Voxel-based morphometry

in clinical neurosciences

Ph.D. Thesis

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1. Introduction

1.1. Similar to other neurodegenerative disorders, age is one of the major risk factors in Parkinson's disease (PD). Since the prevalence of depression is also increasing with age, it is not surprising that depression is a frequent disease among patients with PD, and its incidence can be more than 40%. Early onset, akinetic rigidity, right sided dominance, gait instability, cognitive dysfunctions, and high-level anxiety predispose for depression in Parkinson's Disease. Functional changes in depressed patients with PD have been addressed. Reduced glucose metabolism in caudate nucleus and inferior orbitofrontal cortex has been indicated by PET in depressed PD. Dysfunction of dopaminerg, noradrenerg, and serotoninerg systems may be involved in the patophysiology of depression in PD. In contrast, there have been no reports on MR morphometric changes in depressed PD, although structural alterations related to cognitive impairment has been recently examined by voxel-based morphometry (VBM) in PD. Here we compared depressed, nondepressed patients and healthy controls by VBM, and gray matter density was also correlated with the severity of depression in DPD.

1.2. Schizophrenia is a long-term, deteriorating mental disorder with poor functional outcome. Social cognition, particularly theory of mind (ToM), plays a crucial role in social behaviour and functionality in schizophrenia. ToM (mentalizing) is the capacity to appreciate others mental states and hence to attribute knowledge, beliefs and intentions to others. Studies with healthy subjects suggest the role of prefrontal (e.g. ventromedial prefrontal cortex (PFC), orbitofrontal cortex), temporal (e.g. temporal poles, superior temporal sulcus) and temporo-parietal (temporo-parietal, junction) areas in mentalizing. Several studies demonstrated ToM deficits in schizophrenia. These results suggest that especially higher-order ToM skills are affected in schizophrenia However, it is not yet clear when and why these deficits occur.

1.3. Posterior cortical atrophy (PCA) is a rare type of progressive dementia first described by Pick. The term PCA was originally applied to five patients with higher visuospatial dysfunction. While memory and language may be preserved until late in the course, patients develop early signs of higher visual dysfunction. Although recent data have suggested pathologically verified Alzheimer's disease (AD) as primary etiology in the majority of cases early onset, slow progression, and the predominant bilateral atrophy of the posterior (parieto-occipito-temporal) cortex on magnetic resonance imaging (MRI) characterize and differentiate PCA from typical AD.

2. Aims

2.1. The origin of the high rate of depression in idiopathic Parkinson's disease (PD) is unknown. We applied voxel based morphometry (VBM), as a sensitive tool in detection of gray matter MR density alterations, to find differences in depressed and non depressed patients with Parkinson's disease. Gray matter density was also correlated with the severity of depression in patients with depression cohort.

2.2. To link structural abnormalities with impaired social cognitive abilities, this study aimed to investigate the association between (theory of mind) ToM performance and structural brain changes evolving in the early course of schizophrenia. We predicted that patients with schizophrenia would present impaired ToM skills relative to normal controls. Furthermore, as a clear directional hypothesis, we expected that poorer ToM skills would be accompanied by gray matter loss in brain regions responsible for ToM in a voxel-based morphometric study.

2.3. We applied a complex approach including psychological tests, voxel-based morphometry (VBM) and functional MRI (fMRI) to examine a patient with PCA compared with healthy subjects and patients with early AD (eAD).

