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ORIGINAL ARTICLE

Posterior limb of the internal capsule predicts poor quality of life in patients with Parkinson's disease: connectometry approach

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Abstract

Psychiatric symptoms and motor impairment are major contributions to the poor quality of life in patients with Parkinson's disease (PD). Here, we applied a novel diffusion-weighted imaging approach, diffusion MRI connectometry, to investigate the correlation of quality of life, evaluated by Parkinson's Disease Questionnaire (PDQ39) with the white matter structural connectivity in 27 non-demented PD patients (disease duration of 5.3 ± 2.9 years, H and Y stage = 1.5 ± 0.6, UPDRS-III = 13.7 ± 6.5, indicating unilateral and mild motor involvement). The connectometry analysis demonstrated bilateral posterior limbs of the internal capsule (PLIC) with increased connectivity related to the higher quality of life (FDR = 0.027) in a multiple regression model. The present study suggests for the first time a neural basis of the quality of life in PD in the light of major determinants of poor quality of life in these patients: anxiety, depression, apathy and motor impairment. Results in our sample of non-demented PD patients with relatively mild motor impairment and no apparent sign of depression/anxiety also identify a unique and inexplicable association of the PLIC to the quality of life in PD patients.

Keywords Quality of life · Parkinson's disease · Diffusion MRI · Connectometry

Introduction

Quality of life (QoL) is a subjective, multidimensional concept of well-being covering personal and interpersonal aspects of life, and a main concern and contributor to morbidity in non-curable disorders such as Parkinson's disease (PD) [1].

Patients with PD demonstrate a combination of motor and non-motor symptoms (NMS), which severely impair their physical compatibility as well as emotional and social domains of their health. Apart from devastating motor dysfunctions, NMS such as mood disorders and cognitive symptoms are major culprits of poor QoL in PD patients [2]. The cumulative nature of the symptoms, along with the side effects of long-term dopamine replacement therapy, contributes to worsening patient's quality of life as PD progresses. Early in Parkinson's disease, the non-motor symptoms, rather than motor disabilities, seem to have the greatest impact on patients' QoL [3].

Depressive symptoms are common in early PD and a lifelong prevalence as high as 80% is reported for depression in patients diagnosed with PD. Interestingly, physical disability has less impact on QoL than does clinical depression [4], and regression studies have assigned depression as a main independent predictor of worse QoL [4–6]. Nevertheless, depressive symptoms in PD are usually overlooked in daily clinical practice and misdiagnosed as motor symptoms (rigidity and mask-like expression) [5]. It is important to note that NMS such as anxiety and depression usually coexist in PD and synergistically interfere with patient's routine activity. Although hard to distinguish, one study reported that the effect of anxiety remained significant even after controlling for coexisting depressive traits [7]. These neuropsychiatric disorders are believed to be part of non-motor PD manifestations and are mainly attributed to underlying neurobiological mechanisms of PD rather than a mere psychological response to the ailment [8]. Both depression and anxiety can modify a patient's self-perception of well-being and thus profoundly affect patient's quality of life.

Cognitive deterioration is a usual morbidity in advanced PD stages, most commonly in the domains of executive

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function, memory and attention. Poor cognition can, in turn, reduce the confidentiality of QoL assessment and diminish the validity of patient-reported questionnaires in advanced PD [2].

Brain structural changes in early PD are well described in the literature. The diagnostic pathology in PD has conventionally been considered as Lewy neuritis leading to neural death, mainly in the nigrostriatal pathway [9]. Nevertheless, this does not explain the heterogeneous manifestations of NMS in PD. A diverse group of neural circuits has been shown to lose microstructural integrity in newly diagnosed patients concordant with the inter-individual diverse phenotypes in early PD [10].

