Erratum

Erratum to “Multimodal imaging of residual function and compensatory resource allocation in cortical atrophy: a case study of parietal lobe function in a patient with Huntington’s disease”


Thomas Dierks*, David E.J. Linden, Andreas Hertel, Thomas Günther, Heinrich Lanfermann, Andreas Niesen, Lutz Fröllich, Friedhelm E. Zanella, Gustav Hör, Rainer Goebel, Konrad Maurer

*Department of Psychiatry and Psychotherapy I, University of Frankfurt / Main, Heinrich-Hoffmann-Str. 10, D-60528 Frankfurt, Germany  
Max Planck Institute for Brain Research, Frankfurt, Germany  
Department of Nuclear Medicine, PET Centre, University of Frankfurt, Frankfurt, Germany  
Department of Neuroradiology, University of Frankfurt, Frankfurt, Germany

The publisher regrets that Figs. 2, 3 and 4 of the above article were erroneously published in black and white. The entire article is republished overleaf.
Multimodal imaging of residual function and compensatory resource allocation in cortical atrophy: a case study of parietal lobe function in a patient with Huntington’s disease

Thomas Dierksa,b, David E.J. Lindena,b, Andreas Hertela, Thomas Günthera, Heinrich Lanfermannb, Andreas Niesenb, Lutz Frölicha, Friedhelm E. Zanellad, Gustav Horc, Rainer Goebelb, Konrad Maurera

a Department of Psychiatry and Psychotherapy I, University of Frankfurt, Germany
b Max Planck Institute for Brain Research, Frankfurt, Germany
c Department of Nuclear Medicine, PET Centre, University of Frankfurt, Germany
d Department of Neuroradiology, University of Frankfurt, Germany

Received 21 January 1998; received in revised form 28 May 1998; accepted 8 July 1998

Abstract

In a case of Huntington’s disease (HD) with dementia and pronounced parieto-frontal atrophy, the functional state of the affected regions was investigated using functional magnetic resonance imaging (fMRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET). It was observed that although parietal areas showed extensive atrophy and reduced resting glucose metabolism, the patient performed with similar accuracy but with longer response time in a visuospatial task compared with healthy control subjects. At the same time, the blood oxygen level-dependent (BOLD) fMRI signal in these areas, which are involved in visuospatial processing, showed a similar task-dependent modulation as in control subjects. The signal amplitude (signal percent change) of the task-dependent activation was even higher for the HD patient than in the control group. This residual functionality of parietal areas involved in visuospatial processing could account for the patient’s performance in the task concerned, which contrasted with his poor performance in other cognitive tasks. The increased percent-signal change suggests that a...
higher neuronal effort was necessary to reach a similar degree of accuracy as in control subjects, fitting well with the longer reaction time. We propose that fMRI should be considered as a tool for the assessment of functionality of morphologically abnormal cortex and for the investigation of compensatory resource allocation in neurodegenerative disorders. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Dementia; Magnetic resonance imaging; Functional magnetic resonance imaging; Positron emission tomography; Plasticity; Visuospatial processing

1. Introduction

In many cases of neurodegenerative disorders, the progression of dementia involves different cognitive functions at different velocities. Such an asymmetry of cognitive impairment may reflect different degrees of cortical atrophy. Functions commonly associated with the most rapidly degenerating areas might be expected to show the fastest deterioration. If so, the pattern of cortical atrophy could be used to predict the course of cognitive impairment. Often, however, the deterioration of cognitive function is not so closely linked to the atrophy of the respective brain areas as this theory would posit. When performance in a specific cognitive task is better than would be expected from the morphological picture, two principal explanations must be considered. Other less affected cortical areas may have taken over the relevant function on the basis of preserved brain plasticity (Kansu and Zacks, 1979; Bach-y-Rita, 1990; Chugani et al., 1996; Lazar et al., 1997), or the atrophic region may still be sufficiently functional to execute the required operations.

