Animal Category”. This test measures impairments in verbal production, semantic memory and language. Subjects are asked to name as many animals as possible in one minute. The score is the total number of named animals.

Boston Naming Test. Subjects are asked to name 10 objects presented as line drawing; a maximum of 10 seconds is allowed for each picture.

Mini-Mental State. This is a well-known brief general cognitive battery that measures orientation, immediate and delayed memory, concentration, language and praxis (72).

Word List Learning. This task assesses the ability to remember newly learned information. On the first trial, 10 printed words are presented at the rate of every 2 seconds. The subject is asked to recall as many words as possible (90 seconds allowed). On each of 2 subsequent trials, the 10 words are presented in a new random order and the subject tries to recall all 10 words.

Constructional Praxis. Four line drawings of figures of increasing complexity (a circle, a diamond, intersecting rectangles, and a cube) are presented to the subject for copying; 2 minutes are allowed for each figure.

Word List Recall. This tests delayed memory for the 10 words of the Word List Learning task.

Word List Recognition. This tests recognition for the 10 words of the Word List Memory task when presented among other words.

The values of the CERAD – NP subtests has been verified for influences of age, gender and education that correspond to the standardisation of the German speaking countries. All results of the CERAD – NP subtests were finally controlled by the Z – test.

3.2.2 Clock-drawing test

The clock-drawing test commonly used in the form suggested by Shulman *et al.* (73) is a practical screening of visuo-constructional abilities (74).
On a predrawn circle the subject completes the numbers on the “clock face”. Then the investigator gives the instruction to ‘set the time at 10 after 11’. The scoring system ranges from 1 to 6 with higher scores reflecting a greater number of errors and more impairment (74).

3.2.3 Stroop – paradigm

The Stroop - paradigm is the conflict or interference situation in which the subjects must name the colour of the ink of colour-words when the colour and the word are incongruous. The colour-word interference test was first introduced into American psychology by John Ridley Stroop.
In our study we used the Nürnberger-Alters-Inventar (NAI) Version of the paradigm, which was suggested by Wolf Dieter Oswald in 1995. This test was used as a screening tool for attention. The time to complete the color naming and interference conditions was measured and the difference was reported (seconds).

3.3 Neuroimaging

3.3.1 MRI

All patients underwent clinical MR imaging of the brain that included a 3D contrast-enhanced MPRAGE (Magnetization-prepared Rapid Acquisition Gradient Echo) imaging sequence. MRI was performed on a 1.5T whole body imaging system (Magnetom SP, Siemens Medical Systems) at the Neuroradiology Department of the Institut für Klinische Radiologie, Universität München – Grosshadern. An IV infusion of 0.1 to 0.15 mmol/kg of contrast agent gadolinium-DPTA (Gd-DPTA) was manually administered at a rate of 1 to

2 ml/s and then T1-weighted MR and contrast-enhanced MPRAGE imaging sequences were performed. The study was performed with subjects lying supine and awake with closed eyes. A low flip angle T_1-weighted three-dimensional gradient echo sequence (MPRAGE) provided 128 sagittal images (repetition time = 11.4 ms, echo time = 4.4 ms, inversion time = 400 ms, delay time = 50 ms, matrix 256×256; slice thickness = 1 mm). The field of view was 25 cm. The acquisition time was 5.25 min. Images were transferred to a standard PC for further analysis (see 3.3.3).

3.3.2 FDG-PET

^{18}F-FDG PET study was performed with an ECAT EXACT HR^{+}PET scanner (Siemens/CTI) at the Klinik und Poliklinik für Nuklearmedizin, Universität München – Grosshadern. The scanner acquires 63 contiguous transaxial planes, simultaneously covering 15.5 cm of axial field of view. The transaxial and axial resolutions (full width at half maximum) of the PET system were measured as 4.6 mm and 4.0 mm, respectively, at the center and 4.8 mm and 5.4 mm, respectively, at a radial offset of 10 cm. Data acquisition followed a standardized protocol. Patients fasted for at least 9 h before scanning. The study was performed under resting condition with eyes closed and ears unplugged, and in a quiet environment. The head of the patient was fixed in a foam cushion and adequately positioned in the gantry. Acquisition started with a 15-min transmission scan (68Ge-sources), which was used for subsequent attenuation correction. After the transmission scan ^{18}F-FDG was intravenously administered. A PET study was obtained 30 to 60 min after injection (3 frames, 10 min per frame, 128×128 matrix, 3-dimensional acquisition). For further evaluation, the three 10-min frames were added to a single frame comprising the entire 30-min acquisition. Images were reconstructed by filtered backprojection using a Hann filter and corrected for scatter and attenuation. A time–activity curve of the ^{18}F-FDG concentration in blood plasma was obtained by sampling arterialized venous blood starting immediately after injection and continuing until 45 min after injection. For further evaluation, the PET data were transferred to a HERMES - workstation (Nuclear Diagnostics) (75). The image

voxel values were converted to micromoles of glucose per 100 g of tissue per minute (μmol/min/100g) using the methods described by Phelps et al. (76), generating a regional cerebral metabolic rate of glucose (rCMRglc). Then the data via the DICOM transfer server of the neurological clinic were transferred to a standard PC. Additionally, the differences of voxel intensities between DICOM transfer and HERMES – workstation were calculated.

3.3.3 Image processing

The datasets were analysed with the help of MIPAV (medical image processing, analysis and visualisation application software, Imaging Science Laboratory, CIT, NIH, see http://mipav.cit.nih.gov/).

MRI scans from different individuals will vary greatly due to differences in slice orientation and brain features (i.e. brain size and shape varies across individuals). Therefore, it is generally useful to coregister scans to a standard template. Coregistration is the process of translating, rotating, scaling a brain to roughly match a standard template image. As standard template image we used the MRI data of a control subject.

The control subject is a 57-year-old male, who was examined in our outpatient clinic. After complete neurological, neuropsychological, laboratory and neuroimaging examination the diagnosis of dementia was excluded in this subject.

A detailed description of template image processing, coregistration and standardisation to the Talairach system (77) is presented in the appendix (9.3).

3.3.4 ROI boundaries

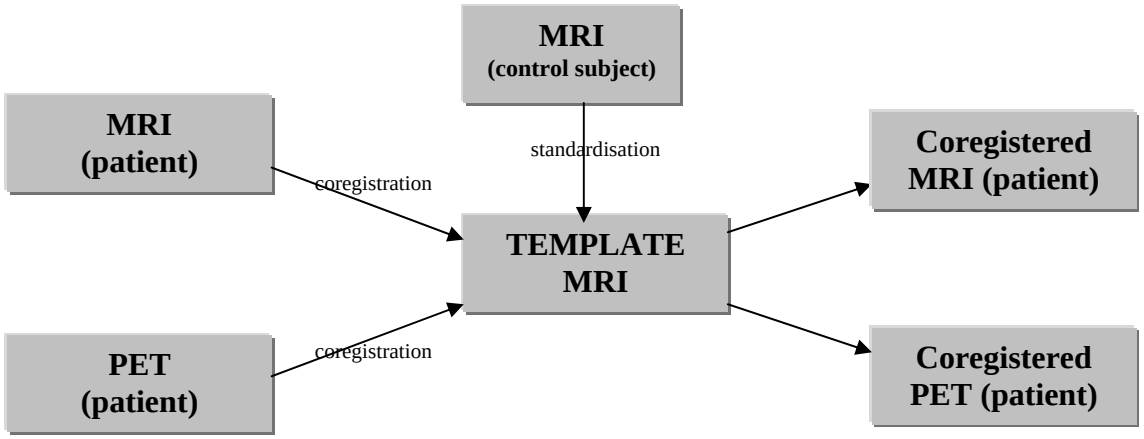
After the template image had been standardized in the Talairach system, the nine anatomical regions of interest (right and left hemispheres, right and left gyrus frontalis inferior, right and left hippocampus, right and left parietal lobe and occipital lobe) were segmented in the MRI template scan according to the protocol of the Laboratory of Neuroimaging (LONI), University of California, Los Angeles (78), see:
www.loni.ucla.edu/NCRR/Downloads/Protocols/LONIR_Protocols.html.
The ROIs were selected on the ten sections, where the best anatomical representation was seen. Hemispheres and gyrus frontalis inferior were segmented in the axial section; parietal and occipital lobe – on the sagittal section and hippocampus – on the frontal view.
In case of doubt, the delineations were verified using the neuroanatomical atlas of Duvernoy (79).

The detailed protocol of ROI delineation is described in the appendix (9.4).

3.4 Image analysis

The image analysis (see Figure 1) was done using the MIPAV software. All MRI and FDG-PET images of 24 patients were coregistered to the template image to make them similar in size and shape using the automatic image registration with the following parameters: degree of freedom – rigid 9, interpolation – trilinear, cost function – normalized mutual correlation, coarse angle increment 5 degrees, fine angle increment – 1, degree and iterations – 5. Coregistered MRI- and FDG-PET images in 3-D rendering view are presented in the appendix 9.2 (Figure 2).

Figure 1. Schematic presentation of the image coregistration



In each of the coregistered PET-images, the voxel value was then calculated in each of the 9 (right and left hemispheres, right and left gyrus frontalis inferior, right and left hippocampus, right and left parietal lobes and occipital lobe) predefined regions of interest, using the standard ROIs of the template image. The image voxel values were converted to micromoles of glucose per 100 g of tissue per minute (μmol/min/100g) using the methods described by Phelps et al. (76), generating a regional cerebral metabolic rate of glucose (rCMRglc). Additionally, the differences of voxel intensities between DICOM transfer and HERMES – workstation were calculated.

3.5 Statistical analysis

Once all neuropsychological and imaging data had been collected, we checked whether data in the pairs came from normal distributions and whether the data were at least in the category of equal interval data using Kolmogorov-Smirnov test. Because our data did not fit to the normal distribution, we used the Rank (Spearman) Correlation Coefficient.

Correlations were computed between the neuropsychological assessment battery of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD), clock – drawing test and Stroop – paradigm and cerebral metabolic rate of glucose in selected ROI. The data were analyzed utilizing SPSS-PC+ V.12.1 software (SPSS Inc., Chicago, IL). Level of statistical significance was set at p-value ≤ 0.05.

4 Results

4.1 Neuropsychological and FDG-PET data

In our study we examined 24 patients with dementia, 12 men and 12 women, (details see in Table 9 and Table 10). Results of the neuropsychological testing of our patients are listed in Table 11. Regional cerebral metabolic rates of glucose of 24 patients are presented in Table 12.

The data of the neuropsychological testing and of the regional cerebral metabolism did not fit the standard normal distribution. Because neuropsychological data were measured on ordinal and interval scales, the correlation was evaluated with Spearman rank - order correlation coefficient.

4.2 Correlation between neuropsychological testing and FDG-PET

In this study the MMSE score was significantly correlated with the hypometabolism in the left and right parietal lobes (r = 0.5; p = 0.021; r = 0.4; p = 0.048), see Table 13.

Table 13. Nonparametric Spearman correlation of the MMSE score with measures of cerebral metabolic rate measured with ^{18}F-FDG – PET in 24 patients with dementia.

Regions	Side	r	p-value
Hemisphere	Left	0,333	0,111
	Right	0,215	0,313
Gyrus frontalis inferior	Left	0,304	0,149
	Right	0,039	0,855
Hippocampus	Left	0,295	0,162
	Right	0,27	0,202
Parietal lobe	Left	0,468	0,021
	Right	0,408	0,048
Occipital lobe	Left	0,337	0,107

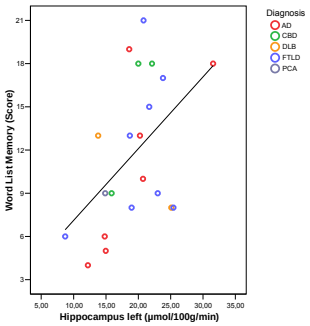
r – correlation coefficient; p- *p* value, was set at p ≤ 0.05, uncorrected. The significant results are marked.

.Significant correlation was detected between word list memory test of the CERAD-NP and metabolic rates of glucose in the left hemisphere (r = 0.6; p = 0.008), left and right hippocampus (r = 0.4; p = 0.05; r = 0.5; p = 0.033) and left parietal lobe (r = 0.5; p = 0.038), see Table 14. The scatterplot-relationship between severity of memory decline determined by the word list memory and the left and right hippocampus metabolic rate is shown in Figure 3. The word list recognition showed a significant correlation with metabolism of the left gyrus frontalis inferior (r = 0.5; p = 0.031), see Table 14. The constructive praxis subtest of the CERAD-NP was significantly correlated with glucose metabolism in the right hemisphere (r = 0.5; p = 0.024), see Table 14.

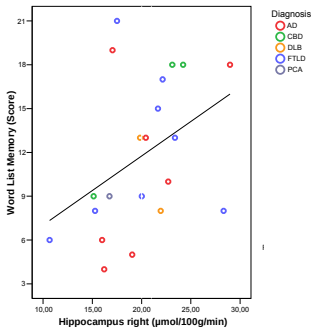
Table 14. Nonparametric rank (Spearman) correlation of the subtests of the CERAD-NP with measures of cerebral metabolic rate measured with ^{18}F-FDG – PET in 24 patients with dementia. Details: see legends from Table 13.

