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Altered thalamic glucose metabolism in cerebellar projections in Parkinson's disease

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ABSTRACT

A pathological communication between the basal ganglia (BG) and the cerebellum (Cb) at the level of the thalamus has been proposed to be causative for the generation of parkinsonian tremor. Recent studies, however, indicated, that altered Cb-thalamic circuitry is not only underlying the genesis of tremor, but is involved in the generation of other parkinsonian symptoms like bradykinesia and rigor.

Hence, we studied the glucose metabolism of akinetic-rigid parkinsonian patients in (i) anatomical (anterior, medial, lateral, posterior) and (ii) projection territory-based (Cb- and BG-thalamic) subdivision of the human thalamus and compared them with healthy controls in order to predict disease progression irrespective of the symptom tremor. The dentate nucleus was representatively chosen as output station for Cb regions, BG regions comprised the pallidum.

Regarding (i) the anatomical subdivision we found no significant difference between patients and controls in the glucose metabolism for the anterior and medial group ($p > 0.05$), but an increase of glucose metabolism for the lateral and posterior group ($p < 0.05$). The glucose metabolism under (ii) the tractography-based subdivision revealed significant differences between patients and controls in the left ($p < 0.05$) and right ($p < 0.01$) Cb-thalamic, but not the BG-thalamic projection territory ($p > 0.05$). In order to test for disease specific alterations, we correlated bihemispherically averaged thalamic glucose metabolism for the anterior, medial, lateral and posterior thalamic group with disease progress (reflected by the Hoehn & Yahr score) and found a significant prediction of the glucose metabolism of the lateral thalamic group and the disease progression ($p < 0.05$; $r = 0.4$). A further subdivision into patients with right and left symptom onset evoked a group of 14 right- and 13 left affected patients. Again, we correlated clinical parameters of disease progression with the results of glucose metabolism and found a significant correlation of the right affected patients ($p < 0.05$) with the right Cb-thalamic region reflected by an up-regulation of glucose metabolism; right affected patients frequently show slower disease progression than left affected patients.

Hence our results support a critical (maybe compensatory) role of the Cb-thalamic projections and forces a more straightforward thinking away from a pure "symptom-oriented" to a "dynamic-circuitry" approach due to functional changes in glucose metabolism with Cb and BG as one of the circuitry key elements defining the clinical parkinsonian phenotype.

1. Introduction

The thalamus integrates and modulates information of the cerebellum (Cb), the basal ganglia (BG) and the cortex. BG-thalamo-cortical circuit dysfunction caused by nigral degeneration has been clearly implicated in the pathogenesis of parkinsonian symptoms [1]. Until now, the role of the Cb-thalamo-cortical circuit in this network imbalance has not been well defined although functional imaging studies more and more postulate a remarkable influence of the cerebellum in the genesis of parkinsonian symptoms [2,3]. Next to a circuit dysfunction also local pathology in the thalamus itself is thought to contribute to the abnormal neural activity characteristic in Parkinson's disease (PD), as recently shown in histopathological [4] and functional imaging studies [5]. Historically, these changes have been conceptualized as a consequence of nigral degeneration [1]. It is however questionable if these pathological intrathalamic changes might rather be a product of

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chronic synaptic firing due to altered Cb signaling in PD [6]. The cerebellum, with its excitatory transmitter glutamate, might act compensatory with metabolic upregulation due to decreasing BG function. The ventral thalamic group was previously assigned for a specific role in resting-tremor in PD, resulting in a hypermetabolism in the anterior part of the ventral-lateral thalamus as shown by Kassubek et al. [5]. Targeting this region by deep brain stimulation is highly effective to suppress resting tremor in PD [7]. Next to a role of the Cb-thalamic projections in the genesis of parkinsonian tremor, it might be possible that the cerebellar upregulation is a physiological answer to the affected BG-circuitry and the genesis of tremor might be the clinical presentation or rather by-product of an "overshooting" glutamatergic cerebellar compensation [8]. This would mean, that metabolic cerebellar upregulation is not only linked to tremor, but should significantly correlate with the disease progression in parkinsonian patients; this has however not been investigated yet. Causative for this informational lack is the rather sparse anatomical information on Cb and BG projections to the thalamus in living humans due to methodological limitations of in vivo tracing and the existence of numerous different thalamic nomenclatures [9]. Nowadays, mathematical models reconstructing thalamic nuclei on histopathological basis integrate information of different thalamic atlases and enable a better inter-individual and inter-methodological comparison of thalamic sub-territories [10]. Next to a pure anatomical classification of thalamic subnuclei probabilistic diffusion tractography opens the possibility to integrate information of different projection systems, as shown recently for BG-thalamic and Cb-thalamic specific connectivity maps in healthy human subjects [11]. Integrating information of a pure atlas-based subdivision of the thalamus (anterior, lateral, medial and posterior) and a tractographic-based subdivision (BG- and Cb-thalamic connectivity maps) now enables a combination of anatomical data, projection systems and functional data and expand the view of the Cb as pure tremor generator to a compensatory system determining the disease progression in PD patients. The aim of the actual study was to examine the glucose metabolism in a volume of interest analysis (VOI) in (i) an atlas- and (ii) tractography-based subdivision of the thalamus; results of metabolic rates of ^{18}fluordesoxyglucose positron emission tomography (FDG-PET) were consecutively correlated with the disease progress of the individual PD patients to elucidate the role of Cb-thalamic projections in the development of PD.