Functional brain imaging can help to differentiate between these two mechanisms. In cases of compensatory resource allocation, the newly recruited areas show an activation that is not observed in normal subjects during the cognitive task concerned (Becker et al., 1996). In cases of residual function of atrophic cortical areas, regional cerebral blood flow (rCBF) would be expected to show a task-dependent modulation similar to that seen in normal subjects in the same area (Müller, 1997). Single photon emission computed tomography (SPECT), positron emission tomography (PET) and, with the highest spatial and temporal resolution, functional magnetic resonance imaging (fMRI) can be used to assess rCBF. In addition, PET with $^{18}$F-deoxyglucose (FDG) can be used to determine the glucose metabolic rate in the atrophic areas, as an expression of their resting function.

Previous studies of the topography of cognitive functions in neurodegenerative disorders used PET to assess rCBF (Becker et al., 1996). We report the first application of fMRI, with its high spatial resolution, to this question. Furthermore, previous studies have focused on cases of reallocation of brain resources. Our case study of a patient with Huntington's (HD) disease is the first demonstration of residual function in atrophic cortex with rCBF measurements.

2. Methods

2.1. Subjects

2.1.1. HD patient

The patient H.M., a 48-year-old male, was admitted to the Department of Psychiatry I of Frankfurt University after an attempted suicide. This attempt followed a conversation with his lawyer, during which he was informed of the diagnosis of HD and his probable life expectancy. There are no records of previous attempts at suicide by the patient. At the time of admission, H.M. exhibited choreiform movements, predominantly of the upper limbs, dystonic movements of the head, and facial grimacing. His speech was continuously interrupted by jerky inspirations and expirations. No signs of psychosis were observed, but the patient had developed a reactive depression after he had been informed of his clinical diagnosis, and a memory defect was apparent.

H.M. reported that he had suffered from move-
ment disturbances for 8 years and from memory impairment for 3 years. The clinical diagnosis of HD was confirmed by genetic testing. The patient’s mother had died 25 years before in a psychiatric hospital, where she had been diagnosed with ‘defect schizophrenia’. His father had died 40 years ago from an unknown cancer. One sister out of three siblings suffers from a similar motor disorder. The patient’s four children are clinically unaffected by HD.

During the week following H.M.’s admission, a series of neuropsychological tests were conducted. He was suffering from a moderate degree of dementia as determined by the Mini-Mental State Examination (MMSE score: 16) (Folstein et al., 1975) and the Alzheimer Disease Assessment Scale (ADAS score: 48) (Mohs and Cohen, 1988). On the Benton Test (Benton, 1968), he made 17 of 24 possible errors (normative range: 0–3 errors). H.M. performed better on tasks from the MMSE and ADAS that involved redrawing figures than on spatial and non-spatial memory tasks.

The acquisition of MRI, fMRI, and FDG-PET data was feasible notwithstanding the patient’s condition because the hyperkinesia abated when he was in a supine position. H.M. gave written informed consent to participate in the study.

2.1.2. Healthy control subjects

Six healthy control subjects were recruited to participate in the study (all male, mean age: 29 years, range: 25–38 years). All subjects gave their informed consent to participate in the study.

2.2. Procedures

2.2.1. Behavioural paradigm

The patient’s capacity for visuospatial operations was assessed using a clock-reading task (Linden et al., 1998). The stimulus consisted of a clock with a yellow face and two white hands, covering 5° of visual angle. The angle between the hands varied from 30° and 180° in steps of 30°. Whenever the angle was 30 or 60° (target stimulus), the subject had to press a button, while all other configurations of the clock hands (non-target stimuli) had to be neglected. One-fifth of presented stimuli were target stimuli. In the MRI environment, visual stimuli were delivered under computer control (STIM® Neuroscan Inc.) to a high-luminance LCD projector (EIKI LC-6000).