Regions	Side	Verbal Fluency		Boston Naming Test		Word List Learning		Word List Recall		Word List Recognition		Constructive Praxis		Constructive Praxis Recall	
		r	p	r	p	r	p	r	p	r	p	r	p	r	p
Hemisphere	Left	0,066	0,765	0,054	0,812	0,56	0,008	0,202	0,38	0,356	0,113	0,33	0,144	0,252	0,271
	Right	0,044	0,841	0,124	0,581	0,409	0,065	-0,003	0,989	0,241	0,292	0,491	0,024	0,147	0,526
Gyrus frontalis inferior	Left	0,039	0,861	0,005	0,981	0,327	0,148	-0,048	0,838	0,472	0,031	0,426	0,054	0,188	0,413
	Right	0,101	0,647	0,181	0,421	0,341	0,131	-0,098	0,672	0,164	0,478	0,351	0,118	0,295	0,195
Hippocampus	Left	0,053	0,812	0,185	0,409	0,433	0,05	0,181	0,431	0,251	0,273	0,398	0,074	0,376	0,093
	Right	0,085	0,7	0,193	0,388	0,467	0,033	0,379	0,09	0,361	0,108	0,36	0,109	0,046	0,841
Parietal lobe	Left	-0,152	0,488	0,132	0,558	0,456	0,038	0,139	0,549	0,15	0,516	0,392	0,078	0,369	0,1
	Right	-0,284	0,189	-0,023	0,918	0,359	0,11	0,01	0,966	0,241	0,293	0,382	0,087	0,322	0,155
Occipital lobe	both sides	-0,093	0,672	0,083	0,713	0,394	0,077	-0,063	0,787	0,102	0,66	0,426	0,054	0,126	0,585

Figure 3. Word list learning (memory) test data plotted against cerebral metabolic rates for glucose in the left and right hippocampus in 24 patients with dementia.



a)



b)

The score of the Word List Learning (Memory) Subtest from CERAD-NP is plotted against metabolic rate of glucose (µmol/100g/min) in the left hippocampus (a), r – 0.4, and right hippocampus (b), r – 0.4, $p \leq 0.05$.

Index by the diagnosis: AD-Alzheimer's dementia; CBD-corticobasal degeneration; DLB-dementia with Lewy bodies; FTLD-fronto-temporal lobar degeneration; PCA-posterior cortical atrophy

No significant correlations were detected between the clock-drawing test and metabolic rate of glucose in selected regions, see Table 15.

Table 15. Nonparametric rank (Spearman) correlation of the clock-drawing test with measures of cerebral metabolic rate measured with ^{18}F-FDG – PET in 24 patients with dementia. Details: see legends from Table 13.

Regions	Side	r	p
Hemisphere	Left	-0,134	0,533
	Right	-0,053	0,804
Gyrus frontalis inferior	Left	0,117	0,586
	Right	0,055	0,799
Hippocampus	Left	0,046	0,831
	Right	-0,204	0,339
Parietal lobe	Left	-0,198	0,355
	Right	-0,202	0,345
Occipital lobe	both sides	-0,086	0,69

A significant negative correlation was detected between Stroop paradigm and right gyrus frontalis inferior (r =- 0.5; p = 0.046), see Table 16.

Table 16. Correlations between Stroop-paradigm and measures of cerebral metabolic rate measured with ^{18}F-FDG – PET in 24 patients with dementia. Details: see legends from Table 13.

Regions	Side	r	p
Hemisphere	Left	-0,238	0,341
	Right	-0,269	0,28
Gyrus frontalis inferior	Left	-0,199	0,428
	Right	-0,476	0,046
Hippocampus	Left	-0,082	0,748
	Right	-0,218	0,385
Parietal lobe	Left	-0,084	0,742
	Right	-0,04	0,874
Occipital lobe	both sides	-0,195	0,438

5 Discussion

This study focused on possible correlations between cognitive domains (CERAD-NP battery, clock-drawing and Stroop paradigm) and decrease of regional cortical metabolism measured with ^{18}F-FDG-PET in patients with dementia. We measured cerebral metabolism in selected regions (right and left hemispheres, right and left gyrus frontalis inferior, right and left hippocampus, right and left parietal lobe and occipital lobe). We correlated cognitive performance score with regional metabolism across patients with dementia to elucidate the cortical substrate of cognitive impairment. In this study a significant correlation was detected between the MMSE score and the regional hypometabolism in the left and right parietal lobes. The word list learning test from the CERAD-NP significantly correlated with the hypometabolism of glucose in the left hemisphere, left and right hippocampus and left parietal lobe. Significant correlations were detected between the score of the word list recognition test and the cerebral metabolism of the left gyrus frontalis inferior and between the constructive praxis subtest and glucose hypometabolism in the right hemisphere. No significant correlation was detected between the clock-drawing test and the metabolic rate of glucose in selected regions. The score of the Stroop paradigm was significantly negatively correlated with the right gyrus frontalis inferior.

Several studies have previously reported a metabolic decrease in the cortex in patients with dementia. Studies with FDG-PET in patients with AD showed a typical hypometabolism in neocortical structures, mainly the parietal, frontal, and posterior temporal association cortices, i.e. the same areas where neuronal as well as synaptic degeneration is most severe in post-mortem studies (54;55;80); further to the regional abnormalities, AD also exhibits a global reduction of cerebral glucose metabolism. Decrease in the cerebral metabolism in the parietotemporal association cortex has been recognised as potentially diagnostic for AD and the use of PET in clinical settings to evaluate patients with dementia has been facilitated by this recognition (56). In patients with DLB cerebral metabolic reductions were detected in the occipital cortex, particularly in the primary visual cortex (62;63;65;81). FDG-PET studies of patients with

FTLD showed a hypometabolism in the frontal cortex, anterior temporal and mesiotemporal areas (18;60;61;82).

Several studies investigated the relation between the regional cortical metabolism and the profile of cognitive impairment in patients with dementia. The individual profile of impairment of different domains of memory correlated with the regional distribution of hypometabolism in resting state FDG-PET (83;84). Left hemispheric hypometabolism (in frontal, temporal and parietal cortices) in patients was associated with greater impairment of language, whereas right hemispheric metabolism was associated with impairment of visuo-constructive abilities (85;86).

5.1 MMSE

In this study the MMSE score significantly correlated with the left and right parietal lobe. These results are consistent with the findings of previous imaging studies. Several studies reported that in patients with AD the MMSE score significantly positively correlated with the hypometabolism of the temporal and parietal lobe on both sides (87;88). Other studies reported that MMSE score significantly correlated with the left parietal and occipital lobe (89) and the parietal lobe and cerebellum (90).

The reduction of the MMSE score seems to be caused by a decline in the visuo-constructional function in the associated parietal lobe in patients with dementia (87-90).

In this study four patients with the MMSE score 28 -29 were also included in this study. Because judgment and insight can not be tested only by the MMSE, the diagnosis of dementia in our patients was not only based on the MMSE score. We included in this study the patients, that had also cognitive declines in other neuropsychological tests, as CERAD (67), Clock – drawing test (68) or Stroop – test (69) and fulfilled to the Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV) (2) and ICD-10 (3) criteria for dementia.

5.2 Memory

The total score of the word list learning test was significantly correlated with the left hemisphere, the hippocampus of both sides and the left parietal lobe. Several previous neuroimaging studies suggested that the hippocampus subserves episodic memory (83;91;92). The significant correlation between memory impairment and hippocampal integrity has been observed previously in patients with AD (93-95). Lesions in other neocortical areas, such as the parietal lobe, appear to subserve the short-term retention of information. The involvement of parietal areas is suggested by several neuroimaging and electrophysiological studies of visuospatial and verbal episodic memory (96-98). Left-sided lesions are associated with defective performance in auditory–verbal short-term memory tasks (99). The left temporo-parietal cortex is thought to be involved in memory compensation processes in AD according to some activation studies (100;101). Federmeier *et al.* examined each hemisphere's tendency to retain verbal information over time, using a continuous recognition memory task, and found that the ubiquitous advantage of the left hemisphere for the processing and retention of verbal information is attenuated and perhaps even reversed over long retention intervals (102). According to this notion, a correlation of hypometabolism in the left hemisphere with the word list recognition test is more likely than with the word list learning test. In our study the word list recognition test correlated significantly with the left inferior frontal gyrus. This is in agreement with previous studies, that reported left prefrontal activation in recognition memory (103-105). Activation of prefrontal cortex during memory retrieval has been connected to top-down activation of memorized materials (106).

The word list recall test in our study did not significantly correlate with any regional metabolism. Significant correlation observed in AD patients involved hippocampal regions, bilateral posterior cingulate and retrosplenial cortices (83).

5.3 Language

In this study language functions measured with naming and verbal fluency tests were not correlated significantly to any brain regions. Previous studies reported

that lesions of cortical areas surrounding the temporo-parietal junction were found in patients with impaired word comprehension and retrieval (107;108) and in semantic dementia (109). Our hypothesis that language processing correlates with hypometabolism in the gyrus frontalis inferior was not confirmed in this study.

5.4 Attention

In this study impairment of selective attention (Stroop paradigm) significantly correlated with reduced metabolism in the right gyrus frontalis inferior. Spatial selective attention and alertness are driven by the prefrontal cortex, which is also responsible for spatial working memory (110;111). A neuroimaging study of spatial selective attention supported the hypothesis of metabolic activity in a right-hemisphere dominant network of prefrontal and parietal lobes (111).

5.5 Visuo-constructional abilities

In our study the subtest “constructional praxis” from the CERAD-NP battery significantly correlated with hypometabolism in the right hemisphere. We hypothesized that visuospatial deficits correlate with hypometabolism in the parietal lobe. In this study only a weak association between the clock-drawing test and parietal lobe was detected. A large range of neuropsychological studies on patients with local cerebral lesions suggested the involvement of bilateral or right parietal lobe in constructional function (112;113). PET studies reported that patients with predominant visuo-constructive dysfunction showed a hypometabolic focus in the right parietal cortex (114;115). In contrast to the constructive praxis of patients with focal lesions, the spontaneous drawings of AD patients were not only simplified, but often incoherent, and the visuo-spatial relationships were lost not only in spontaneous drawing of items but also when copying an object (116). The deficits in patients on copying tasks might be partially attributable to attention deficits whereby the patients fail to integrate separate features of an object into a coherent whole. The correlation between constructive praxis and reduced metabolism in the right hemisphere in our patients may, therefore, in part reflect attention deficits. Attention, as it has been

reported above, was associated in our study with right-hemisphere hypometabolism.

Additionally, in order to interpret the successfulness of the ROIs alignment the test-retest reliability was used. Intra-class correlations (ICC) in all ROIs showed good test/retest reliability . For example, in the parietal lobe (range *r*=0.958 - 0.992 with 95% confidence) or left hippocampus (range *r*=0.764 - 0.956 with 95% confidence) the values of glucose metabolism were good reliable, suggesting that the identification of ROIs in this study was successful.

This study has some limitations. The most important study limitation is its small sample size. Unfortunately we were unable to investigate more patients using both structural and functional imaging, and the small number of subjects clearly compromised the statistical power of this investigation. We also used a low level of significance that set at 0.05. Because of the small sample size the two-sample test was used. This was a potential limitation in our study. But it would be interesting in the perspective study to proof our data with the higher sample of subjects. Furthermore, no correction for multiple comparisons (for example, Bonferroni) was done in view of the exploratory character of the study. Nevertheless, our results show some correlation between structural and functional measurements which might well have clinical significance.

There is also methodological lack, which have to be considered with our data. We had selected 9 independent regions of primary interest in the ROI-based analysis. The limitation of the above approach is that we may not interpret the exact coordinate location too heavily, i.e. if we find a significant activation in the left hemisphere, we cannot put emphasis on the specific function of a subdivision of the left hemisphere. An additional analysis of our data using a voxel-based morphometry method would therefore be of interest.

The unexpected pattern of observed correlations may be accounted for by the small sample size of patients.

There is also a methodological shortcoming that any restricted regions of interest were chosen for analysis.

An additional analysis of our data using a voxel-based statistical approach would therefore be of interest.

6 Summary

We examined 24 patients with dementia aged 69.2 ± 7.5 years, diagnosed according to the ICD-10 (3) and DSM-IV (2) criteria for dementia. Cognitive function was assessed using the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NP), which incorporates the Mini-Mental State Examination (MMSE) (67), clock-drawing test as modified by Shulman (68) and a Stroop-paradigm - Nürnberger-Alters-Inventar (NAI) Version (69). Neuroimaging data used to establish a clinical diagnosis were obtained solely from MRI, and all diagnoses were made before and independently from the PET scan. The MRI AND FDG-PET datasets were analysed within medical image processing, analysis and visualisation application software (MIPAV). The cerebral metabolism in FDG-PET data were calculated in the nine predefined set of regions of interest (ROI) (right and left hemispheres, right and left gyrus frontalis inferior, right and left hippocampus, right and left parietal lobe and occipital lobe). The correlation between neuropsychological and imaging data using Spearman's rank correlation coefficient was calculated. In this study a significant correlation was detected between the MMSE score and the regional hypometabolism in the left and right parietal lobes. On memory tests, the word list learning test from the CERAD-NP, the hypometabolism of glucose in the left hemisphere, the left and right hippocampus and the left parietal lobe approached significance. Additionally, the word list recognition test from the CERAD-NP significantly correlated with cerebral metabolism of the left gyrus frontalis inferior. On the nonverbal task of the constructive praxis, decreased glucose metabolism was detected in the right hemisphere. Visuo-constuctional praxis, particularly the clock-drawing test, was not significantly correlated to any brain regions. On attention test, the Stroop paradigm, hypometabolism in the right gyrus frontalis inferior was observed.

Our findings support the notion that profiles of cognitive impairment and regional cortical metabolism can identify cortical regions that are affected by dementia. Some findings from this study correspond to the brain-behaviour relationships and show that image fusion and correlation with neuropsychological data is feasible in clinical practice.

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9 Appendix

9.1 Tables

Table 1. Diagnostic criteria for dementia according to DSM-IV .

A1. The development of multiple cognitive deficits manifested by both Memory impairment (impaired ability to learn new information or to recall previously learned information)
A2. One (or more) of the following cognitive disturbances: a. Aphasia (language disturbance) b. Apraxia (impaired ability to perform motor activities despite intact motor function) c. Agnosia (failure to recognize or identify objects despite intact sensory function) d. Disturbance in executive functioning (that is, planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause severe impairment in social or occupational functioning and represent a major decline from a previous level of functioning
E. The deficits do not occur exclusively during the course of a delirium
F. The disturbance is not better accounted for by another axis I disorder (for example, major depressive disorder, schizophrenia)

* clinical criteria for all types of dementia

Table 2. Diagnostic Criteria for dementia according to ICD-10.

