Limbic and Frontal Cortical Degeneration Is Associated with Psychiatric Symptoms in *PINK1* Mutation Carriers

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Background: Mutations in the *PINK1* gene can cause Parkinson's disease and are frequently associated with psychiatric symptoms that might even precede motor signs.

Methods: To determine whether specific gray matter degeneration of limbic and frontal structures might be liable to different psychiatric symptoms in *PINK1* mutation carriers, observer-independent voxel-based morphometry was applied to high-resolution magnetic resonance images of 14 *PINK1* mutation carriers from a large German family and 14 age- and gender-matched healthy control subjects.

Results: Psychiatric diagnoses in *PINK1* mutation carriers comprised major depression without psychotic symptoms and schizophrenia-spectrum, panic, adjustment, and obsessive-compulsive personality disorders. As hypothesized, the categorical comparison between all *PINK1* mutation carriers and control subjects demonstrated atrophy of limbic structures, especially the hippocampus and parahippocampus. More specifically, multiple regression analysis considering all psychiatric subscores simultaneously displayed different frontal (prefrontal, dorsolateral, and premotor cortex) and limbic (parahippocampus and cingulate) degeneration patterns. The duration of the psychiatric disease was also correlated with the extent of limbic and frontal gray matter volume decrease.

Conclusions: Our results support the hypothesis that limbic and frontal gray matter alterations could explain various psychiatric symptoms observed in *PINK1* mutation carriers. Factors determining individual susceptibility to degeneration of certain brain areas remain to be elucidated in future studies.

Key Words: Hippocampus, Parkinson's disease, *PINK1*, psychiatric disorders, voxel-based morphometry

Parkinson's disease (PD) is a common, slowly progressive neurodegenerative disorder. Although characterized by its motor symptoms, recent findings point to the impact of mental impairment and psychiatric symptoms in PD patients (1). Although the origin of the disease in the majority of PD patients currently remains unknown, approximately 2%–3% of all cases can be explained by a monogenic cause. To date, there is evidence for at least six genes being associated with monogenic PD (2). Mutations in the *PINK1* gene are the second common known single factor responsible for early-onset PD (3) and can lead to a phenotype indistinguishable from that of idiopathic PD (3–5).

A number of studies support the hypothesis that psychiatric disorders are associated with an increased risk of PD (6–9). The most common psychiatric syndrome seen in PD is depression (10), followed by psychotic symptoms (11), anxiety syndromes, or cognitive impairment (11), which can antedate motor symptoms by several years (6). Psychiatric symptoms in genetically determined PD syndromes have been described in *Parkin* and *PINK1* mutation carriers (*PINK1*-MC) (12–14). Recently, we reported about the clinical spectrum covering both neurological and psychiatric symptoms in a large German pedigree with *PINK1*-associated PD (5,15). Systematic evaluation revealed that psychiatric disorders were present in 72% of the homozygous and heterozygous *PINK1*-MC and had mostly preceded the manifestation of PD motor signs (15).

The aim of the present study was to evaluate whether the psychiatric symptoms observed in the *PINK1*-MC could be explained by specific gray matter volume (GMV) alterations in brain areas that are suggested to be involved in disease mechanisms of psychiatric disorders. Following an explorative approach based on previously published morphometric data in affective disorder, schizophrenia, and anxiety disorder, we hypothesized that limbic and frontal structures would be of special interest.

Methods and Materials

We compared structural magnetic resonance images (MRI) (T1-weighted three-dimensional [3D] magnetization prepared rapid acquisition gradient echo [MPRAGE]) of 14 *PINK1*-MC (5 female, mean age: 49.6 years [± 12.6]) with those of 14 age- and gender-matched healthy control subjects (5 female, mean age: 49.0 years [± 10.7], $p = .90$). All subjects gave their written informed consent for participation in this study, which was approved by the ethics committee of the University of Luebeck. The *PINK1*-MC belonged to a large family originating in the southwestern part of Germany and were identified as part of large-scale genetic studies (16–18). Although 4 individuals (II.1, II.3, II.5, and II.7) were homozygous for the 1366C>T mutation in *PINK1*, the remaining 10 carried only one mutated allele and were therefore heterozygous. We have to note that our subjects were only screened for a mutation in the *PINK1* gene.

All control subjects had a normal neurological and psychiatric examination and tested negative for the *PINK1* mutation.

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Neurological Motor Examination

All participants underwent a detailed neurological examination by a blinded movement disorder team. The videotaped assessment of the Unified Parkinson's Disease Rating Scale (UPDRS) part III protocol was blindly evaluated by an independent movement disorder specialist (5,15). The diagnosis of definite PD was based on the United Kingdom Brain Bank diagnostic criteria.