The psychophysical data of the patient and control subjects were acquired in sessions outside the MRI scanner, during which 250 clocks were presented. Each clock was shown for 800 ms with an interstimulus interval of 2 s. Each fMRI experiment consisted of 120 volumes, each of 4-s duration. The 120 volumes were divided into 15 epochs of eight volumes (= 32 s) each. Resting epochs, during which only a fixation cross was presented, alternated with four stimulus and three visuomotor control (presenting only the face of the clock) epochs in a pseudo-randomized sequence (Fig. 1). Each clock was shown for 800 ms with an interstimulus interval of 1.2 s. The session with H.M. consisted of two functional experiments, which were separated by the acquisition of a three-dimensional MP RAGE scan.

2.2.2. fMRI data acquisition and analysis

Imaging was performed at 1.5 T (Siemens Magnetom Vision) using the standard head coil and a gradient echo EPI sequence. The Siemens Magnetom gradient overdrive allowed functional scans with high spatial and temporal resolution (1 volume = 15 axial slices; TR = 4000 ms, TE = 69 ms, FA = 90°, FOV = 200 × 200 mm², voxel size 1.6 × 1.6 × 5.0 mm³). A high-resolution T₁-weighted three-dimensional MP RAGE scan (magnetization prepared rapid acquisition gradient echo sequence) of the whole head lasting 8 min was recorded in the same session as the functional measurements to allow the localization of activated areas in a normalized Talairach space (Talairach and Tournoux, 1988) (voxel size 1.0 × 1.0 × 1.0 mm³).

Data analysis, including preprocessing (motion correction, Gaussian spatial and temporal smoothing, linear trend removal), cross-correlation analysis, determination of Talairach coordinates (Talairach and Tournoux, 1988), and volume and surface rendering, was performed using custom software (Goebel, 1997). Cross-correlation analysis was used to evaluate the statistical differences between experimental conditions. For
the computation of correlation maps, the stimulation protocol served as the basis of appropriate reference functions specifying experimental and control conditions (experimental condition = 1, control and resting condition = 0; Fig. 1). On a pixel-by-pixel basis, the signal time course was cross-correlated with the reference function (Bandettini et al., 1993). Pixels were included in the statistical map if the obtained correlation value was > 0.3, given a lag value of 1 (corresponding to a 4-s delay after the beginning of a stimulation in order to adapt to the haemodynamic response). Statistical cross-correlation maps were transferred into the high resolution three-dimensional data sets and interpolated to the same resolution. For the patient and the healthy subjects, the structural (three-dimensional data set) and functional data were transformed into Talairach space (Talairach and Tournoux, 1988), a procedure that permitted the comparison of activated areas between patient and control subjects and the determination of Talairach coordinates of these areas. The mean time course for all voxels of an activated volume for all pixels in this volume, \( r > 0.3 \) (see above) was correlated with the reference function (Table 1). The co-registered high-resolution \( T_1 \)-weighted three-dimensional recordings were also used for surface reconstruction of the posterior part of the brain. To test the statistical strength of the difference between experimental conditions, an exploratory one-way analysis of variance (ANOVA) was com-
Table 1
Cerebral areas activated during visuospatial processing

<table>
<thead>
<tr>
<th>HD patient</th>
<th>Control subjects mean and S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x$</td>
<td>$y$</td>
</tr>
<tr>
<td>$-29$</td>
<td>$-66$</td>
</tr>
<tr>
<td>$25$</td>
<td>$-65$</td>
</tr>
<tr>
<td>$-45$</td>
<td>$-76$</td>
</tr>
<tr>
<td>$36$</td>
<td>$-75$</td>
</tr>
<tr>
<td>$-54$</td>
<td>$9$</td>
</tr>
<tr>
<td>$54$</td>
<td>$2$</td>
</tr>
</tbody>
</table>

Cerebral structure
- L intraparietal sulcus
- R intraparietal sulcus
- L occipito-temporal
- R occipito-temporal
- L superior precentral sulcus
- R superior precentral sulcus

Notes. Talairach coordinates, correlation coefficients, and corresponding anatomical locations of areas activated by the visuospatial task ($^{*} P < 0.001; ^{**} P < 0.00001; $ uncorrected).

puted in the two most extensively activated areas; if there was a significant main effect, a Scheffé test was calculated post hoc. For a detailed description of three-dimensional data analysis, see Goebel et al. (1998a,b) and Dierks et al. (1999).