G 1.1. *A decline in memory,* which is most evident in the learning of new information, although in more severe cases, the recall of previously learned information may be also affected. The impairment applies to both verbal and nonverbal material. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments.
G 1.2. *A decline in other cognitive abilities* characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information. Evidence for this should be obtained when possible from interviewing an informant, supplemented, if possible, by neuropsychological tests or quantified objective assessments. Deterioration from a previously higher level of performance should be established.
The *overall severity of the dementia* is best expressed as the level of decline in memory or other cognitive abilities, whichever is the more severe (e.g. mild decline in memory and moderate decline in cognitive abilities indicate a dementia of moderate severity).
G 2. *Preserved awareness of the environment* (i.e. absence of clouding of consciousness (as defined in F05, criterion A)) during a period of time long enough to enable the unequivocal demonstration of G1. When there are superimposed episodes of delirium the diagnosis of dementia should be deferred.
G 3. *A decline in emotional control or motivation, or a change in social behaviour,* manifest as at least one of the following: (1) emotional lability; (2) irritability; (3) apathy; (4) coarsening of social behaviour.
G 4. For a confident clinical diagnosis, G1 should have been present for *at least six months;* if the period since the manifest onset is shorter, the diagnosis can only be tentative.

Table 3. NINCDS/ADRDA criteria for probable AD.

I. Criteria for the clinical diagnosis of PROBABLE Alzheimer`s disease

- dementia established by clinical examination and documented by the Mini-Mental Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

II. The diagnosis of PROBABLE Alzheimer`s disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
    - normal lumbar puncture as evaluated by standard techniques,
    - normal pattern or non-specific changes in EEG, such as increased slow-wave activity,
    - evidence of cerebral atrophy on CT with progression documented by serial observation

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer`s disease, after exclusion of causes of dementia other than Alzheimer`s disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age

IV. Features that make the diagnosis of PROBABLE Alzheimer`s disease uncertain or unlikely include:

- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

Table 4. Diagnostic features for FTLD (Neary et al., 1998)

Form of Dementia	Core diagnostic features	Supportive diagnostic features
Frontotemporal degeneration	Insidious onset Gradual progression Early decline in social Interpersonal conduct Early impairment of personal conduct Early emotional blunting Early loss of insight	Behavioral disorder 1. Decline in personal hygiene and grooming 2. Mental rigidity and inflexibility 3. Distractibility and impersistence 4. Hyperorality and dietary changes 5. Perseverative and stereotyped behavior 6. Utilization behavior Speech and language 1. Altered speech output 2. Echolalia 3. Perseveration 4. Mutism Physical signs 1. Primitive reflexes 2. Incontinence 3. Akinesia, rigidity, and tremor 4. Low and labile blood pressure
Primary progressive aphasia	Insidious onset Gradual progression Nonfluent spontaneous speech: agrammatism, phonemic paraphasias, anomia	Speech and language 1. Stuttering or oral apraxia 2. Impaired repetition 3. Alexia, agraphia 4. Early preservation of word meaning 5. Late mutism Behavior 1. Early preservation of social skills 2. Late behavioral changes similar to FTD Physical signs: Late contralateral primitive reflexes, akinesia, rigidity, and tremor
Semantic dementia	Insidious onset Gradual progression Language Disorder characterized by 1. Progressive, fluent, empty spontaneous speech 2. Loss of word meaning, manifest by impaired naming and comprehension 3. Semantic paraphasias and/or Perceptual disorder Preserved perceptual matching and drawing reproduction Preserved single-word repetition Preserved ability to read aloud and write to dictation orthographically regular words	Speech and language 1. Press of speech 2. Idiosyncratic word usage 3. Absence of phonemic paraphasias 4. Surface dyslexia and dysgraphia 5. Preserved calculation Behavior 1. Loss of sympathy and empathy 2. Narrowed preoccupations 3. Parsimony Physical signs 1. Absent or late primitive reflexes 2. Akinesia, rigidity, and tremor

Table 5. Proposed criteria for the diagnosis of the corticobasal syndrome (117) .

Core features	Insidious onset and progressive course No identifiable cause (i.e., tumor or infarct) Cortical dysfunction as reflected by at least one of the following: Focal or asymmetrical ideomotor apraxia Alien limb phenomenon Cortical sensory loss Visual or sensory hemineglect Constructional apraxia Focal or asymmetric myoclonus Apraxia of speech / nonfluent aphasia Extrapyramidal dysfunction as reflected by at least one of the following: Focal or asymmetrical appendicular rigidity lacking prominent and sustained L-dopa response Focal or asymmetrical appendicular dystonia
Supportive investigations	Variable degrees of focal or lateralized cognitive dysfunction with relative preservation of learning and memory, on neuropsychometric testing Focal or asymmetric atrophy on computed tomography or magnetic resonance imaging, typically maximal in parietofrontal cortex Focal or asymmetric hypoperfusion on single-photon emission computed tomography and positron emission tomography, typically maximal in parieto-frontal cortex +/- basal ganglia +/- thalamus

Table 6. Proposed clinical diagnostic criteria for posterior cortical atrophy (Mendez et al., 2002)

Core features	Insidious onset and gradual progression Presentation with visual complaints with intact primary visual functions Evidence of predominant complex visual disorder on examination - Element of Balint's syndrome - Visual agnosia - Dressing apraxia - Environmental disorientation Proportionally less impaired deficits in memory and verbal fluency Relatively preserved insight with and without depression
Supportive features	Presenile onset Alexia Elements of Gerstmann's syndrome Ideomotor apraxia Physical examination within normal limits Investigations - Neuropsychology: predominantly impaired perceptual deficits - Brain imaging : predominantly occipitoparietal abnormality (especially on functional imaging) with relative sparing of frontal and mesiotemporal regions)

Table 7. Consensus criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (McKeith et al., 1996)

Central features	Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.
Core features	Fluctuating cognition with pronounced variations in attention and alertness Recurrent visual hallucinations that are typically well formed and detailed Spontaneous motor features of parkinsonism
Supportive features	Repeated falls Syncope Transient loss of consciousness Neuroleptic sensitivity Systematized delusions Hallucinations in other modalities
A diagnosis of DLB is less likely	Stroke disease, evident as focal neurologic signs or on brain imaging Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

Table 9. List of patients with demographic data and diagnosis, case index by diagnosis

Patient Nr	Patient initials	gender	Age	Age of onset	Diagnosis
001	BO	f	67	65	AD
002	BR	f	78	77	AD
003	BA	m	68	68	AD
004	AM	f	76	76	AD
005	DH	m	69	68	AD
006	MC	m	74	73	AD
007	MB	f	54	53	AD
008	SB	m	78	77	AD
009	KH	m	65	63	AD
010	FK	f	76	75	CBD
011	WV	m	66	65	CBD
012	SK	f	75	71	CBD
013	WH	f	74	71	FTLD
014	SA	m	63	60	FTLD
015	WA	f	61	60	FTLD
016	IR	f	62	60	FTLD
017	KC	m	68	67	FTLD
018	EF	m	72	69	FTLD
019	NR	f	63	61	FTLD
020	JD	f	60	59	FTLD
021	GF	m	81	79	DLB
022	KE	m	82	81	DLB
023	WE	f	59	58	PCA
024	KF	m	69	59	PCA

f – female, m – male; AD – Alzheimer's dementia, CBD – corticobasal degeneration, FTLD – frontotemporal lobar degeneration, DLB – dementia with Lewy's bodies, PCA – posterior cortical atrophy;

Table 10. Index of symptoms of 24 patients with dementia

Pat.Nr	memory	concen tration	orienta -tion	visuocon -struction	word fluency	motor aphasiar	sensory aphasia	alexia	perse- veration	ideomotor apraxia	limb- kinetic apraxia	visuo- motor ataxia	gait	rigidity tremor	orthosta- tic hypoten- sion	optical hallucina tion	behaviour disorder
001	1	1	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0
002	1	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0
003	1	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0
004	1	1	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0
005	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
006	1	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0
007	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
008	1	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0
009	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
010	1	0	0	0	0	0	0	0	0	1	left	0	0	0	0	0	0
011	1	1	0	0	0	0	0	0	0	1	left	0	0	0	0	0	0
012	1	1	0	1	1	1	0	0	0	1	right	0	1	0	0	0	0
013	1	0	0	1	1	0	0	1	1	0	0	0	0	0	0	0	1
014	1	1	0	0	1	0	1	0	1	0	0	0	0	0	0	0	0
015	1	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	1
016	1	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	1
017	1	1	0	1	1	0	1	0	1	0	0	0	0	0	0	0	1
018	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1
019	1	1	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0
020*	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0
021	1	1	0	0	1	0	0	0	0	1	0	0	1	1	1	0	0
022	1	0	0	0	1	0	0	0	0	1	0	0	1	1	1	0	0
023	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0
024	1	0	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0
Total	24	19	9	14	19	2	2	2	8	12	3	2	3	2	2	0	5

1 – presence of the symptom; 0 – absence of the symptoms; left *and* right – presence of symptom on the left or on the right side. * - patient had in the anamnesis an old arteria carotis anterior (ACA) infarction left (for several years before the cognitive impaiments)

Table 11. Neuropsychological testing in 24 patients with dementia.

Pat. Nr.	CERAD								Clock drawing test	Stroop paradigm
	MMSE	Verbal Fluency	Boston Naming Test	Word List Memory	Word List Recall	Word List Recognition	Constructional Praxis	Constructional Praxis/Recall		
001	15	6	11	6	0	8	4	0	5	42
002	12*	N/D	N/D	N/D	N/D	N/D	N/D	N/D	3	N/D
003	20	9	14	10	3	19	11	6	3	N/D
004	15*	12**	15	N/D	N/D	N/D	N/D	N/D	1	N/D
005	24	12	15	4	2	6	11	6	1	21
006	16	8	11	5	0	13	7	0	3	36
007	29	18	15	19	2	7	11	6	1	18
008	26	14	15	18	4	9	11	9	1	23
009	26	20	14	13	1	14	11	1	3	20
010	26	14	15	9	4	9	7	4	4	29
011	29	16	15	18	6	20	11	2	3	24
012	27	12	14	18	6	10	4	2	1	52
013	27	9	6	8	0	17	7	7	5	67
014	25	15	14	17	6	10	10	2	3	31
015	28	7	13	13	4	20	11	0	1	45
016	22	9	15	9	0	7	11	4	4	50
017	25	9	11	8	0	20	11	4	3	27
018	9	8	9	6	0	11	11	3	1	118
019	28	5	13	15	3	20	11	11	3	25
020	28	6	13	21	9	20	10	7	1	54
021	26	13	15	13	10	20	9	5	1	N/D
022	26	10	14	8	2	19	11	11	3	82
023	18	17	13	9	1	15	5	0	6	N/D
024	24*	11**	14	N/D	N/D	N/D	N/D	N/D	3	N/D
HC	30	25	15	20	10	20	11	11	1	14

Numbers represent raw data from the specific subtests, except for the Stroop paradigm (seconds, difference between color naming and interference conditions).

* MMSE according to (70);

** semantic fluency according to (71);

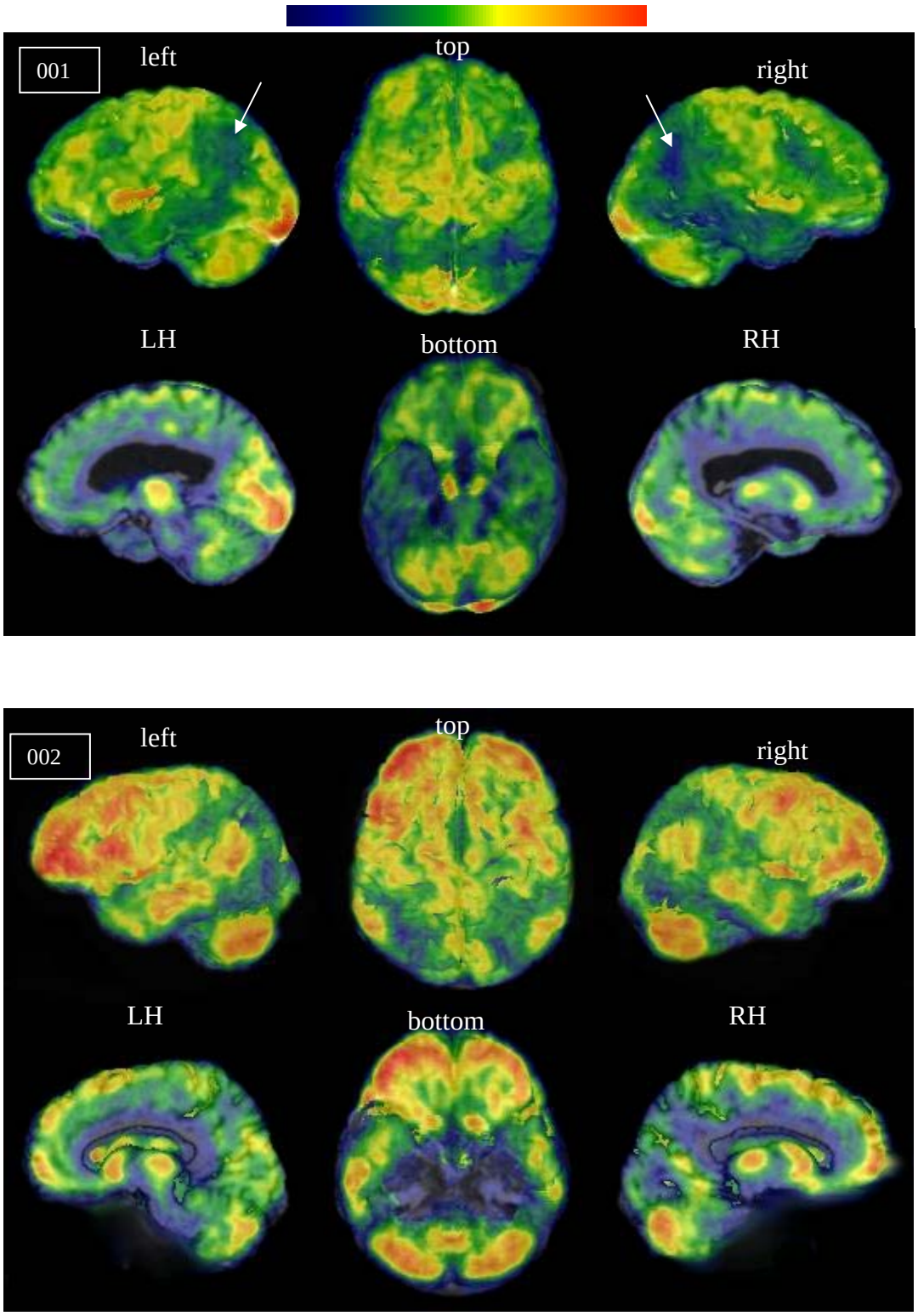
HC – healthy control subject; N/D – not done

