at baseline and at endpoint. The rCBF SPET study was performed with ^{99m}Tc-ECD at baseline and at completion of the study. A 2-head gamma camera equipped with LEHR collimators was used for data acquisition (128 x 128 matrix, pixel size 3 mm, 128 projections, 360° circular orbit). FBP with a Butterworth prefilter (0.55 cycles/cm, order 10) was used for reconstruction, applying uniform attenuation correction. Voxel-based SPM approach was used for SPECT analysis using a paired t-test to compare baseline and post-treatment data. **Results:** A clear-cut cognitive improvement was observed in PDD pts after 6-month treatment with ChEIs ($p< 0.01$ for the total ADAS.cog score). While the total MMSE score increased slightly but non-significantly at 6 months, the MMSE subscores improved significantly ($p<0.01$), deteriorating again upon drug withdrawal. No difference in motor performance (UPDRS) was observed. Sequential SPECT analyzed by SPM showed a significant rCBF increase ($p < 0.01$) in several clusters within anterior cingulated and frontal regions bilaterally after ChEIs vs baseline, without any associated reduction in rCBF. No difference in the pattern of changes of rCBF was observed between PDD pts treated with rivastigmine and those treated with donepezil. **Conclusion:** Chronic treatment with ChEIs produced in PDD a striking improvement in cognitive mainly pre-frontal functions, without worsening of parkinsonian features. These findings confirm the pivotal role played by the cholinergic system in dementia associated with PD. The increase of frontal perfusion after ChEIs treatment might suggest that the clinical improvement is associated with a sort of re-afferentation in the caudate-cortical connecting systems.

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Muscarinic receptor density in patients with Parkinson's disease and Parkinson's disease related dementia as measured by [^{123}I]-Iododexetimide SPET

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Aim: Parkinson's disease (PD), primarily characterized by loss of dopaminergic neurons and consequently motor disturbances, is often accompanied by subtle cognitive deficits, involving executive functions. In a number of patients, cognitive deficits may develop into Parkinson's disease related dementia (PDD). Deterioration of the ascending cholinergic projections from the nucleus basalis is thought to contribute to development of this condition. Therefore, demented PD-patients may benefit from administration of cholinesterase inhibitors and, in these patients, SPET imaging of cholinergic receptors may be of value in order to predict therapy response. We studied the muscarinic receptor density in the brain of PD and PDD patients, as well as control subjects in this study. **Methods:** 7 PD patients (mean age 64 yrs), 8 PDD patients (76 yrs) and 5 controls (68 yrs) were injected with 185 MBq of the muscarinic receptor antagonist [^{123}I]-Iododexetimide (IDEX), and scanned with a 12-headed brain-dedicated SPET at 8 hours post-injection. In nearly all subjects, MRI was performed and used to estimate brain tissue volume, to correct the acquired data for brain atrophy. A ROI template was used to determine the number of counts per mL within several brain parts. Next, the measured counts in each ROI were corrected for background as well as alterations of brain volume, which was estimated using the MRI data sets as a reference. **Results:** There were no significant differences in brain volume between groups. A negative linear relation was found between age and brain volume. In both the PD and PDD group, SPET data revealed a decrease of muscarinic receptors per mL compared to controls, except for the temporal cortex. In all other areas, this decrease was even larger in the PDD group compared to the PD group. After correction for differences in brain volume, still a lower density of muscarinic receptors per mL brain tissue was calculated in the PDD group compared to controls, except for the temporal cortex. However in PD patients, a lower density of muscarinic receptors could not be detected in the studied brain areas after correction compared to controls. **Conclusion:** A decrease of muscarinic receptor density can be detected with [^{123}I]-Iododexetimide in PDD patients in cortical areas as well as in the striatum after correction for brain volume, except for the temporal cortex. In PD patients, such a decrease cannot be found after correction for differences in brain volume.