3. Materials and methods

3.1. High-resolution T1-weighted 3D MP-RAGE scans were acquired by 1.0 T MRI (Siemens, HarmonyExpert, Germany) scanner with repetition time (TR) 2110 msec; echo time (TE) 3.93 msec; flip angle 15°, field of view (FOV) 172x230, thickness 2 mm without gap. All volumes were parallel aligned to the AC-PC line. Imaging data were processed by SPM2 (Wellcome Department of Imaging Neuroscience, London, UK). Optimized VBM method was applied to compare DPD, NDPD, and age-matched controls. First, an individual template image was created from all volumes and transformed to the same stereotaxic space by registering to standard SPM T1 template. The high-resolution 3D MPRAGE volumes were transformed to the same Talairach stereotaxic space and registered to our template image. Spatial normalization was performed by a 12-parameter affine transformation (3 rotations, 3 translations, 3 zooms, 3 shears), and nonlinear normalization was accomplished by 7x 9 x7 discrete cosine transform basis function with 16 nonlinear iteration steps. The normalized images were resampled by tri-linear interpolation to 1 x 1 x 1 mm3 isotropic volumes and segmented into gray matter, white matter, and cerebrospinal fluid spaces. These segmented and normalized images were modulated to correct volume changes by the Jacobian determinant of the transformation matrices and smoothed by an 8 mm full width at half maximum (FWHM) gaussian kernel.

3.2. To identify the brain regions of gray matter density alterations in patients with schizophrenia (SG) relative to the healthy controls (CG), group comparison was performed by SPM2 between CG and SG. WAIS scores, total intracranial volume (TIV), age and gender were entered as nuisance covariates. Because of the relatively small sample size and the exploratory nature of this study to generate hypotheses for further research a = 0.005, uncorrected was regarded as the statistical threshold of significance for all analysis. According to Hayasaka, we used uncorrected t threshold at 3.00 or above when the df> 30. We set the study uncorrected threshold at a level that allows examination of spatial extent of the contrast differences while attaining a reasonable degree of cluster separation. By setting the primary threshold within these parameters, a reasonable compromise has been found between reporting cluster extent and maintaining separation between maximal voxel results. Extended cluster size was set at k = 25 in between-group analysis. Then, regression analysis was performed between the FP scores and the gray matter probability maps of 18 patients with schizophrenia, to detect a correlation between gray matter density and FP scores. WAIS scores and TIV were used as nuisance variables.

3.3. Image acquisition T1-weighted axial MP-RAGE scans were acquired by a 1.0 T MRI scanner (Siemens HarmonyExpert, Germany) for VBM. Functional MRI was performed using a 1.5

T MRI system (Siemens Avanto, Germany). Echo-planar imaging sequences were acquired with TR=3560 ms, TE=50 ms, FA=90°, FOV=240 mm2, thickness=3 mm, matrix=128×128. Structural scans were acquired in the same session using a T1-weighted MP-RAGE sequence (TR = 1160 ms, TE = 4.24 ms, matrix = 448 × 512, thickness=0.8 mm, gap=0.85 mm, FOV=240 mm2). All imaging data were processed by using SPM2 (Wellcome Department of Imaging Neuroscience, London, England). 2.2.4. Image analysis The single subject versus groups comparisons were performed by an optimized VBM according to previously validated methods. We accepted a level of significance of P <0.05, corrected for multiple comparisons. Functional MRI data were analyzed using the General Linear Model with the canonical form of HRF. All data were motion-corrected, spatially normalized and smoothed with an 8-mm FWHM kernel. Significantly activated voxels were identifiedusing an initial p value threshold of 0.001, uncorrected.

4. Results

4.1. By applying VBM, group comparisons were performed. There was no difference in gray matter density when controls were compared to all PD, DPD or NDPD groups, respectively. However, significant decrease in gray mater density was found in the left inferior orbitofrontal gyrus, bilateral rectal gyrus, and right superior temporal pole of DPD patients compared to the NDPD group. MADRS depression scores were correlated with gray matter density within the DPD subgroup. There was a negative correlation between the severity of depression (MADRS scores) and morphometric changes in the right rectal gyrus and bilateral middle/inferior orbitofrontal regions in DPD patients. Of note, density of the very same structures was significantly different between DPD and NDPD. Gray matter density of several additional structures including the right medial temporal gyrus, right parahippocampal gyrus, right medial and anterior cingular cortex, left medial and right superior orbitofrontal regions and part of the right cerebellum also correlated with MADRS scores in the DPD subgroup.