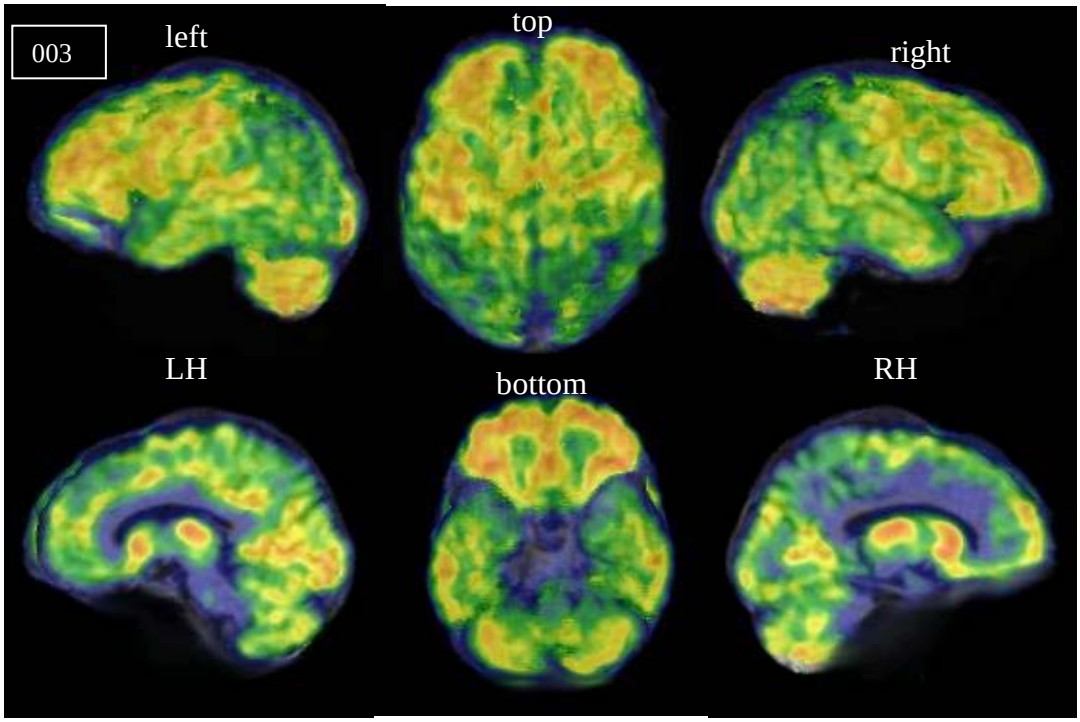
Table 12. Regional cerebral metabolic value of glucose (μmol/100 g/min) in 24 patients with dementia

Pat.Nr	Hemisphere left	Hemisphere right	Gyrus frontalis inferior left	Gyrus frontalis inferior right	Hippocampus left	Hippocampus right	Parietal lobe left	Parietal lobe right	Occipital lobe
001	24,87	22,45	23,93	25,51	14,81	15,99	20,75	20,50	31,70
002	32,11	35,25	30,30	40,84	18,38	20,41	29,73	31,12	33,90
003	28,15	27,05	27,92	29,21	20,73	22,71	28,47	25,13	28,09
004	32,18	29,86	29,01	33,67	21,68	19,84	34,32	34,06	39,31
005	21,81	23,38	21,18	23,87	12,21	16,20	27,00	26,34	27,26
006	21,18	23,92	20,96	23,41	14,97	19,05	23,31	27,43	29,65
007	28,92	28,66	28,71	32,28	18,60	17,05	29,49	29,55	38,29
008	38,48	38,55	29,34	33,19	31,56	28,98	44,36	37,36	49,12
009	29,42	33,09	30,08	27,15	20,26	20,43	33,61	28,37	37,94
010	21,79	19,00	20,37	17,22	15,87	15,13	23,75	20,31	24,38
011	35,11	34,24	35,20	31,08	22,12	23,12	35,90	35,49	38,73
012	24,96	25,78	21,17	22,82	20,00	24,22	36,17	31,89	29,29
013	31,82	29,52	33,10	29,26	18,97	15,28	41,82	37,61	35,08
014	25,27	23,01	20,71	17,20	23,81	22,14	25,97	24,61	33,26
015	31,33	31,94	29,36	24,84	18,69	23,39	41,35	36,76	45,37
016	23,01	32,31	27,56	26,82	23,01	20,02	44,45	42,41	54,85
017	35,86	34,93	33,14	28,59	25,43	28,33	42,35	38,99	47,39
018	18,90	18,32	18,43	16,15	8,71	10,66	21,28	21,69	22,49
019	28,18	30,09	29,69	32,53	21,69	21,66	35,21	34,60	34,86
020	32,10	28,85	27,12	24,72	20,81	17,51	42,70	43,60	39,91
021	21,23	21,99	25,21	23,54	13,80	19,85	22,72	20,75	20,89
022	23,73	22,63	22,06	20,56	25,10	21,94	23,82	25,02	29,96
023	22,60	22,96	27,11	26,92	14,89	16,74	17,89	16,43	26,86
024	29,11	33,30	31,44	33,63	24,47	24,34	33,71	33,39	32,01

9.2 Figures

Figure 1. 3D-rendering view of coregistered MRI and FDG-PET of twenty-four patients with dementia. Hypometabolism in cerebral cortex (arrows). The numbers of patients according to Table 9 are marked in the left corner.
LH – left hemisphere; RH – right hemisphere.