To date, no study has investigated white matter alterations in patients with PD in relation to QoL, which would alarm the development of symptoms with the highest impact on disability and morbidity in PD patients. Here, we applied a novel diffusion-weighted imaging approach, diffusion MRI connectometry, to investigate the neuropathological disturbances underlying poor quality of life in PD.

Methods

Participants

27 patients clinically diagnosed with Parkinson's disease (mean disease duration of 5.3 ± 2.9 years) were recruited from a previous study by Ziegler et al. [11]. Hoehn and Yahr scale and Unified Parkinson's Disease Rating Scale (UPDRS) were measured to assess disease stage and its severity in the "on" state. Only 24 patients of the study group were on a combination of antiparkinsonian drugs: levodopa (immediate and controlled release), non-ergot-derived dopamine receptor agonists (pramipexole, ropinirole), and a monoamine oxidase B inhibitor (rasagiline). Dosages of dopaminergic drugs were pooled and summarized using the levodopa equivalent daily dose (LEDD) [12], which ranged from 0 to 900 mg.

The study was performed according to the guidelines of the Ethics Committee of the University of Liège and written informed consent was obtained from all participating subjects in accordance with the Declaration of Helsinki.

Clinical measures

The quality of life as the main study variable was evaluated by the Parkinson's Disease Questionnaire (PDQ39) [13]. Other tests as cofounders included Mattis Dementia Rating Scale, Mini-Mental State Examination and Symbol Digit Modalities test to assess global cognition, Rey auditory verbal learning test to measure episodic memory, Judgment of Line Orientation for visuospatial judgment, as well as Hospital Anxiety and Depression Scale (HADS) for psychiatric evaluation [11].

Imaging data acquisition

This dataset was acquired on a 3 T Siemens scanner, producing 120 DWI images (repetition time = 6800 ms, echo time = 91 ms; voxel size: 2.4 × 2.4 × 2.4 mm^3; field of view = 211 × 211 mm) with a twice-refocused spin–echo sequence with EPI readout at b value of 2500 s/mm^2 acquired in 54 transverse slices using an 88 × 88 voxel matrix. 2 b0 volumes were also acquired for motion correction. To reduce eddy current distortions in DWI, electrostatic repulsion sequence was used to uniformly distribute 120 gradient vectors in space [11].

Diffusion MRI data processing

Diffusion MRI data were corrected for subject motion, eddy current distortions, and susceptibility artifacts due to the magnetic field inhomogeneity using ExploreDTI toolbox.

Connectometry analysis

Diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function (SDF) [14]. A diffusion sampling length ratio of 1.25 was used, and the output resolution was 2 mm.

Diffusion MRI connectometry [15] was used to study the effect of quality of life (PDQ39). Connectometry is a novel approach in the analysis of diffusion MRI signals that simply tracks the difference of white matter tracts between groups, or correlation of white matter fibers with a variable of interest, by searching into subcomponents of the neural pathway. Connectometry approach extracts the SDF in a given fiber orientation as a measure of water density along that direction. Quantitative anisotropy (QA) is a diffusion index derived from spin density, i.e., SDF. QA of each fiber orientation gives the peak value of water density in that direction. A multiple regression model was used to consider the age, sex, HADS (anxiety), HADS (depression), duration of disease, UPRDS-III, Hoehn and Yahr scale, LEDD, cognitive measures and dominant side of motor symptoms as covariates in a total of 27 subjects. A t threshold of 2.5 was assigned to select local connectomes, and the local connectomes were tracked using a deterministic fiber tracking algorithm [16]. Track trimming was conducted with ten iterations. All tracks generated from bootstrap resampling were included. A length threshold of 40 mm was used to select tracks. The seeding density was 50 seeds per mm^3. To estimate the false discovery rate (FDR), a total of 2000 randomized permutations were applied to the group label to obtain the null distribution of the track length. The analysis

was conducted using DSI Studio (http://dsi-studio.labsolver.org), released in November 2017.