4.2. When patients with schizophrenia were compared with control subjects significant reduction in gray matter density was found in inferior frontal gyrus, medial orbitofrontal gyrus, fusiform gyrus, insula, superior temporal gyrus, hippocampus, parahippocampal gyrus and inferior occipital gyrus of the left hemisphere. Reduced gray matter density was detected in rectus gyrus, precentral gyrus and medial occipital gyrus of the right hemisphere. Moreover, bilateral volume reduction was observed in superior frontal, superior orbitofrontal, inferior temporal, medial temporal gyri and in the cerebellum. No significant increase in gray matter density was found in SG compared with CG. As a second step, regression analysis was performed to detect a correlation between gray matter density and FP test scores in SG where TIV was a nuisance variable. Because of the significant between-group differences in full scale IQ, WAIS scores were entered as nuisance variable as well. FP scores were correlated with gray matter densities in VBM regression analysis. There was a significant positive correlation between decreased FP performance and gray matter density reduction in right medial frontal gyrus, left orbitofrontal superior gyrus, left inferior temporal gyrus and bilaterally in temporal poles.

4.3. By using VBM revealed a significant reduction in grey matter density in the bilateral occipital inferior andright medial occipital regions in our patient with PCA. In addition, density of the right fusiform gyrus, anterior cingulate cortex (ACC), frontal superiorand precentral areas was also decreased. In contrast, eAD was characterized by left

hippocampal atrophy and reduction of gray matter density in thetemporal and frontal lobes bilaterally. Although the density of the ACC was also reduced in eAD, it was more pronounced in PCA. Two fMRI experiments were performed to examinevisual attention and search: the feature conjunction taskand the clock test. In the feature conjunction task, high activation of the left occipital superior area was found in HS and eAD controls, whileactivation of this region was reduced in PCA. No activation of the left occipital inferior area wasdetected in PCA in contrast to the control groups (HS and eAD), corresponding to the density reduction of these areas revealed by VBM. Activation of the ACC was also absent in PCA contrary to both healthy and eAD controls, corresponding again to the reduced density of the ACC shown by VBM In the clock test, the highest activation in HS and eAD was observed in the primary and secondary occipital cortical regions. In PCA, activation of all these specific occipital areas was absent. Instead, the medial part of both occipital lobes was activated.

5. Discussion

5.1 Comparing the whole PD group to controls, gray matter densities were not different. These results correspond to previously published morphometric studies. There were no significant differences either when depressed and nondepressed subgroups of PD were compared to healthy controls, respectively. However, gray matter density of specific areas was significantly different in depressed PD patients compared to nondepressed patients. Particularly, we found left-sided orbitofrontal and bilateral rectal gyrus density alteration in depressed patients with PD. In addition, we also found a negative correlation between MADRS score and gray matter density of the right medial temporal gyrus, right parahippocampal gyrus, medial and anterior cingular cortex, and right cerebellum. essive disorders. Our findings demonstrated negative correlations between gray matter density of the right anterior and medial cingular cortex and MADRS scores in the DPD subgroup. Our data suggest that several cortical areas are differentially affected in depressed versus nondepressed patients with PD. These morphometrical gray matter density alteration were only related to depression and were independent from duration of disease, impairment of motor function, age and sex and cognitive abilities. In particular, the lateral and medial parts of the bilateral orbitofrontal cortex, right medial temporal and parahippocampal gyrus and also the subdominant anterior and medial cingular cortex may play a major role in Parkinsonian depression.

5.2. We detected gray matter decrease in several GM regions in patients with early phase of schizophrenia compared with age- and sex-matched healthy controls. Differences were observed in frontal, temporal, occipital, GM areas and in the cerebellum. These results are in line with previous peri-onset morphometric studies describing structural abnormalities early in the course of schizophrenia. In this study, the most pronounced correlations between GM density and FP performance were found in certain prefrontal and temporal cortical areas: the more pronounced the structural abnormalities of these areas were, the greater was the impairment of the mentalizing ability. Prefrontal regions (especially orbitofrontal and medial areas) have been repeatedly found to be involved in social cognitive tasks in patients with schizophrenia. The overlay of the VBM maps suggested that the reduction in gray matter density in orbitofrontal and temporal regions could play a role in deficient ToM in the SG. Reduced gray matter density of this region can influence the generation of a wider semantic and emotional context on the bases of past experiences.