2. Material and methods

2.1. Behavioral data

The recruitment of the patients was retrospectively performed out of two previous studies from our group [12,13]. In total 27 akinetic-rigid PD patients (mean age 65.2 ± 8.9 yrs., 6 female) and 11 healthy controls (mean age 38.7 ± 13.8 yrs., 1 female) were examined. Healthy controls also served as a control group in a previous study [14]. Due to the risk of gamma radiation and the possible resulting medical side effects for individual healthy controls we decided against a new aged-matched control group. Thus, no better match between both groups was possible (see discussion). Patients with mild to moderate PD were included in the study (mean Hoehn & Yahr stage [15] 2.1 ± 0.8). Disease duration was 5.8 ± 5.0 years. Subtypes were assigned according to clinical predominant symptoms. The average daily levodopa equivalent dosage (LEDD) was 527 ± 453 mg [16]. Thirteen patients had a left and fourteen patients right side predominance. All clinical data was encompassed retrospectively out of the existing medical reports; unfortunately no further neuropsychological testing or neurological scales (like the Unified Disease Parkinson Rating Scale) were retrospectively available. Because of the retrospective nature of the study, an ethical vote was for the clinical data of the PD patients (FDG-PET) was not mandatory according to German federal laws. However, the ethics committee of the Medical Faculty of the University of Cologne approved the protocol on request. Patients were not asked for informed consent as case records were made anonymous and de-identified prior to analysis. For the healthy controls, volunteers gave informed consent and the study was approved by the local ethics committee in a previous study [14]. Likewise, the ethics committee approved the MRI acquisition. The subjects were diagnosed with PD according to the UK Brain Bank Criteria [17] and therefore subjects without any clinical response to levodopa treatment were excluded from the study. Also patients with relevant concomitant neurological diseases were pre-selectively excluded from the study like patients with signs and symptoms of dementia, or past history of stroke or brain surgery. Family histories were negative for neurological and psychiatric diseases in all patients. There was also no history of toxin exposure, head injury, encephalitis, and metabolic diseases.

2.2. Image acquisition

2.2.1. ^{18}FDG-PET

Patients underwent FDG-PET imaging that was performed using a high-resolution 24-detector ring scanner (ECAT EXACT HRRT, Siemens CTI, Knoxville, TN) with 207 transaxial image planes and 1.219 mm voxel size. FDG-PET images were obtained according to a previously published protocol [18]. Briefly, during scanning procedures, subjects lay comfortably in the supine position in a room with dimmed lighting and low background noise. After the injection of 370 MBq of ^{18}F-fluorodeoxyglucose, cerebral glucose metabolism was measured representing the regional metabolic activity. Data were acquired in a 3D mode, subsequently reconstructed, including a correction for random coincidences, attenuation, and scatter. The reconstructed resolution of the PET scans was almost isotropic with 2.2 mm full width at half maximum (FWHM) in the center and 2.5 mm FWHM at 10 cm off-axis. Patients were fasting overnight while taking their regular daily dopamine replacement therapy in the morning of the PET scan. We examined patients with their regular clinical ON-state medication to avoid excessive head movement and increase their comfort as most of our patients had akinesia in the OFF-state. Images between 20 and 60 min of data acquisition and multiple arterialized venous blood samples were used to calculate the regional cerebral metabolic rate of glucose (rCMRGlc; µmol/100 g/min). To avoid arterial puncture, we used the so-called 'heated hand method'. For arterialization of venous blood, one hand was put into a 38 °C warm water-bath and blood samples from a venous catheter were taken, which was placed opposite to the conventional position. Arterialization was controlled by blood gas analyses where oxygen levels (pO2) had to exceed 50 mm Hg. Blood samples were taken according to a standard scheme and the activity was measured in a radiocounter (Berthold MAG 312, Berthold Technologies, Bad Wildbad, Germany.

2.2.2. Structural magnetic resonance imaging

In each study participant, a clinical routine T1- and T2-weighted magnetic resonance image (MRI) was recorded on different 1.5 T MR-tomographs and co-registered to the PET datasets by in-house software (VINCI 435; http://www.nf.mpg.de/vinci3/doc/vinci-about.html) using an automatic iterative procedure. Before including MR images into the analysis, all MR images were pre-checked for pathological abnormalities and excluded, if any abnormalities (like white matter hyperintensities and/or lacunar pathologies) were present. To compare the PET-scans with differing sizes and proportions in voxel-wise statistics, scans were preprocessed in SPM8 (The Welcome Department of Cognitive Neurology, London, UK). Images were smoothed by a 6 mm full width at half maximum (FWHM) Gaussian filter and subsequently spatially normalized to a standard stereotactic space using the standard SPM PET-template. The rather low smoothing filter was obtained to account for the high resolution of the PET images. In order to determine the metabolic rates in different thalamic sub-regions we performed a VOI analysis by the implementation of the Krauth-Atlas [10]. This atlas contains a subdivision in a ventral, anterior, medial and posterior