Results

Clinical measures

PD patients showed only mild motor impairment in on-drug status (UPDRS-III = 13.7 ± 6.5). Fifteen patients had unilateral motor involvement, three had unilateral plus axial involvement, eight had bilateral involvement without balance impairment, and only three had mild to moderate disability with impaired postural reflexes. The HADS score revealed only one patient with a definite diagnosis of depression [17]. None of the participants scored below the cutoff thresholds of cognitive tests to be marked as demented (Table 1).

Connectometry

Results from multiple regression models in diffusion MRI connectometry revealed a significant positive association (FDR = 0.027) between PDQ39 scores of PD patients and white matter QA of the posterior limb of the internal capsule tracts bilaterally (Fig. 1). In other words, lower quality of life is correlated to lower connectivity in the mentioned area.

Table 1 Descriptive statistics of parkinsonian patients

	PD patients (n = 27)
Age (mean ± SD years)	65.6 (8)
Sex (male:female)	14:13
Years of education (mean ± SD)	11 (3)
Hoehn and Yahr stage (mean ± SD)	1.5 (0.62)
Disease duration (mean ± SD years)	5.3 (2.9)
Most affected side (left:right)	10:17
LEDD (mg) (mean ± SD)	323 (255)
UPDRS2 (mean ± SD)	9 (6)
UPDRS3 (mean ± SD)	13.7 (6.5)
PDQ39 (mean ± SD)	188.5 (114)
MDRS (mean ± SD)	135.5 (4)
MMSE (mean ± SD)	27.7 (1)
HADS total (mean ± SD)	12.8 (6)
Rey auditory verbal learning test (mean ± SD)	44.1 (11)
SDMT (mean ± SD)	44.9 (12)
JOLO (mean ± SD)	24.8 (4)

LEDD L-DOPA equivalent daily dose (Hobson et al. 2002), *UPDRS* Unified Parkinson's Disease Rating Scale, *PDQ*-39 Parkinson's Disease Questionnaire, *MDRS* Mattis Dementia Rating Scale, *MMSE* Mini-Mental State Examination, *HADS* Hospital Anxiety and Depression Scale, *SDMT* Symbol Digit Modalities Test, *JOLO* Judgment of Line Orientation test

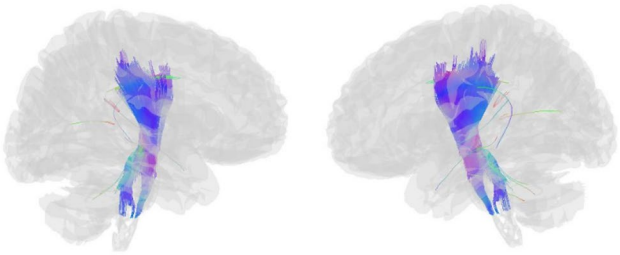

Fig. 1 Results of diffusion MRI connectometry multiple regression analysis regarding the quality of life in patients with Parkinson's disease, using DSI Studio software. Lower quantitative anisotropy in bilateral posterior limbs of the internal capsule is correlated with lower Parkinson's disease questionnaire scores

To highlight whether this finding is truly bilateral or dependent on the side of the motor symptoms dominancy, we repeated the analysis considering the dominant side as the main variable. The multiple regression model did not reveal any significant association with left or right posterior limb of the internal capsule with the dominant side of the motor symptoms.

Discussion

In this study, we investigated the association between white matter microstructure and quality of life in PD patients using diffusion MRI connectometry. It was demonstrated that higher PDQ39 scores in PD patients are significantly correlated with higher QA values of the posterior limb of the internal capsule (PLIC), while controlling for age, gender, depression, anxiety, cognitive disturbances, side of the motor symptoms dominancy, duration and severity of the disease and the treatment dosages.