For display purposes, a grand mean signal intensity time course for each voxel and a grand mean three-dimensional data set over all control subjects were calculated. The grand mean data were treated in the same way as individual data to display activated areas (see above and Fig. 1).

2.2.3. PET imaging
Cerebral glucose metabolism of the resting state in the HD patient (in a noise- and light-reduced room) was assessed using a Siemens ECAT-47 PET tomograph. PET images (47 slices, slice thickness = 3.3 mm, scan duration = 30 min) were acquired 30 min after an i.v. injection of 252 MBq $^{18}$F-DG.

3. Results

3.1. Behavioural results
In the clock-reading task, the HD patient recognized 45 out of 50 target stimuli (10% false-negatives; normal subjects: 0–6%). He erroneously identified three non-targets as targets (1.5% false-positives; normal subjects: 0–2%). His mean reaction time for correct responses was 713 ms compared with 539 ms (S.D. = 95 ms) in the control subjects.

3.2. PET
Resting glucose metabolism was markedly reduced in the temporo-parietal cortex in the HD patient, while metabolism in the occipital and motor cortices appeared normal. No glucose metabolism could be detected in the caudate nuclei, a finding that has been recognized as a typical and highly sensitive criterion for HD in PET imaging (Kuwert et al., 1990).

3.3. MRI

3.3.1. Structural $T_1$- and $T_2$-weighted MRI
A routine MRI scan ($T_1$ and $T_2$ weighted) showed, in addition to an atrophic caudate nucleus, global brain atrophy with fronto-parieto-temporal accentuation.

3.3.2. Task-dependent changes of MRI BOLD signal
The strongest correlation and the most significant increase of BOLD signal with the visuospatial vs. visuomotor control task was observed both for the HD patient and the control subjects in the left intraparietal sulcus (Tables 1 and 2, Figs. 2–4), an area that showed severe atrophy and reduced glucose metabolism in the HD patient (Fig. 4). The BOLD activation could be clearly
Table 2
Signal intensity changes for left extrastriate cortex and intraparietal sulcus

<table>
<thead>
<tr>
<th></th>
<th>R-C (%)</th>
<th>R-T (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrastriate</td>
<td>1.6</td>
<td>2.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Ips</td>
<td>0</td>
<td>1.4</td>
<td>&lt; 10^{-4}</td>
</tr>
<tr>
<td>Huntington patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrastriate</td>
<td>3</td>
<td>2.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Ips</td>
<td>0.8</td>
<td>2.1</td>
<td>&lt; 10^{-4}</td>
</tr>
</tbody>
</table>

Notes. Mean percent signal intensity difference between rest and control task (R-C) and between rest and spatial task (R-T) in left extrastriate cortex (Talairach coordinates: control subjects mean: x = −9, y = −85, z = 1; Huntington's disease patient: x = −31, y = −81, z = −1) and left intraparietal sulcus (for Talairach coordinates, see Table 2). An exploratory one-way ANOVA exhibited significant differences over all conditions for both areas in the patient and the control group. F_{116} = 48–120, P < 10^{-4}. Post hoc P values (Scheffe test) are shown for the comparison between the control task and the spatial task.

linked to the remaining grey matter (Fig. 2). Additional areas demonstrating a significant correlation predominantly with the visuospatial compared with the visuomotor task included the right intraparietal sulcus, occipito-temporal cortex, and precentral sulci bilaterally, both in the control group and the HD patient (Fig. 3 and Table 1). Neither the patient nor the control subjects exhibited any significant activation in the basal ganglia.