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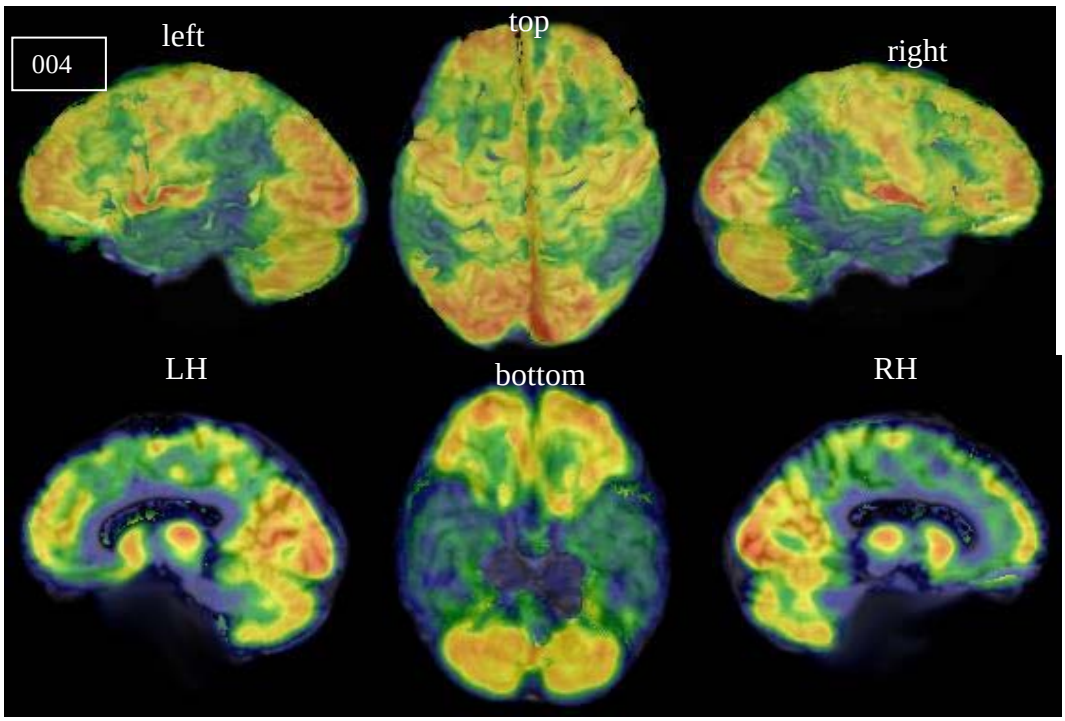
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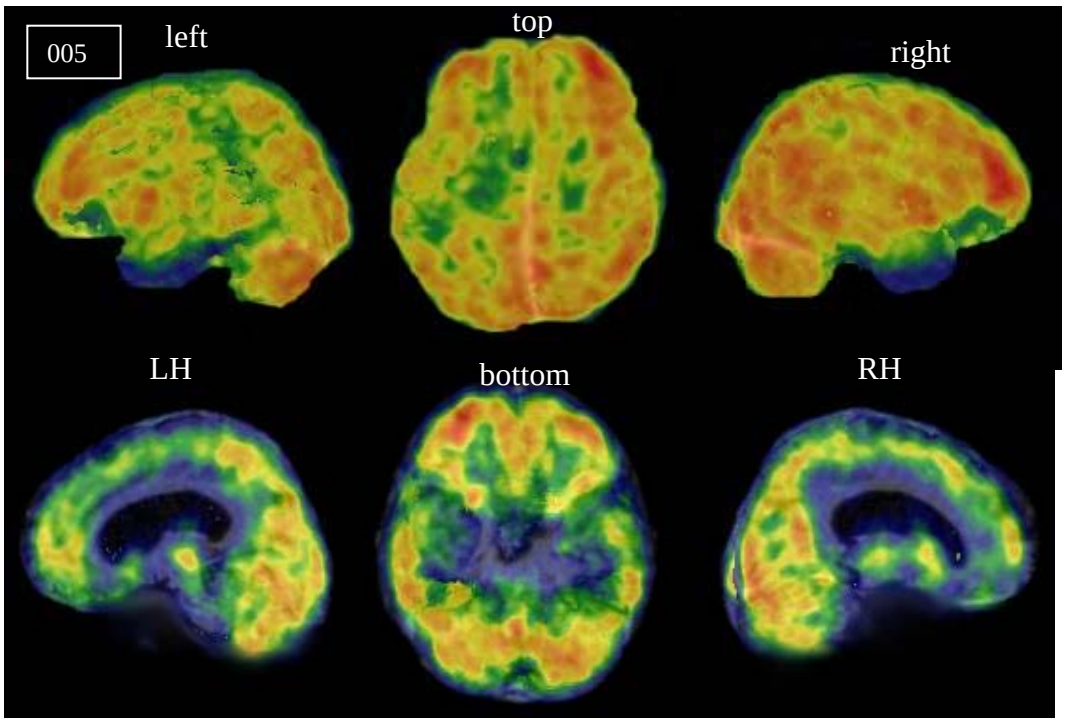
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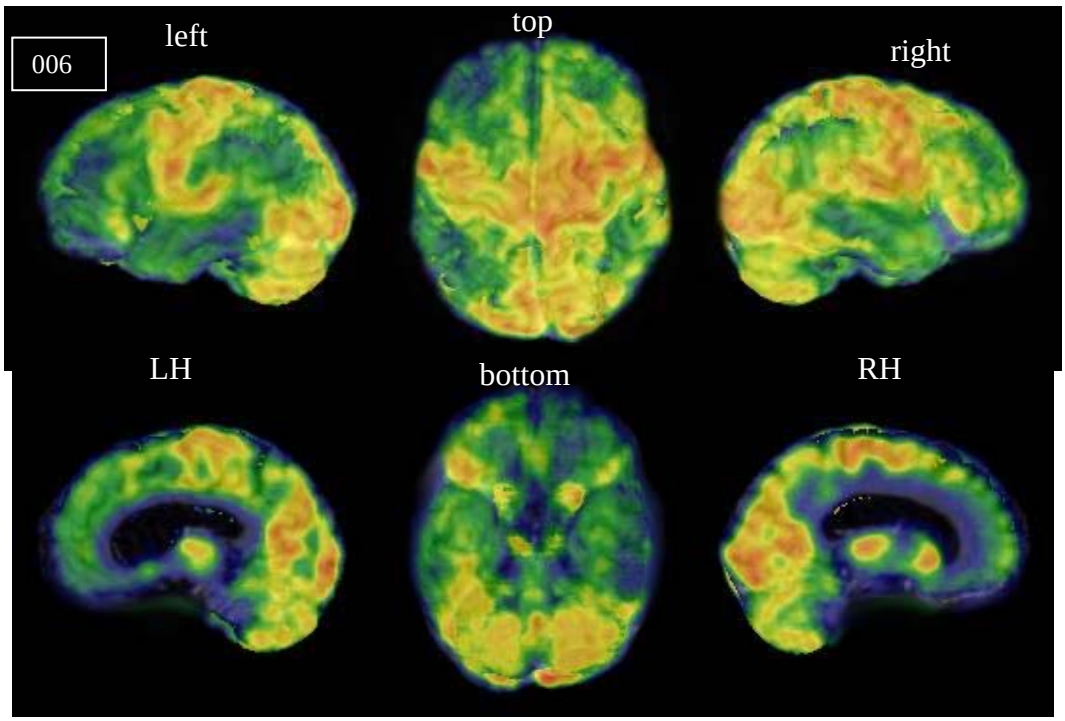
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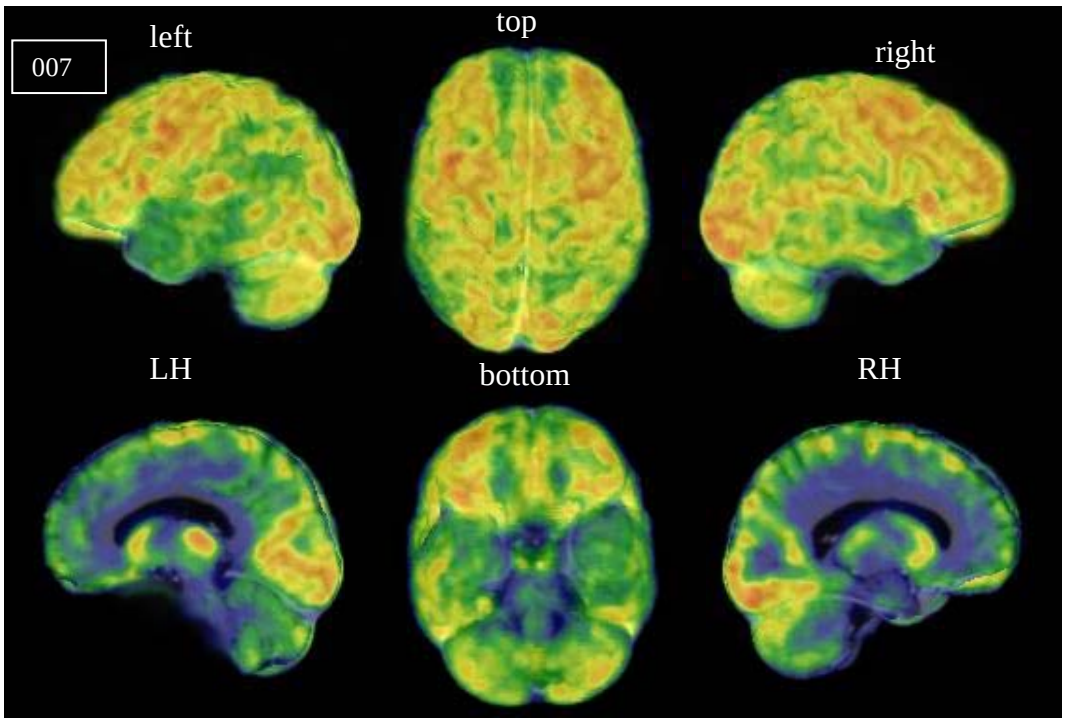
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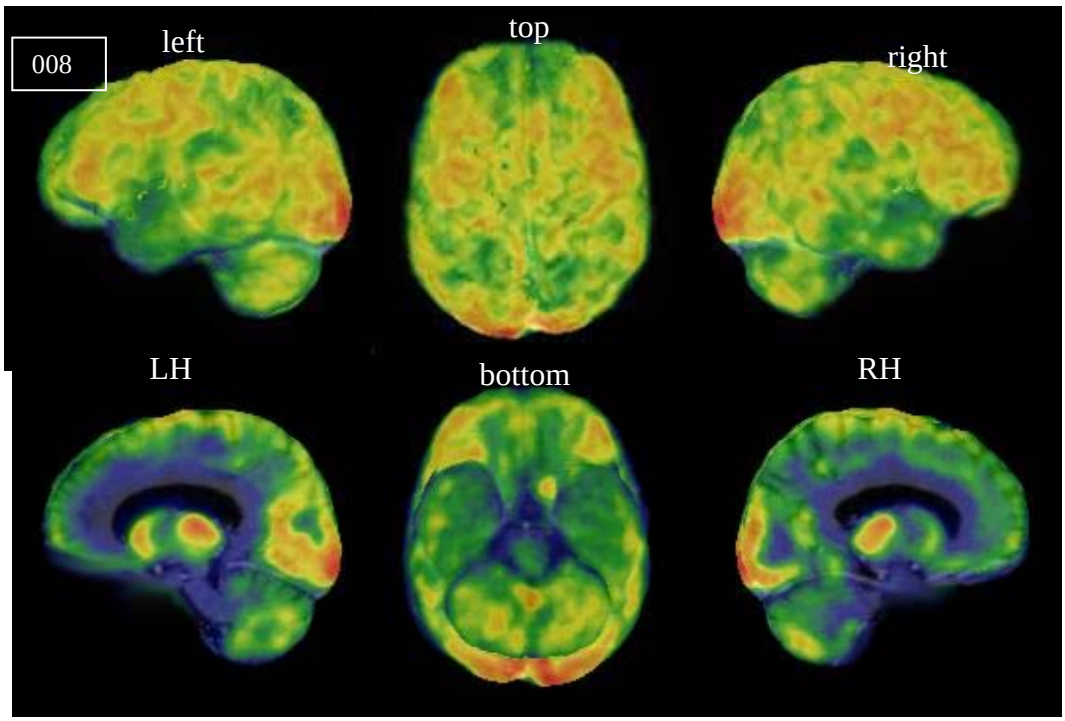
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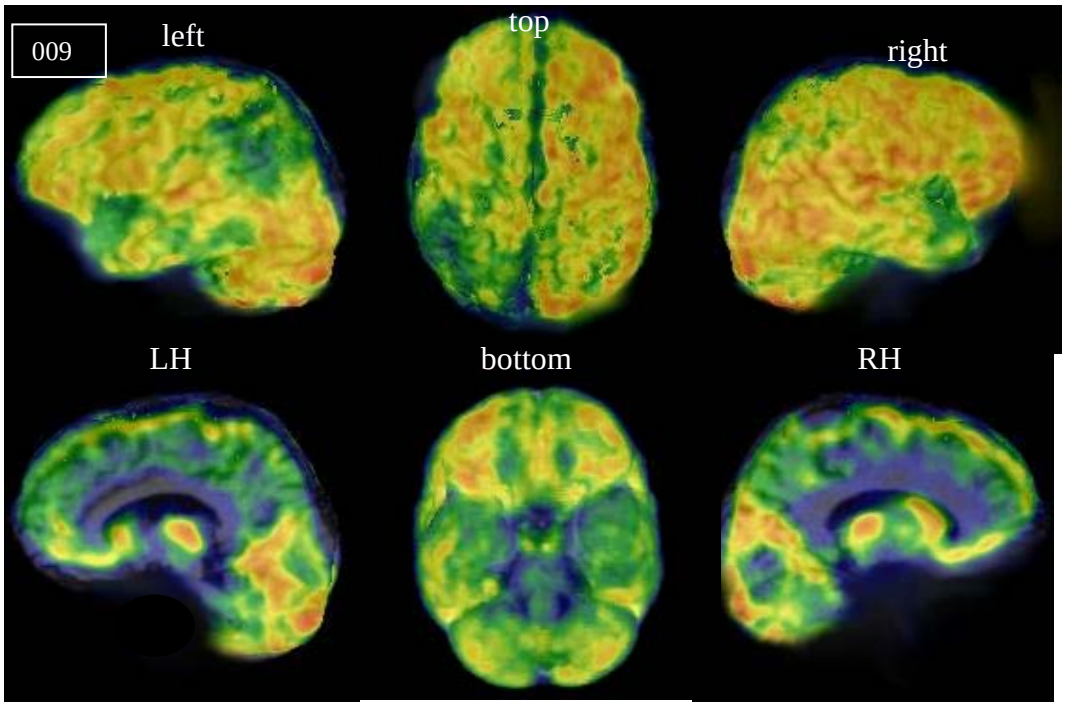
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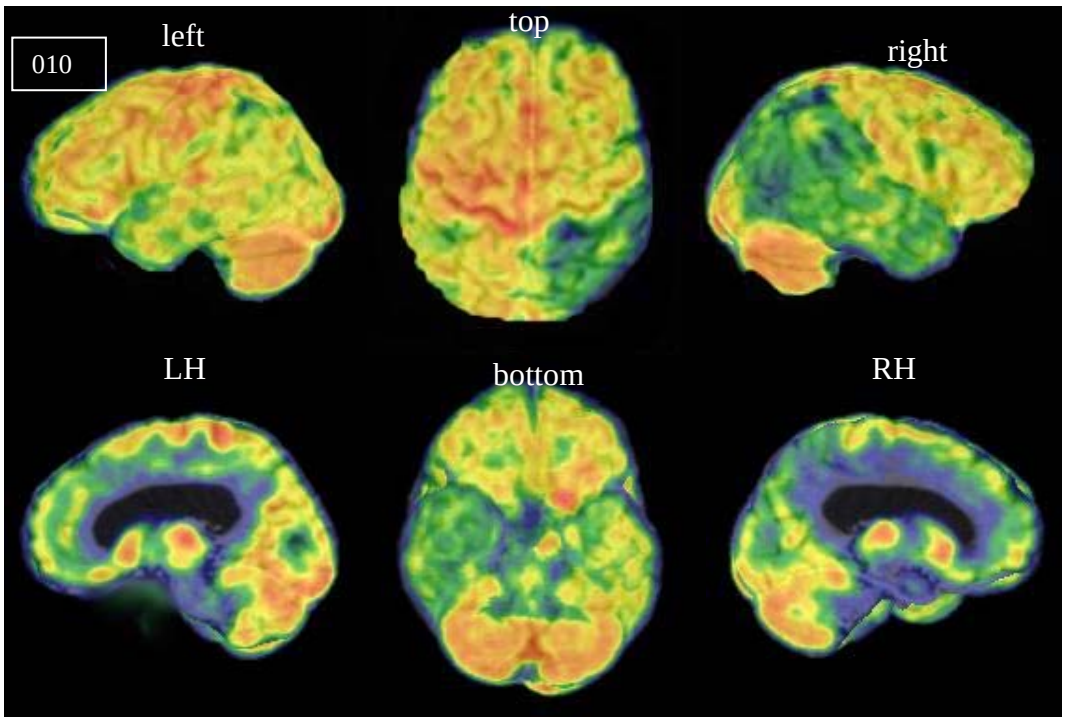