All four homozygous *PINK1*-MC manifested definite clinical motor signs (5), received a dopaminergic medication, and were tested in the on-phase. Two of the heterozygous *PINK1*-MC showed signs of probable PD, and another four of them showed signs of possible PD. All of them were unaware of these signs. The remaining four heterozygous *PINK1*-MC were clinically unaffected.

Psychiatric Examination

To assess lifetime Axis I (clinical) and Axis II (personality) psychiatric disorders, one of two experienced psychiatrists, who were blind with respect to the individual's neurological diagnosis and mutational status, administered the German version of the Structured Clinical Interview for DSM-IV (15). Diagnoses were confirmed at consensus conferences with a third senior psychiatrist, considering all available clinical data, including information on the medical health status. Diagnoses comprised major depression without psychotic symptoms, schizophrenia-spectrum disorders, panic disorder, adjustment disorder, and obsessive-compulsive personality disorder (OCPD; Table 1) (15). None of the *PINK1*-MC or control subjects showed evidence for cognitive impairment (mean Mini Mental State Examination score: 28.9 [±.9]).

For the purpose of the parametric regression analysis with structural data, psychiatric disorder scores were defined with a value of "2" encoding definite and "1" encoding probable affection. Multiple regression analysis including the individual diagnostic scores for each subject was used to evaluate potential interactions and account for the fact that five subjects were diagnosed with a combination of at least two psychiatric disorders.

MRI Scanning

Scanning was performed on a 1.5-T whole-body scanner (Symphony; Siemens, Erlangen, Germany). All subjects underwent MRI imaging with a T_1-weighted FLASH-3D MR sequence (echo time [TE] = 5 msec; repetition time [TR] = 15 msec; flip angle = 30°; isotropic voxel size 1 × 1 × 1 mm^3). Images were analyzed with voxel-based morphometry (VBM), a fully observer-independent automated technique for computational analysis of differences in local GMV with SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, United Kingdom), for further details of the procedure, please see (19).

The spatial normalization to the standard anatomical space was performed in a two-stage process. First, we registered each image to the International Consortium for Brain Mapping Template (Montreal Neurological Institute [MNI], Montreal, Canada). We applied a 12-parameter affine transformation to correct image size and position. Regional volumes were preserved, while corrections for global differences in whole-brain volume were made. All normalized images were averaged and smoothed with a Gaussian kernel of 8 mm full-width at half maximum (FWHM) and then used as a new template with reduced scanner- and population-specific bias. Second, we locally deformed each image to the new template with a nonlinear spatial transformation. With a modified mixture-model-cluster analysis, normalized images were corrected for non-uniformities in signal intensity and partitioned into gray and white matter, cerebrospinal fluid (CSF), and background. To remove unconnected non-brain voxels, we applied a series of morphological erosions and dilations to the segmented images (20). A gray matter mask was used to reduce edge effects around the ventricles, meninges, and veins. Finally, images were smoothed with a Gaussian kernel of 12 mm FWHM.

Statistical Analysis

A voxel-by-voxel one-way analysis of variance (ANOVA) was computed to detect differences in GMV between groups and with an absolute gray matter threshold of .25 to avoid possible edge effects around the border between gray and white matter or CSF. On the basis of previous morphometric data in patients with these psychiatric disorders (21–27), we hypothesized reduced GMV in: 1) limbic structures (hippocampus, parahippocampus, and cingulate); and 2) the frontal lobe (dorsolateral, fronto-mesial, and fronto-orbital areas).

First, an explorative categorical comparison was calculated between the 14 *PINK1*-MC and their control subjects. Although

Table 1. Demographic Data and Clinical Findings in 14 *PINK1* Mutation Carriers

Code	Age	Gender	Genetic Status	Duration of Psychiatric Disorder	Major Depression	Schizophrenia Spectrum-Disorder	Panic Disorder	Adjustment Disorder	Obsessive-Compulsive Personality Disorder	Summarized Psychiatric Score
III.1	50	M	heterozygous	27	0	2	0	0	0	2
II.5	68	W	homozygous	15	2	0	0	0	2	4
II.3	69	W	homozygous	0	0	0	0	0	0	0
II.7	60	W	homozygous	20	2	0	2	0	0	4
III.11	31	M	heterozygous	4	2	0	2	0	0	4
II.1	71	W	homozygous	28	2	0	0	0	0	2
III.5	43	M	heterozygous	25	0	1	0	0	0	1
III.10	47	M	heterozygous	0	0	0	0	0	0	0
III.8	39	M	heterozygous	21	0	0	0	0	2	2
III.9	35	M	heterozygous	0	0	0	0	0	0	0
III.3	47	W	heterozygous	18	2	1	0	0	0	3
III.4	45	W	heterozygous	24	0	2	0	2	0	4
III.6	45	M	heterozygous	1	0	0	0	2	0	2
III.7	44	M	heterozygous	0	0	0	0	0	0	0