5.3. VBM and SPECT data were also typical of PCA indicating atrophy and reduced perfusion of theoccipital lobes. In addition to the occipital atrophy, structures involved in attention (ACC, left inferior occipital lobe, frontal superior and precentral areas) also showed a significant decrease in gray matter density, which corresponded to the marked deficit in attention revealed by neuropsychological tests. In contrast to PCA areas related to memory functions were affected in eAD indicated by VBM similar to previously reported data. Next, fMRI experiments were performed to examine activation of areas related to attention, particularly during visual attention, in PCA compared with HS and eAD. Corresponding to the severe atrophy of the ACC, no activation of with ACC was observed during a visual attention task (conjunction task) in PCA in contrast to eAD, indicating deficient attention that was also revealed by clinical examinations. The bilaterally decreased activation of the primary and secondary visual cortex during visual attention and the clock test corresponded to the most prominent atrophy as well. The missing activity of the left inferior occipital region may also indicate that maintaining attention during visual tasks is insufficient in PCA. In addition, instead of the specific occipital areas, the medial part of both occipital lobes was activated, contrary to findings inhealthy controls and the AD cohort.

6. Summary of new findings presented in this thesis

6.1. Here we examined morphometric changes in depressed and nondepressed patients with PD usinggroup comparisons and regression analysis. Our datasuggest that several cortical areas are differentially affected in depressed versus nondepressed patients with PD. These morphometrical gray matter density alterationwere only related to depression and were independentfrom duration of disease, impairment of motor function, age and sex and cognitive abilities. In particular, the lateral and medial parts of the bilateral orbitofrontal cortex, right medial temporal and parahippocampal gyrus and also the subdominant anterior and medial cingular cortex may play a major role in Parkinsonian depression.

6.2. Our result suggests that deficient ToM skills in early phase schizophrenia might be the functional manifestations of structural abnormalities in orbitofrontal and temporal regions. The interpretation of our data is limited by the relatively small number of subjects, the significant difference in IQ between the groups and by the heterogeneity of the antipsychotic treatment.

6.3. Our data indicate early changes in gray matter density and function of certain brain areas in PCA, which differ from findings in both healthy controls and eAD. In contrast to eAD, marked a decrease of gray matter density in the occipital lobes and activation of medial occipital areas characterize PCA.

7. List of Publications

7.1 This work is based on the following articles:

1. FELDMANN A, ILLES Z, KOSZTOLANYI P, ILLES E, MIKE A, KOVER F, BALAS I, KOVACS N, NAGY F. Morphometric changes of gray matter in Parkinson's disease with depression. A voxel-based morphometry study. Movements Disorders 2008 (23) 42-46.IF = 3.32, CIT = 82,

2. FELDMANN A, KOVACS N, KOVER F, TENYI T, FEKETE S, HEROLD R. Structural MRI investigation in schizophrenia with optimised voxel-based morphometry - a pilot study. Psychiatr Hung. 2007;22(6):456-461.

3. HEROLD R, **FELDMANN A**, SIMON M, ÉNYI T, KÖVER F, NAGY F, VARGA E, FEKETE S. Regional Gray Matter Reduction and Theory of Mind Deficit in the Early Phase of Schizophrenia: a Voxel-based Morphometric Study. Acta Psychiatrica Scandinavica. 2009. 119(3):199-208 IF = 3.85, CIT = 45,

4. FELDMANN A, TRAUNINGER A, TOTH L, KOTEK GY, KOSZTOLANYI P, ILLES E, PFUND Z, KOMOLY S, NAGY F, ILLES Z. Atrophy and decreased activation of fronto-parietal attention areas contribute to higher visual dysfunction in posterior cortical atrophy. Psychiatry Reseasrch: Neuroimaging. 2008 okt 20. IF = 2.75, CIT = 9,

Impact factor: 9.92
Citation (without self reference): 136;

Cummulative impact factor: 24.3
Citation (without self reference): 201

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