4. Discussion

The increased evaluation time of the stimulus in connection with similar accuracy of response in the HD patient compared with findings in the normal healthy subjects could be interpreted as supporting the assumption that new cerebral regions were recruited for stimulus evaluation. However, the main focus of task-dependent activation during the discrimination of the angles between the hands of a clock compared with stimulus-dependent activation was located in the cortex along the intraparietal sulcus. Recent studies have confirmed the involvement of this cortical region in visuospatial processing, both in monkeys (Sakata et al., 1997) and in humans (Kosslyn et al., 1994; Goebel et al., 1998b). It is therefore likely that the patient’s relatively normal performance in the clock-reading task, which stands in striking contrast to his severe overall cognitive deterioration, is linked to the preserved modulation of rCBF in the intraparietal area during this task. Thus, the patient’s performance reflects residual function rather than compensatory reallocation. No newly recruited area was observed with fMRI. The additional areas with a predominant task-dependent modulation of BOLD signal appeared both in the patient and in the healthy control subjects. They include areas in the precentral sulci, probably the frontal eye fields, whose most common location they match (Paus, 1996), and areas in occipito-temporal cortex (Goebel et al., 1998a). The latter areas are involved in object recognition and the discrimination of contours, and they form part of the ventral pathway of visual processing, which is thought to be specialized for the processing of information about the physical properties of objects (Ungerleider and Mishkin, 1982). Although atrophy and reduced glucose metabolism did not affect occipito-temporal areas as much as parietal ones, occipito-temporal areas were less strongly modulated during angle discrimination than were intraparietal areas, which are part of the dorsal pathway and held to be responsible for the detection of spatial relations between objects (Mishkin and Ungerleider, 1982).

In patients demonstrating gross cortical atrophy, like the case presented here, the exact relationship between neocortical landmarks will not be preserved and the Talairach normalization procedure may lead to erroneous results in comparisons between normal and atrophic brains (Mega et al., 1998). We therefore put more emphasis on the individual anatomical localizations of activated regions than on normalized Talairach coordinates.

It may be speculated that the elevated percent signal intensity change in the HD patient compared with the control group during task perfor-
Fig. 2. Coronal, sagittal, and transverse MRI slices with superimposed areas that show a high correlation with a visuospatial task in six healthy control subjects (upper row) and in a patient with Huntington’s disease (lower row). The colour bar indicates the level of correlation between signal intensity time course and reference function (stimulus paradigm).

Fig. 3. Posterior view of the three-dimensional reconstructed brain and superimposed areas activated by a visuospatial task in a patient with Huntington’s disease.

Performance in fMRI indicates a higher neuronal effort than that in healthy subjects. Heightened effort is reflected in the behavioral results, where the patient achieved a degree of accuracy similar to that in healthy subjects but needed a longer processing time.

The fMRI findings suggested that the patient’s partially preserved capacity of spatial analysis can be parsimoniously explained by assuming remaining function and physiological regulatory mechanisms of rCBF in precisely the same areas that had been responsible for the execution of such tasks before the onset of the disease. Our results suggest that fMRI possesses sufficient sensitivity and spatial resolution to be used as a method for the non-invasive differentiation between the residual function of cortical areas and the compensatory reallocation of brain resources. Such a differentiation is important for the design of multimodal approaches to the investigation of cognitive deficits, for the understanding of the mechanisms of neurodegenerative disorders, and for the development of prophylactic, therapeutic, and rehabilitation strategies.
Fig. 4. Upper row: Imaging of cerebral glucose metabolism with FDG-PET. Absent metabolism is observed in both caudate nuclei (fourth slice from left). Reduced metabolism is seen in parietal and temporal cortices. The colour bar indicates the glucose metabolism scaled to the maximum activity in each slice. Lower row: corresponding transversal MRI slice positions with superimposed areas that show BOLD signal increase during the visuospatial task. The colour bar indicates the level of correlation between signal intensity time course and reference function (stimulus paradigm).

Acknowledgements

The investigation was supported by the Alzheimer Research Centre, and Hoechst Marion Roussel Deutschland GmbH, Frankfurt, Germany. The authors are grateful to David Prvulovic for assistance in the psychophysical testing and for the DNA testing performed by the Department of Molecular Human Genetics at Ruhr University in Bochum (Director: Prof. T. Epplen).

References