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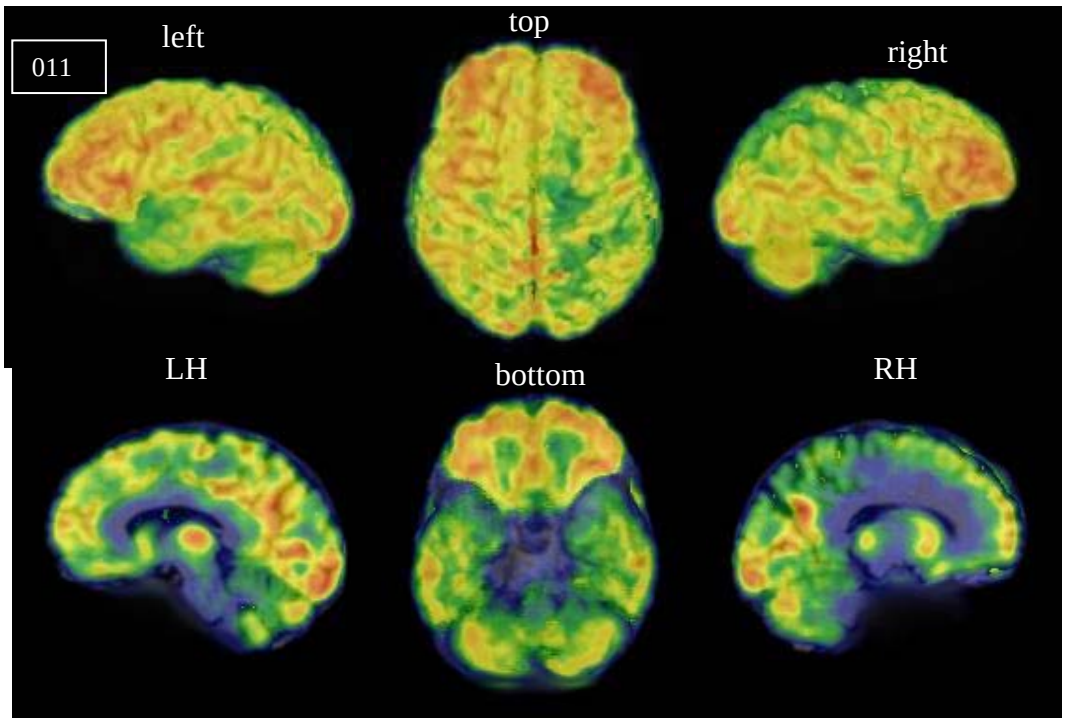
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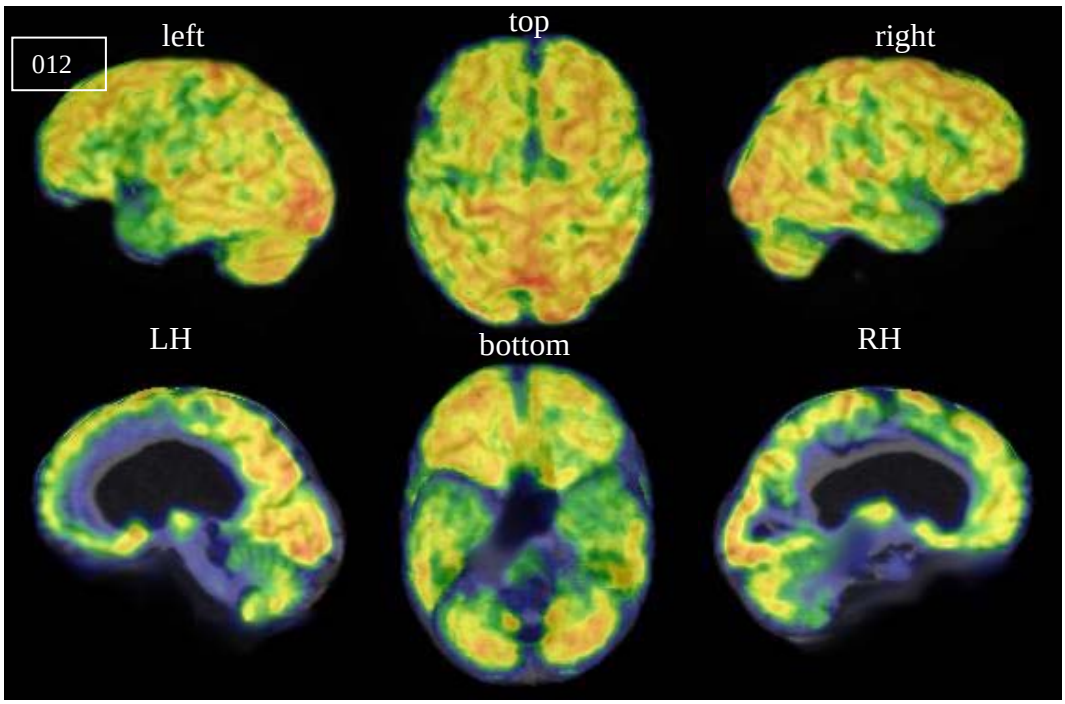
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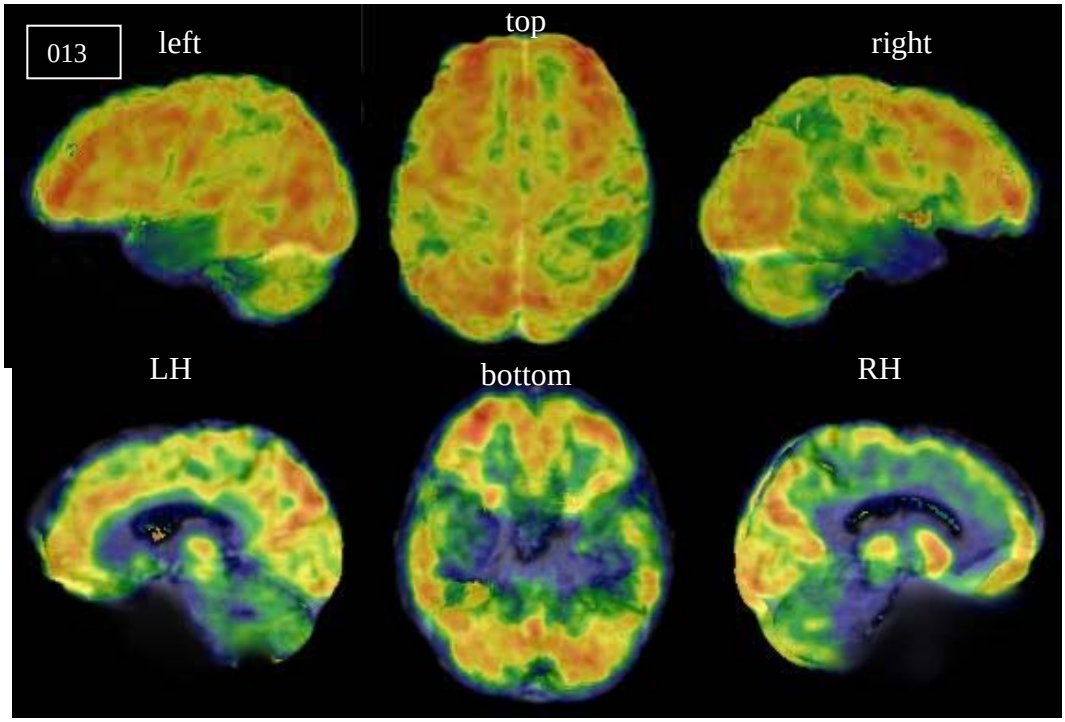
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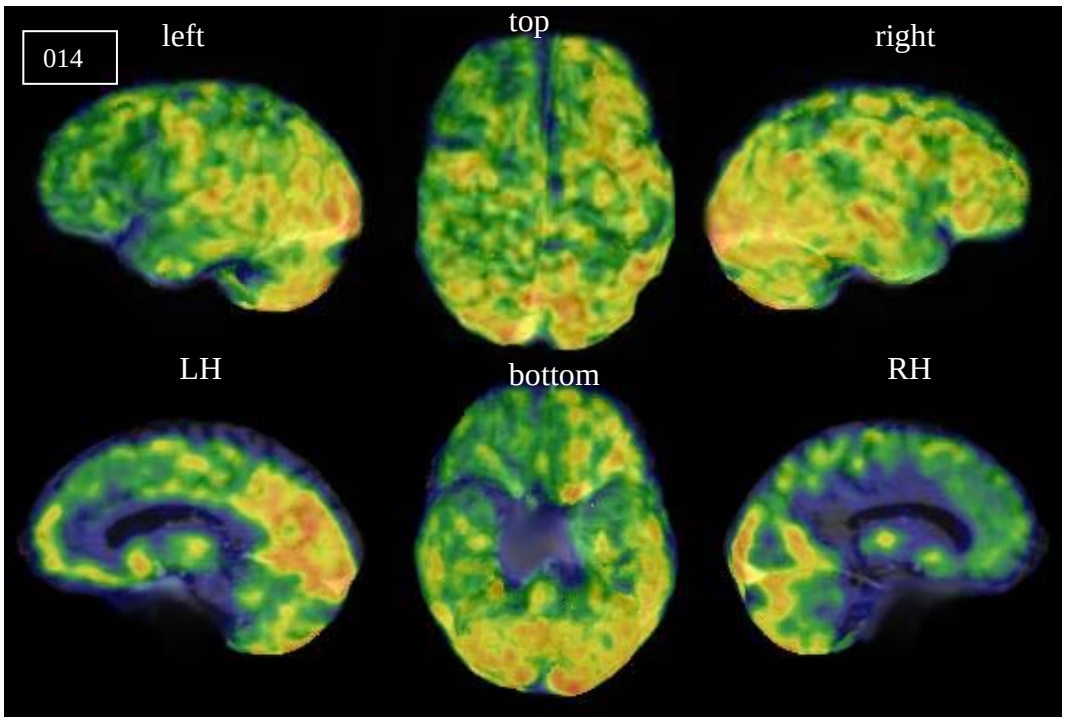
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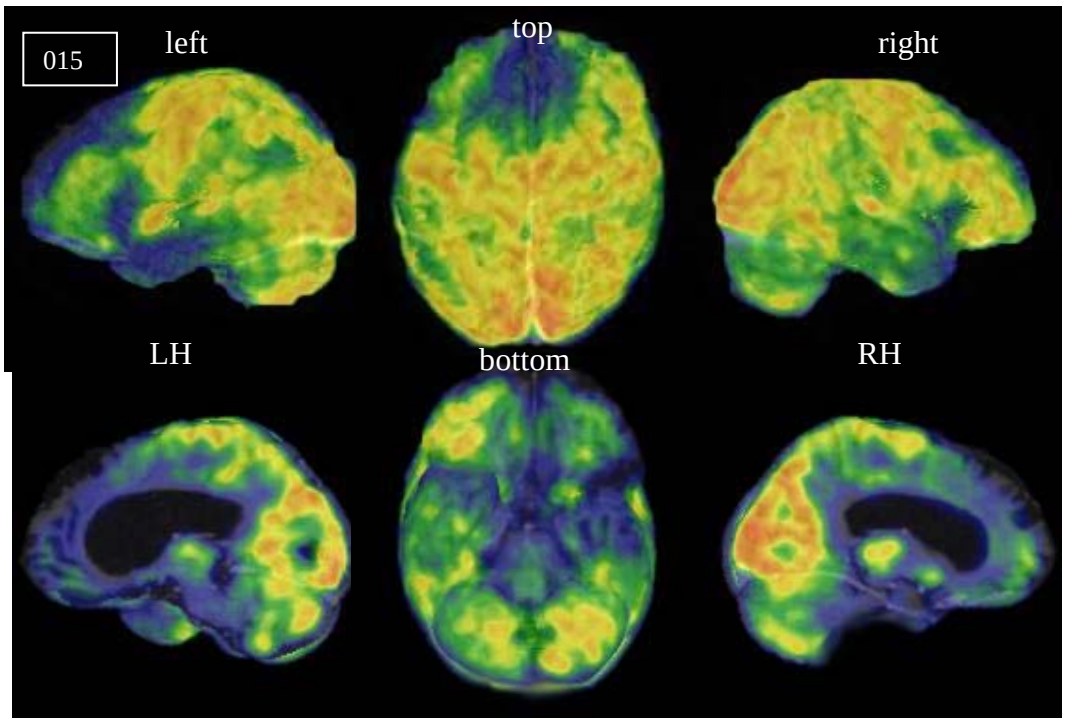
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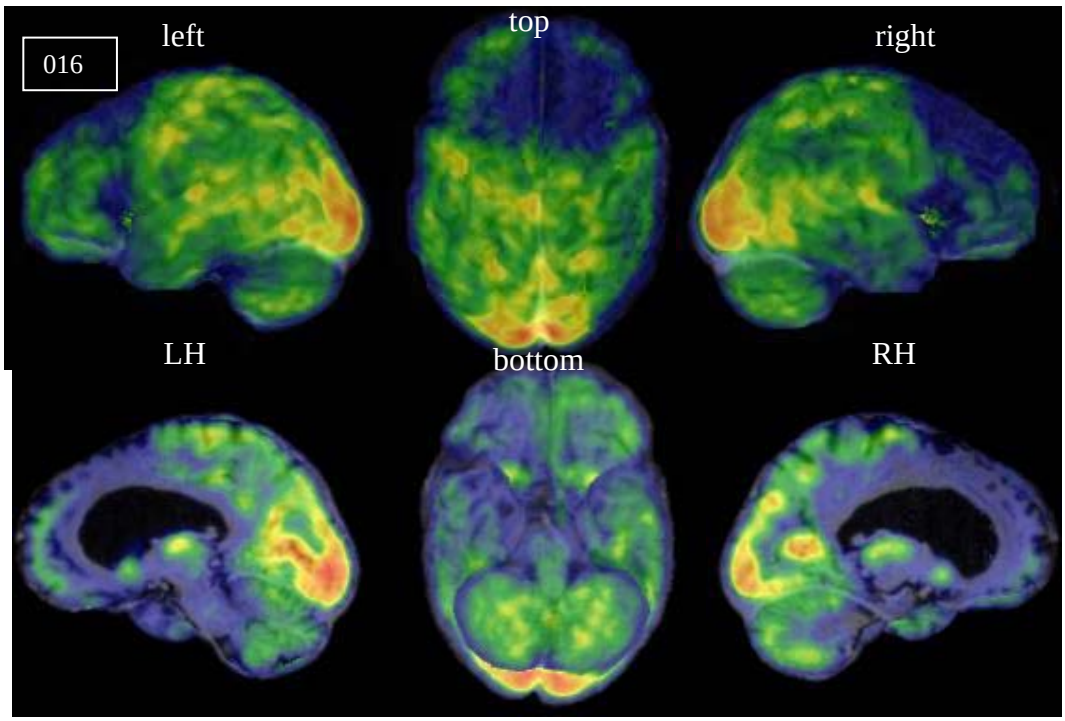
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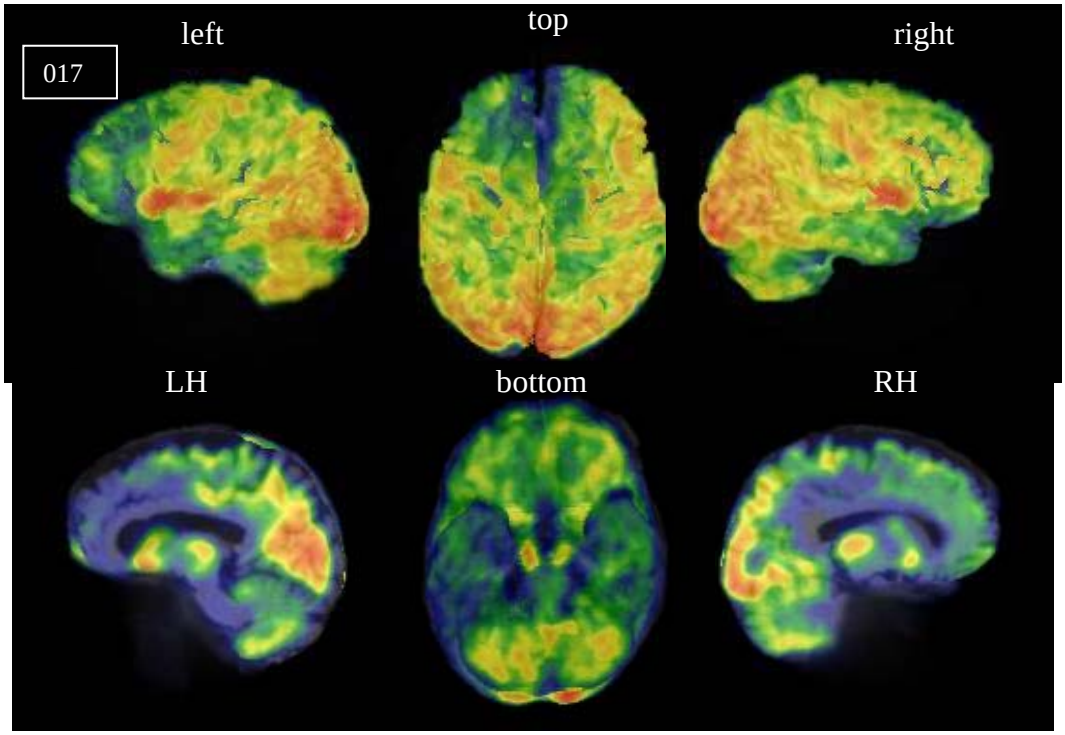
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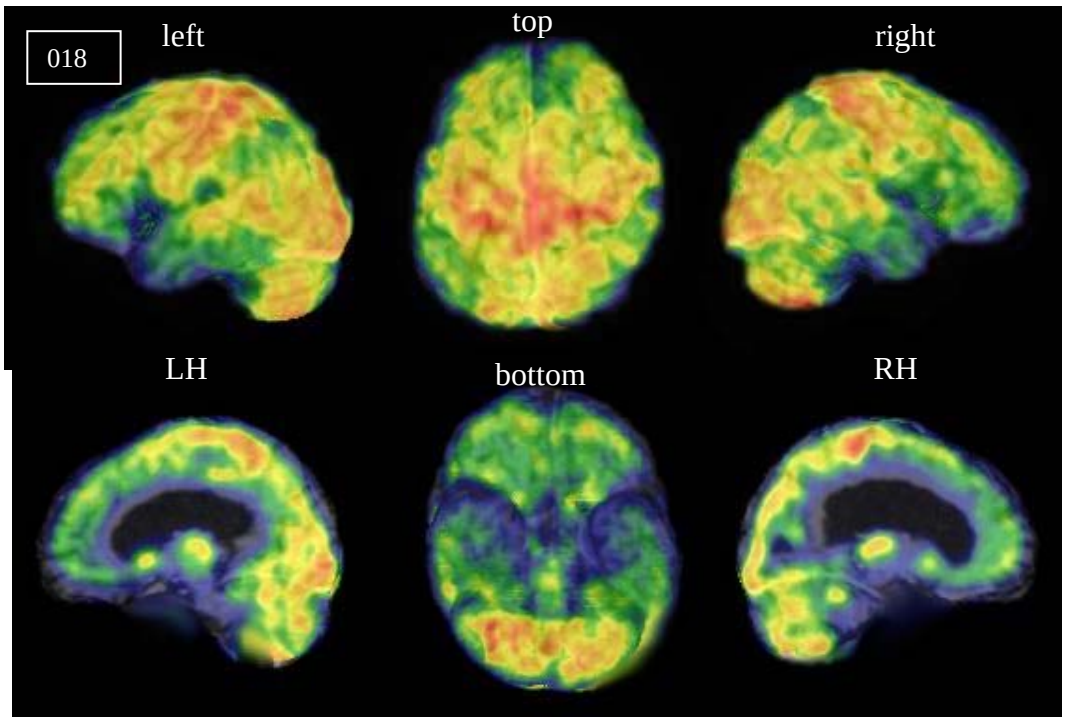