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An Investigation of the Effect of Acetylcholinesterase Therapy on rCBF in Alzheimer's Disease using SPECT and SPM

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Aim: Acetylcholinesterase inhibitor (AChEI) therapy is known to stabilise the cognitive and behavioural decline in some patients with Alzheimer's disease (AD). The Aim of this study was to investigate the effect of AChEI therapy on regional cerebral blood flow (rCBF) in patients with AD using brain SPECT imaging and statistical parametric mapping (SPM). Method: 30 patients with mild-to-moderate AD underwent cognitive and neuropsychiatric assessment and Tc-99m HMPAO SPECT imaging before and after 12 weeks of treatment with an AChEI. Patients were subsequently divided into 'responder' or 'non-responder' groups determined by changes in rating scale scores. SPM was used to test for any significant differences in rCBF between the pre and post treatment groups and between the various responder and non-responder groups. **Results:** The total patient group showed a significant decrease in rCBF in the left precentral gyrus and left inferior frontal gyrus, despite treatment. When subdivided according to cognitive improvement, this rCBF decrease was evident in the non-responders but statistically absent in the responders. It was subsequently found that the non-responders were less cognitively impaired than the responders at baseline and also had significantly higher rCBF in the right inferior temporal lobe including the lingual gyrus and parahippocampal gyrus. These differences had disappeared post-treatment. No rCBF differences were found using behavioural response groups. **Conclusion:** This study confirms that AChEI therapy may arrest cognitive decline in some patients with mild-to-moderate AD and this may be correlated with areas of rCBF difference between the cognitive response groups. The treatment benefits may depend on the degree of cognitive and neuropsychiatric deficits.

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Partial Volume Effect Correction Of rCBF SPET Studies In Mild Cognitive Impairment And Alzheimer`S Disease

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Impairment of glucose metabolism or rCBF is already detectable in posterior cingulate, hippocampus, and temporal neocortex of subjects with mild cognitive impairment (MCI). This impairment increases in severity and extent in patients with Alzheimer's disease (AD). Grey matter (GM) loss, essentially limited to hippocampal cortex in MCI, progresses into a more widespread cortical loss in AD. It is not currently known whether this pattern of progression is characterized by a strict coupling of the two phenomena, or if metabolism/rCBF impairment exceeds the rate of GM loss. **Aim:** The Aim of this study was to compare rCBF decrease independently of GM loss in MCI and AD patients, using a region of interest (ROI)-based method for partial volume effect (PVE) correction which takes into account both WM and CSF. **Material and Methods:** Twelve MCI subjects (mean age 74.8 yrs, MMSE 27.8±2.0) and 10 AD patients (mean age 79.5 yrs, MMSE 21.2±2.4) underwent [^{99m}Tc]HMPAO SPET and volumetric MRI (magnetization-prepared 3D T1-weighted fast-GrE images, TR/TE/TI 11/2/600 ms, 1.5T, voxel size 0.98x0.98x1.2 mm). MRI data were segmented into GM, WM and CSF maps by probabilistic segmentation and co-registered to SPET studies. A set of ROI including cerebral lobes, hippocampus and posterior cingulate for each side, and a single region for cerebellum, was defined in the MNI space and adapted to each co-registered segmented GM using normalization parameters derived from the SPM99 affine normalization matrix. For each ROI, uncorrected and PVE-corrected mean tracer concentrations were calculated and normalized by corresponding cerebellum values. Comparison between MCI and AD groups was performed by Student's t-test, with significance set at $p<0.05$. **Results:** Before PVE-correction, temporal lobes (both hippocampus and lateral cortices) and posterior cingulate bilaterally ($p<0.01$), as well as left dorso-lateral prefrontal cortex ($p<0.05$), showed reduced rCBF in AD as compared with MCI. After PVE-correction, only the posterior cingulate showed reduced rCBF with a slight right prevalence ($p<0.05$). **Conclusion:** Accurate voxel-based comparisons of metabolic/CBF changes and GM loss in AD have shown that the atrophy explains the GM hypometabolism with the exception of the posterior cingulate, an area known to be affected very early in AD. Our results extend these findings, showing in PVE-corrected rCBF-SPET data from AD patients, as compared to MCI, the same pattern of posterior cingulate involvement independent of GM loss, which may be related to remote functional disruption.

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SPM and ROI analyses of ^{123}I-FP-CIT SPECT compared using ROC curves for diagnosis in Dementia with Lewy Bodies and Parkinson's Disease versus Alzheimer's Disease and healthy controls.

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Dopaminergic loss in Parkinson's disease (PD) and dementia with Lewy bodies (DLB) can be visualised using ^{123}I-FP-CIT. Previous studies have adopted region of interest (ROI) or visual methods for analysis, both of which can be subjective and operator-dependent. The **Aims** of this study were (a) to investigate differences in striatal binding of FP-CIT using the automated technique of statistical parametric mapping (SPM99) and (b) to compare this method with results of ROI analysis. The subjects studied were 23 patients with DLB, 38 with PD, 34 with Alzheimer's disease (AD) and 33 healthy age-matched controls. For comparisons the subjects were divided into two groups: those with Lewy body disease (PD and DLB) and those without (controls and AD). SPM analysis involved spatial normalisation of each subject's image to a customised template, followed by smoothing and intensity normalisation of each image to its corresponding mean occipital count per voxel. Group differences were assessed using a two sample t-test. For ROI analysis, square regions of fixed size were placed systematically in the caudate, anterior and posterior putamen on each side, and uptake compared with non-specific occipital uptake. Applying a height threshold of $p\leq0.05$ corrected, the SPM maps showed significant bilateral reduced uptake in caudate, anterior and posterior putamen in DLB and PD subjects compared to AD subjects and controls. Striatal binding was indistinguishable between patients with DLB and PD. Receiver operating characteristic (ROC) curve analysis was performed on four derived parameters from single-subject SPMs and used to compare the areas under the curves from with results from ROI analysis. With the exception of the caudate ROI, the areas under all the ROC curves were similar and greater than 0.92, demonstrating good and comparable discriminatory power. The automated voxel-based approach is therefore a viable alternative to the subjective and often time-consuming method of ROI.

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Accuracy of possible and probable Alzheimer Disease diagnosis: a methodological comparison using SPM and Principal Component Analysis.

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Aim: Principal Component Analysis (PCA) has recently been proposed as statistical tool to investigate functional connectivity in human brain. The Aim of the present study is to compare the diagnostic accuracy of PCA as compared to Statistical Parametric Mapping (SPM) in discriminating Alzheimer Disease patients (AD) from control subjects (CTR). **Material and Methods**: 53 CTR, 30 possible AD (eAD) and 17 probable AD (AD) were investigated with 99m-Tc-HMPAO and a three headed gamma camera. Regional cerebral blood flow (rCBF) differences were compared between the three groups with both SPM (z-score differences at clusters of voxels level, significance set at $p<0.05$ corrected) and PCA. The latter identified 11 factors representing regions with strong anatomo-functional correlations that were submitted to ANCOVA for group analysis. Discriminant analysis was used to identify the factors mostly predictive of group differences and to calculate the accuracy of the method. **Results:** SPM analysis identified CBF distribution differences in 5 large temporo-parietal cortex clusters bilaterally at CTR/AD comparison, in 2 smaller right parietal cortex clusters at CTR/eAD comparison and did not show any difference at AD/eAD comparison. PCA identified, in fronto-parietal-temporo-limbic cortex, 7 factors at CTR/AD and 4 at CTR/eAD comparisons in which CBF was statistically different at $p<0.05$ level between groups. The involved factors in both comparisons covered a brain area far larger than the one covered by the corresponding SPM clusters. At eAD/AD comparison CBF resulted to be statistically significant in one factor in the left parieto-frontal cortex ($p<0.025$). The overall accuracy of the 3 mostly predictive factors in assigning the subjects to the correct clinical group was 90%. **Conclusion:** As compared to SPM, PCA showed a better accuracy in identifying CBF differences and discriminating between groups when comparing CTR, eAD and AD. The appearance of significant regional differences absent at voxel-to-voxel analysis emphasised the value of analysing the relationships among brain regions for rCBF investigations.