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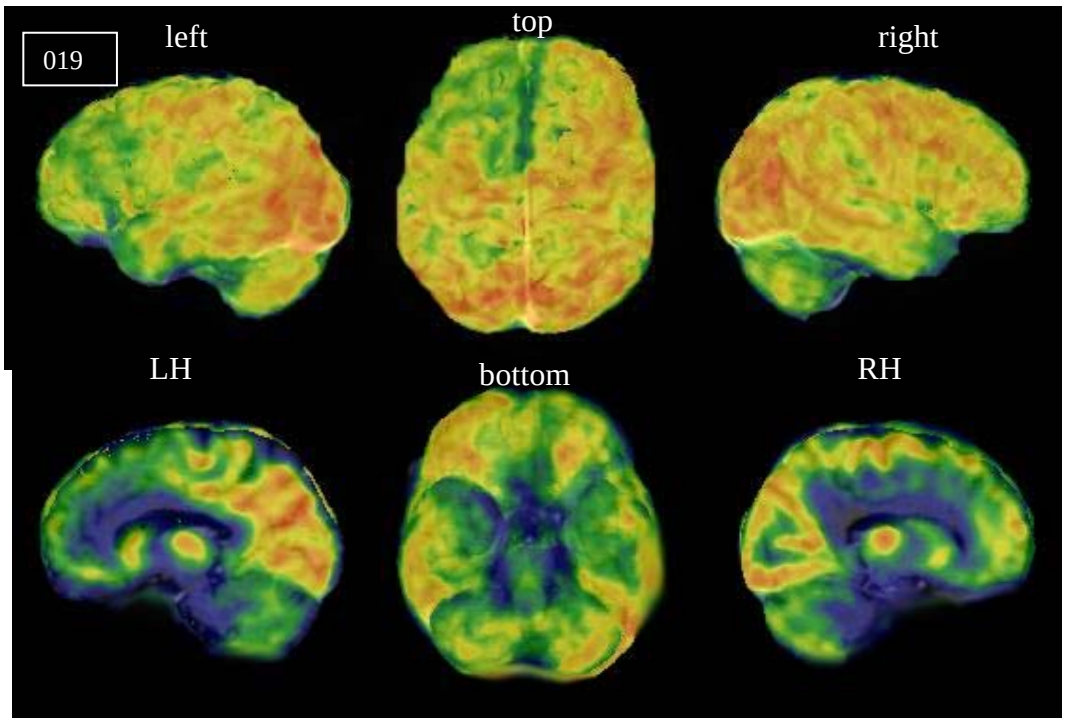
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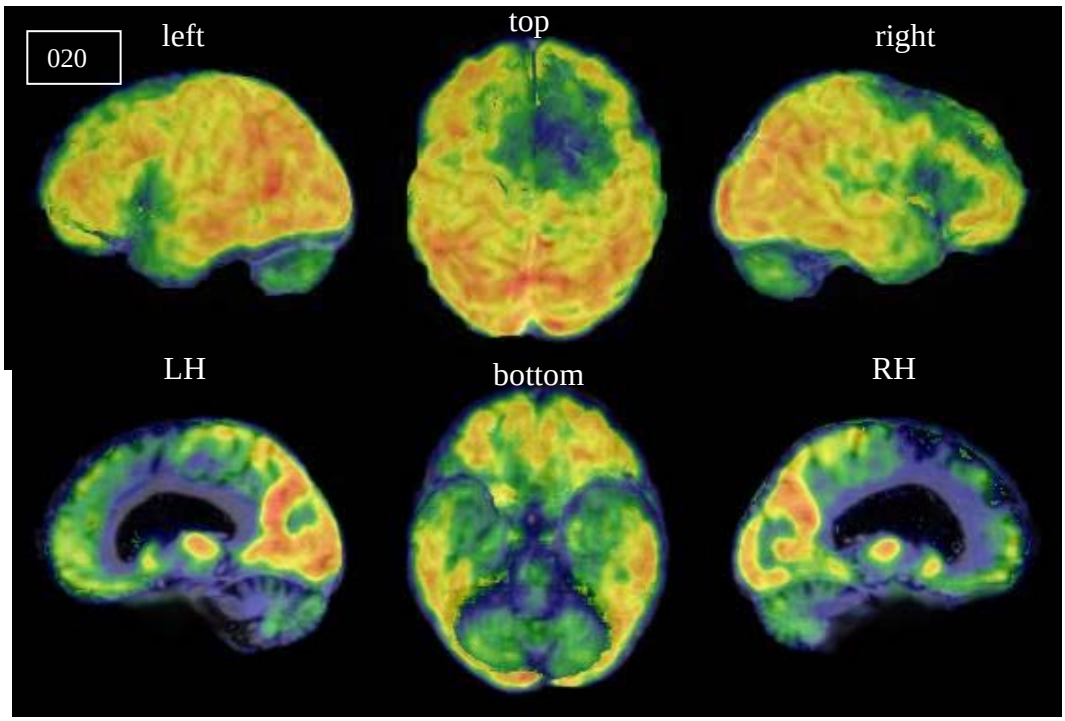
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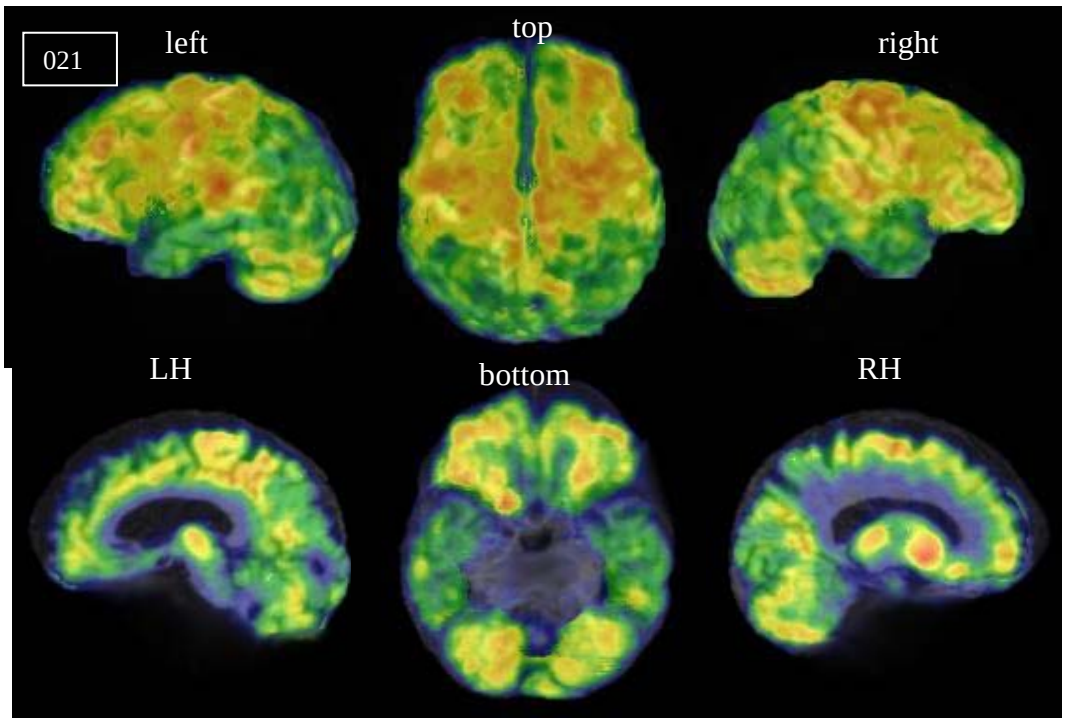
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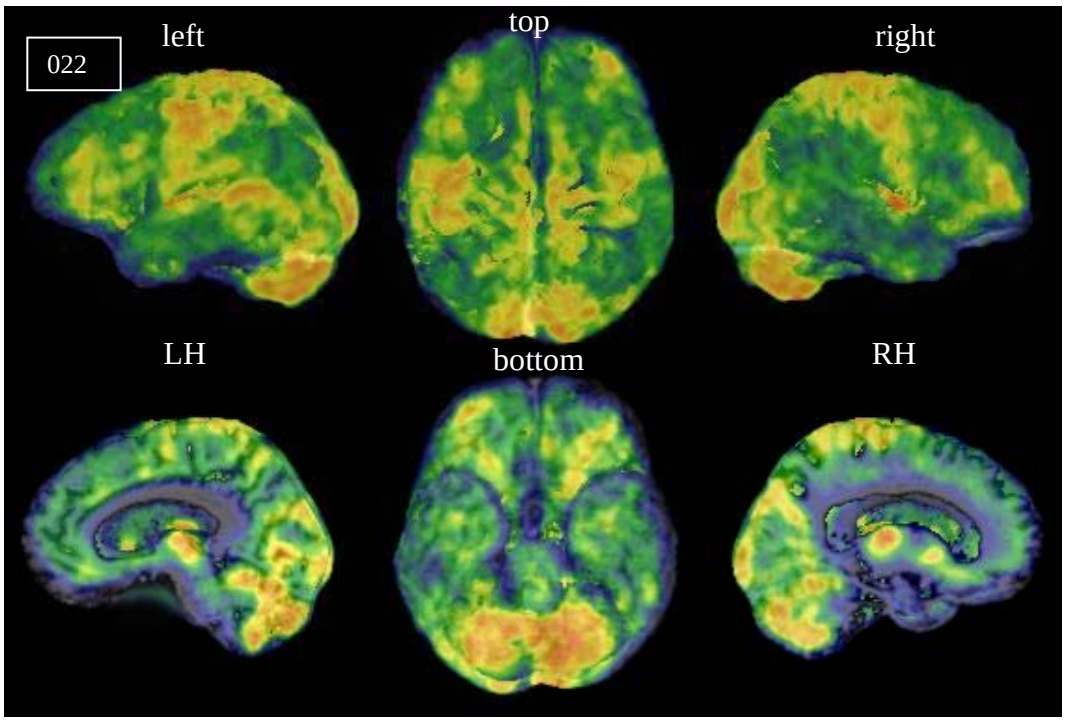
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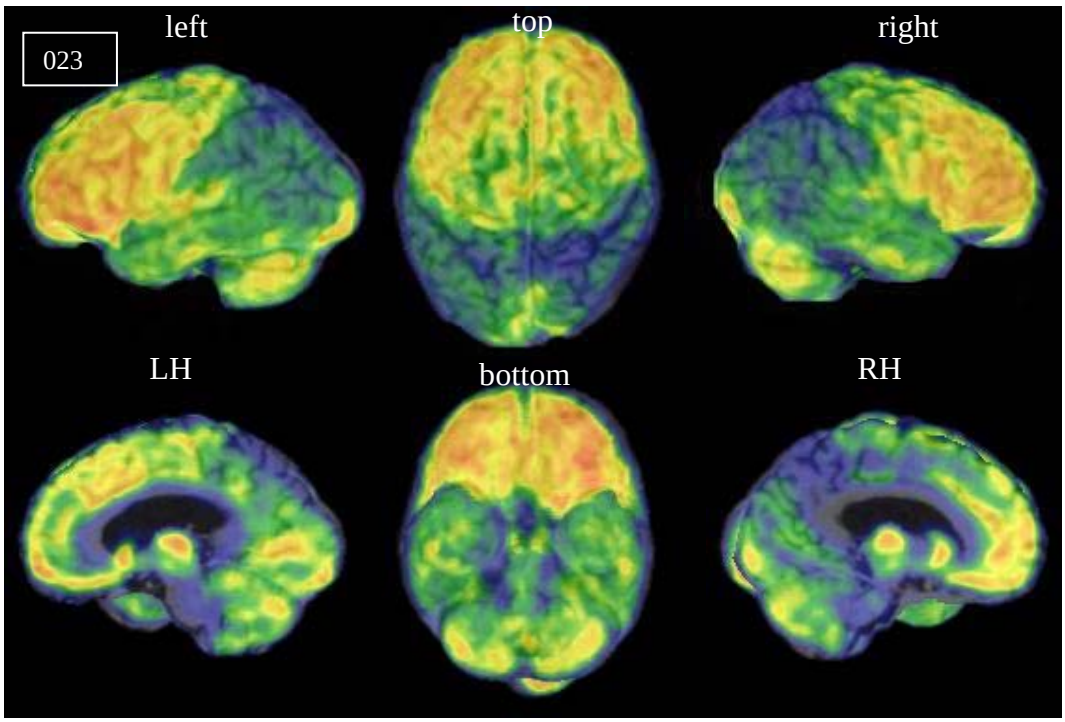
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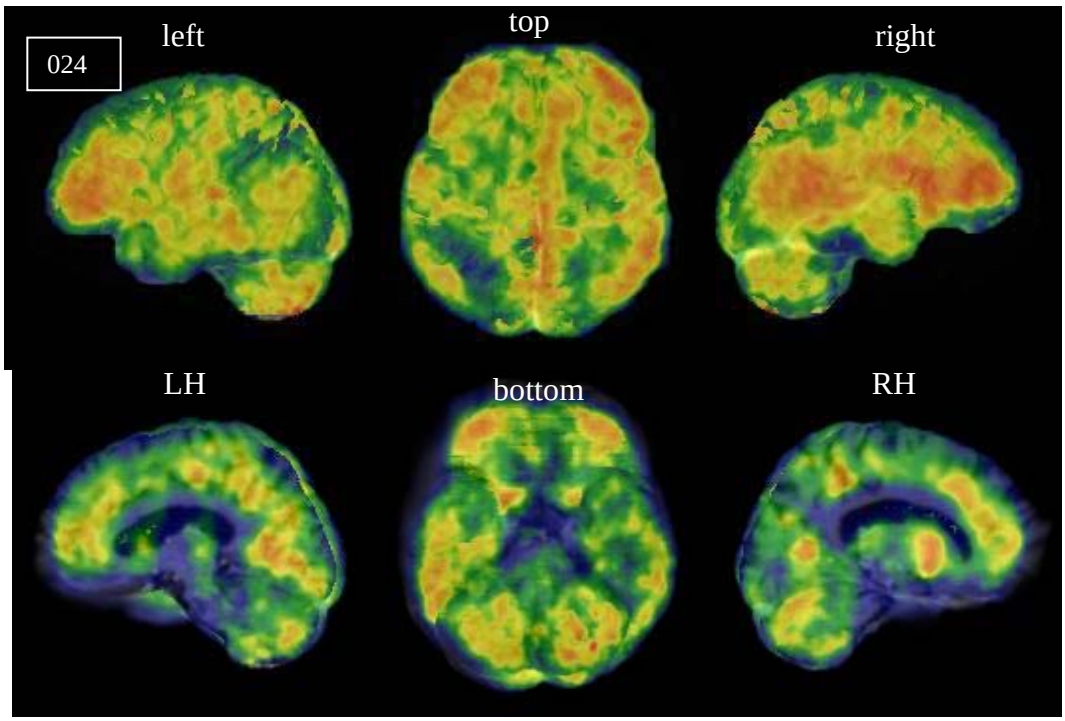
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9.3 Image standardization