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DaTSCAN SPECT for the differential diagnosis between dementia with Lewy bodies and Alzheimzer's disease

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Aim: Dementia with Lewy bodies (DLB) is the second most common cause of degenerative dementia after Alzheimer's disease (AD). Pre-mortem diagnosis can only be made clinically using the International Consensus Criteria 96-97 (ICC) (Mc Keith 1996). It has been shown (Walker 2002) that unlike in AD, specific D2 dopaminergic degeneration in DLB could be demonstrated by SPECT. We evaluated DaTSCAN™ (123I-Ioflupane) SPECT in the differential diagnosis between these two diseases. **Materials and Methods**. 22 patients (8 females) were prospectively included. AD diagnosis was made on DSM-IV criteria and DLB on the 96-97 ICC. 9 patients were diagnosed as probable DLB with a mean age of 72 years (range 56-84) and a mean MMSE of 19.6 (range 17-24) and 13 as probable AD with a mean age of 74 years (range 58-83) and a mean MMSE of 20.9 (range 17-24). SPECT acquisitions were performed 4 hours after the injection of 185 MBq of 123I-Ioflupane. A 3 headed Prism 3000 XP camera equipped with very high resolution low energy fan beam collimators was used. Sequential transmission scan was obtained with an external 99mTc line source. 3D T1-weighted MRI images (2 mm thick slices) were also acquired (GEMS 1.5T scanner). Images were reported visually and quantitative analysis was performed. Caudate (C) and putamen (P) nuclei were segmented manually on the MRI. SPECT data were reconstructed by OSEM. The binding potential values (BP) were measured on the SPECT images using MRI-derived volumes of interest (VOI) after coregistration by mutual information maximization. They were calculated by reference to an occipital non-specific VOI (NS) as BP=[(C or P)-NS]/NS. BP were calculated without physical corrections (NC BP) and after correction (C BP) of attenuation, scatter (TEW) and partial volume effect (using MRI VOI). **Results:** On visual analysis, severe reduction of putamen uptake was clearly seen on both sides in all DLB. 2 AD patients had moderate reduction and 11 appeared normal. The right to left mean putamen NC BP values were 1.6±0.3 (minimum =1.2) for AD and 0.8±0.3 (maximum=1.0) for DLB. The C BP were 8.4±1.6 (minimum=6.2) for AD and 2.0±0.5 (maximum=2.8) for DLB. There was no overlap of putamen BP values between AD and DLB. **Conclusion:** DaTSCAN™ SPECT is able to clearly differentiate in vivo probable DLB from probable AD. In these selected patients the diagnosis can be done by visual analysis and/or quantitative analysis with or without physical corrections.

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A SPECT Study of the Dopamine and Serotonin Transporters in Treatment Resistant Compared with Treatment Responsive Depression

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Aim: Treatment resistant depression (TRD) is a serious and under-investigated clinical problem. Of those treated for depression, 30% remain symptomatic and disabled. The biology of treatment resistance is unclear. Antidepressants are the mainstay of treatment for depression and the sites of action of many antidepressants are the monoamine transporter systems. Transporter behaviour may be an indicator of treatment response and a number of recent findings provide biological plausibility for the notion that the difference in treatment response in TRD lies in an imbalance in dopamine-serotonin interaction. **Methods:** This study involved 12 Treatment Non-responders [TN] and 12 Treatment Responders [TR]. Patients met criteria for DSM IV major depression and were matched on a case by case basis for age, gender, duration of illness and medication. Depression was assessed using the Hamilton Rating Scale. Treatment reflected typical clinical practice and was by Venlafaxine in 12 subjects (6TR, 6TN, combined with SSRI in 1TR), SSRIs in 5 (2TR, 3TN) and other antidepressants in 7. Each patient was scanned with the high resolution NeuroFocus using 123I beta-CIT, which binds with high affinity to both the dopamine transporter (DAT) and the serotonin transporter (SERT). SPECT studies have shown that 123I Beta-CIT accumulates in two distinct brain regions. Striatal binding is mainly DAT and midbrain-thalamus mainly SERT. Differences in kinetics amplify the regional differences and allow measures of DAT and SERT binding to be analysed using ROI templates derived from the Talairach Atlas. **Results:** To illustrate the results, the striatal specific/non-specific (occipital) binding index was 7.86 in both responders and non-responders but was 8.26 in patients from both groups treated with venlafaxine. The thalamic/striatal binding index was 0.064 for both responders and non-responders but was 0.046 for patients treated with venlafaxine and 0.086 for those treated with a general mood stabiliser. **Conclusions:** Although the action of most of the antidepressants used in this group of patients is mediated through inhibition of SERT, no differences were detected in any imaging measure between responders and non-responders. As expected venlafaxine and SSRIs caused greater blockade of SERT than other antidepressants, although surprisingly venlafaxine had as large an effect as more potent SSRIs. In addition, the blockade of SERT is associated with increased DAT binding.

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Serotonin transporter availability in drug free depression patients using a novel SERT ligand

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Aim The current monoamine hypothesis regarding the cause of depressive illness in adults is based mainly on findings of abnormal availability of noradrenaline, dopamine and serotonin in the brain. The Aim of this study was to evaluate serotonin transporter (SERT) availability in drug free patients with major depression using a novel specific SPET tracer ^{123}I ADAM. Our previous studies with SERT blocking agent citalopram have shown ^{123}I ADAM to be more specific for SERT than e.g. β-CIT. **Methods** We have carried out SERT studies with ^{123}I ADAM so far for 10 patients with depression (without any antidepressant treatment, aged 18 - 65 y, mean = 34 y) and 14 healthy volunteers (aged 22 - 54 y, mean = 35 y). SPET studies were performed 10 minutes, 5 hours and 7 hours after injection of the tracer. Imaging was carried out using a triple head gamma camera equipped with ultra high-resolution fan beam collimator. ROIs were drawn into one MR image and copied onto the SPET image (Multimodality on HERMES). A template and a predefined VOI map of healthy volunteers was created from ^{123}I ADAM scans (BRASS). Thereafter, the scans of depression patients were automatically fitted to the template of healthy volunteers and specific binding ratios (SBRs) were calculated at 5 and 7 h after injection. SBR for each predefined VOIs (midbrain area, thalamus, caudatus, putamen and pons) were calculated using formula = (target -cerebellum)/cerebellum. **Results** In patients with major depression SERT binding ratios in the midbrain area at 5 h and 7 h after injection were 2.04 ± 0.28 and 2.18 ± 0.55 and in healthy controls 1.90 ± 0.29 and 2.06 ± 0.50, respectively. The difference did not reach statistical significance. However, individual variations in midbrain SERT values both in depressive patients and controls were very high. Regarding other predefined VOIs, there was no statistically significant differences between the study groups. **Conclusions** Our preliminary results revealed no statistically significant difference between SERT ratios in the midbrain area of the healthy volunteers and depressive patients. This could at least partly be explained with small amount of patients and large individual variation in SBR. The clinical significance of the large individual variation in SBRs has to be studied in details in a more representative sample of depressive patients. Preferable method for quantification might be graphical, because only extended equilibrium was reached with ^{123}I ADAM.

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The personality traits vulnerability and self-discipline are associated with regional 5-HT2A-receptor binding in healthy subjects

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Aim: To evaluate the association between regional cortical 5-HT_{2A}-receptor density and personality traits in healthy subjects. **Material and Methods**: Sixty-five healthy volunteers, 41 men and 24 women, with an age range of 18-79 years were investigated with MRI and [^{18}F]-altanserin PET. The distribution volumes of specific binding (DV_3') were calculated for 19 brain regions using cerebellum as a reference region and metabolite corrected plasma-curves. MRI and PET images were coregistered and volumes of interest were applied automatically using a predefined MRI-based template (Svarer, unpublished). All subjects completed the NEO-PI-R personality questionnaire, which evaluates the broad personality dimensions of neuroticism, extraversion, openness, agreeableness, and conscientiousness based on 6 personality traits for each dimension. The personality traits were correlated to [^{18}F]-altanserin DV_3' data with adjustment for age and gender in multiple linear regression analysis with the personality trait as