Template image processing

The MRI template image was reconstructed and standardized with a semi-automated method, which included 2 main steps.

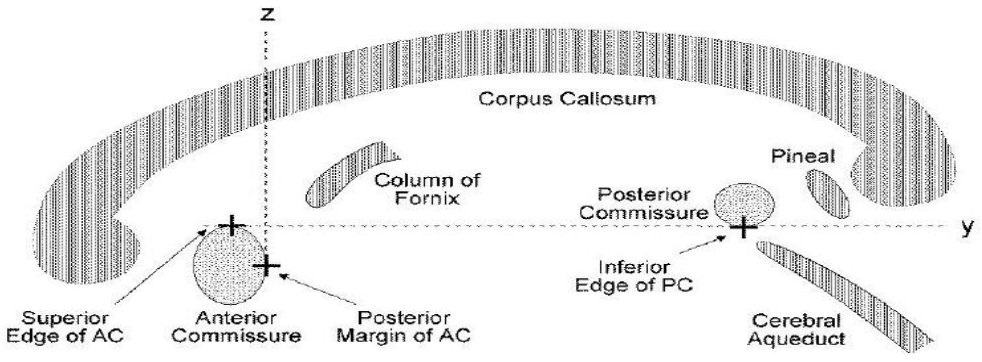
Step 1. Deskulling the image

The surface of the brain was first extracted from a MPRAGE - image using Extract Brain Surface Tool of the MIPAV.

Step 2. AC-PC (anterior commissure – posterior commissure) alignment

First the dataset was aligned with the stereotactical coordinate system by identifying the five crosspoints (see Fig. 1), according to the semiautomated AC-PC alignment procedures. AC-PC line (X axis) – a horizontal line running though the anterior and posterior commisures. The landmark points are shown in Fig. 1.

Fig. 1. Five landmark points to perform AC-PC alignment



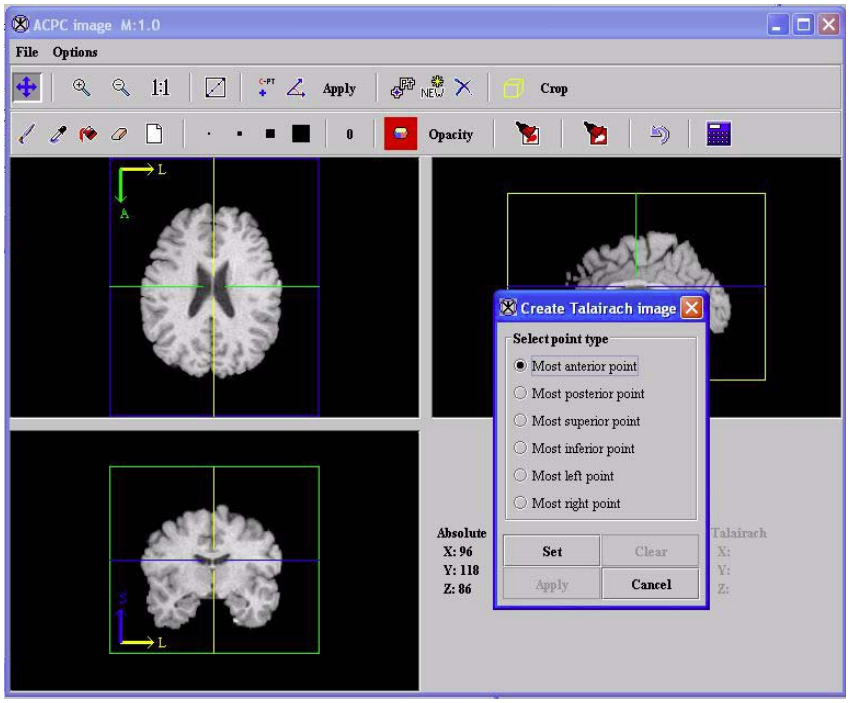
The landmark points to perform AC-PC alignment: AC superior edge – top middle of anterior commissure; AC posterior margin – rear middle of anterior commissure; PC inferior edge – bottom middle of posterior commissure.

To find all these landmark points we used the methods developed by Bazin *et al.*, Laboratory for Medical Image Computing, Johns Hopkins University, see details at: http://mipav.cit.nih.gov/documentation/presentations/talairach.pdf.

Step 2. Talairach alignment

The AC-PC template image that was generated needs to be aligned in the Talairach coordinate system. Talairach alignment consists in scaling the brain to match its boundaries with those of the Talairach atlas. It is a 12-degrees-of-freedom, piece-wise linear transformation. It brings the AC, PC, and anterior, posterior, left, right, inferior, and superior boundaries of the brain to normalized positions (see Fig. 2).

Fig. 2. The Create Talairach Image dialogue box on the triplanar view



Talairach alignment of the template image along the three dimensions of the Talairach coordinates. The six most anterior, posterior, left, right, inferior, and superior points, or, alternatively, the bounding box enclosing the brain.

9.4 Regions of interests

Delineation of ROI according to the standard protocol of the Laboratory of Neuroimaging (LONI), University of California, USA, see details at http://www.loni.ucla.edu/NCRR/Downloads/Protocols/LONIR_Protocols.html

I. Hemisphere left/right were delineated using the automated draw levelset VOI tool (MIPAV). The CSF was excluded.

II. The inferior frontal cortex

1. The inferior frontal cortex (IFC) is traced in the axial plane. The IFC is defined as the cortex anterior to the precentral sulcus, inferior to the inferior frontal sulcus and superior and posterior to the lateral orbital sulcus. The IFC includes three subregions, pars opercularis, pars triangularis, and pars orbitalis, which can be identified using the vertical and horizontal rami of the sylvian fissure.

   Tracing begins on the most superior axial slice in which the inferior frontal sulcus can be delineated or where the pars orbitalis appears.

2. In the axial viewing plane, colour the region that is both between the precentral sulcus and inferior frontal sulcus and also lateral to the point where these two sulci meet. When the inferior frontal sulcus and precentral sulcus do not meet, draw a straight line between the most medial point of the inferior frontal sulcus to the most medial point of the precentral sulcus.

III. Parietal Lobe

The landmarks for delineating the parietal lobe include:

- central sulcus
- parieto-occipital sulcus
- lateral ventricle

- Sylvian fissure
- superior temporal sulcus (horizontal and ascending)
- anterior calcarine sulcus

1. The parietal lobe is traced in the sagittal plane. The parietal lobe is defined as the portion of the cerebrum superior and anterior to the parieto-occipital sulcus, posterior to the central sulcus, and superior to the corpus callosum.

2. Delineation begins slightly off centre from midline and proceeds laterally in the sagittal plane. As you move laterally, the corpus callosum disappears and the parietal lobe is then traced as all matter above the lateral ventricle down to the tip of the hippocampus.

3. Next, a line is drawn from the hippocampus to the parieto-occipital sulcus to distinguish the inferior boundary

4. Going back to the sagittal slice view, once the lateral ventricle disappears, the medial most segment of the sylvian fissure is connected to the horizontal ramus of the superior temporal sulcus. Drawing is continued laterally until you can no longer distinguish brain matter.

III. Occipital Lobe

1. Begin tracing at the most mid-sagittal slice at the parieto-occipital sulcus.

2. The cortex of the occipital lobe is delineated by following the parieto-occipital sulcus and temporal-occipital sulcus. In the absence of any distinguishable sulci, which may occur, straight lines are drawn to box off the region.

IV. Hippocampus & Amygdala

1. The hippocampus is traced in the oblique coronal viewing plane. Images are first reoriented to the long axis of the hippocampus by selecting the most anterior and posterior limits of the hippocampus and reorienting the images so that the anterior and posterior limits of the hippocampus are in parallel along the long axis. This has been previously reported to promote the clear and easy identification of hippocampal anatomy.

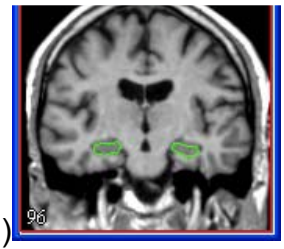
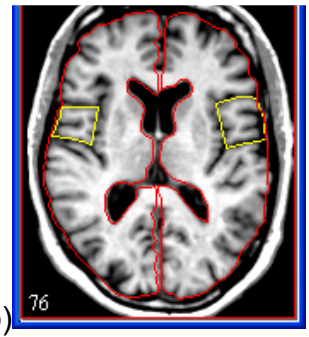
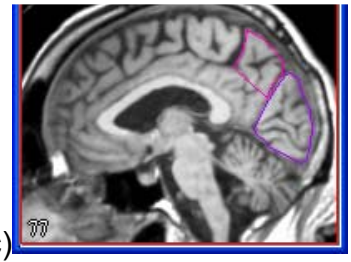
2. The posterior hippocampus is first traced on the slice in which the crus of the fornix can be delineated . As the fornix is the major efferent pathway of the hippocampus this has proved to be a reliable landmark that is based on hippocampal anatomy rather than on structures unrelated to the hippocampus.

3. Following the identification of the crus of the fornix, the hippocampus is traced using the alveus as the superior boundary and the white matter of the parahippocampal gyrus as the inferior boundary. The inferior temporal horn of the lateral ventricle is used as the lateral boundary and the ambient cistern the medial boundary.

4. The hippocampus tracings include the head of the hippocampus (CA1, CA2, CA3 fields) and the subiculum. The inferior temporal horn of the lateral ventricle and alveus clearly separate the hippocampus from the amygdala .

The overlay of nine ROIs is shown in Fig. 3

Fig. 3. ROIs on the template image.

a)  b)  c) 

ROIs of the template image: hippocampus - in the coronal view (a); hemispheres and gyrus frontalis inferior - in the axial view (b); parietal and occipital lobe – in the sagittal (c) plane.

10 Curriculum Vitae

Djyldyz Sydykova, 30th March 1978

Education

2003 - 2006	Ludwig-Maximilians-Universität München Hospital Grosshadern, Neurology Department (Prof. A. Danek) Doctoral thesis
2001 – 2003	Kyrgyz State Medical Academy, Postgraduate study Neurology Department. Bishkek, Kyrgyzstan
1995 – 2001	Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan Graduated with honours
1985 – 1995	Gymnasium Nr.6, Bishkek, Kyrgyzstan

Employment

Since 2005	Alzheimer Memorial Centre, Dementia and Neuroimaging Section; Department of Psychiatry; LMU (Prof. H. Hampel) Resident physician and resident research assistant

Honors and awards

2006	Research Grant from the Hirnliga Foundation, Nürmbrecht, Germany
2005	Poster prize at the 9th Congress of the European Federation of Neurological Societies, Athens, Greece
2003 – 2005	Governmental Educational Program of the Kyrgyz Republic "Cadres of the XXI Century" in cooperation with DAAD, PhD Fellowship
2004	Fellowship of the International Neuropsychological Society - Vivian Smith Advanced Studies Institute
2002	Award from the SOROS Foundation, USA in Kyrgyzstan for Medical Students

Publications

1. D. Sydykova, H. Hampel MD, R. Stahl MD, M. F. Reiser MD, S. O. Schoenberg MD, S. J. Teipel, MD. Fiber connections between the cerebral cortex and the corpus callosum in Alzheimer's disease: a diffusion tensor imaging and voxel-based morphometry study. Cerebral Cortex, 2006.

2. D.K. Sydykova, E.M. Mamytova. Autonomic nervous system in the acute period of mild craniocerebral trauma on the plain region. Central Asian Medical Journal; Vol VIII, 2002 Supplement 2; 22-25

Abstracts of scientific meetings:

1. D. Sydykova, C. H. Hamann, A. Danek. Differentiation of Alzheimer's disease and frontotemporal degeneration: structural and functional neuroimaging. European Journal of Neurology, Vol.12, Supp 2, Sept 2005

2. D. Sydykova, Ch. Hamann, Th. Göhringer, N. Ackl, A. Danek. Neural correlates between neuropsychological testing and functional imaging with ^{18}F-FDG-PET in dementia. International Conference "Cortical Dementias – Cognitive Deficits in Alzheimer's Disease", June 2005

3. Sydykova D, Göhringer T, Hamann C, Danek A.. Posteriore Kortikale Atrophie: Sechs Fälle. Z Neuropsychol 15, 139

4. D.K. Sydykova, E.M. Mamytova, E.A. Djailobaeva. Changes of heart rhythm in the acute period of mild craniocerebral trauma on the plain region. Abstract book of 6-th International Medical Students' and Young Doctors' Meeting, Timisoara, Romania 2002; 69-70

5. D.K. Sydykova, E.M. Mamytova, E.A. Djailobaeva. Disturbances of heart rhythm in the acute period of mild craniocerebral trauma. Abstract book of III International Congress of Cardiologist of Turkish-speaking countries, II International Symposium of Highlands Medicine 2002