Internal capsule is an important subcortical structure where a high concentration of motor and sensory fibers project in a vertical manner to and from cortical areas. Besides the well-known corticospinal tract, PLIC encompasses the thalamic radiation relaying somatosensory signals to cortical levels of interoceptive processing networks [18], as well as corticofugal fibers. Structural disruption of the PLIC is implicated in executive dysfunction, attention deficit, visuospatial deficit, memory loss and cognitive impairment [10]. Disruption of PLIC is also observed in mood disturbances associated with differential emotional stimuli interpretation such as anxiety, depression and apathy, top listed in neuropsychiatric disturbances contributing to lower QoL in PD [19].

There exists high-level evidence for anxiety and depression as prodromal markers for PD. Meanwhile, hardships of measurement, the low positive likelihood of depression and uncertain lead time prior to initiation of PD discourage using

depression and anxiety as prodromal PD markers [20]. Anxiety, as an entity and apart from other mood disorders such as depression and apathy, has proved the strongest indicator of poor QoL, in cognitively intact PD patients [21]. In an exploratory track-based spatial statistics study, Liao et al. demonstrated significantly reduced FA in the right posterior limb of the internal capsule in adolescent patients suffering general anxiety disorder compared to matched controls [22]. Kim and his colleagues have shown that integrity of the optic radiations emerging from the posterior thalamus passing through the posterior limb and the retrolenticular part of the internal capsule is significantly correlated with the presence and severity of anxiety sensation in PD patients [23]. Moreover, gray matter alterations occur in consort to the white matter disruptions, where Tinaz and colleagues [24] well discussed cortical atrophy in the orbitofrontal, ventrolateral prefrontal and occipitoparietal cortices and striatal volume loss in MRI of early PD patients with regard to anxiety [24]. Disruptions of the described somatosensory loop from subcortical pathways that regulate the external sensory information before they reach the cortex, including predominant sensory pathway in the PLIC, may evolve into psychomotor and psychiatric manifestations.

The pallidomesencephalic pathway, partly crossing the PLIC, is the major neural circuit of goal-directed locomotor behavior. These fibers originate from the internal globus pallidus and project onto the pedunculopontine nucleus of the midbrain and are directly implicated in loss of goal orientation and apathy in striatal strokes [25]. Apathy, defined as a reduction in interest for aimed motivations, is the core mood disturbance in PD, with a relatively high predictive value in upcoming severe executive and motor impairment. Apathy is, therefore, a predictive marker of poor QoL in PD patients [26]. Post-stroke mood symptoms are described following PLIC disruptions in the literature. In a prospective study, Starkstein and colleagues revealed a strong association between apathy in post-stroke patients and lesion in the PLIC while controlling the effect of minor and major depression. Apathetic patients in this study showed higher cognitive and physical impairments in comparison with patients without apathy [27]. Cognitive dysfunction is a comorbid feature of apathy, and the emergence of apathy in PD patients strongly predicts upcoming dementia [28]. Cognitive deterioration in advanced PD might reflect disruption of frontal cortical projections, penetrating the internal capsule to reach the subcortical regions [29]. This is in line with decreased FA seen in the internal capsule with the implication of executive dysfunction and the attention domains of cognition in PD patients [10].

Several studies have explored neural pathways in depressed PD patients. Cortico-limbic network, projections of the left amygdala to the bilateral mediodorsal thalamus, and prefrontal and posterior cingulate cortices are among the circuits shown to be related to depression and its severity in PD [29]. Similar to the other described mood disorders, depression shares many structural pathologies with other psychomotor features of neurodegenerative disorders. Frontal–striatal–thalamic and limbic–thalamic–frontal loops are shown to underlie the neurobiology of depression [30]. PLIC plays a role in the regulation of emotion, cognition and behavior encompassing parts of the fronto-limbic-striatal circuit and is implicated in major depression or post-stroke depression [31]. An increased fractional anisotropy (FA) in bilateral posterior limbs of the internal capsule in patients with early-onset major depressive disorder further supports this fact [32]. Apathy and depression have a bimodal pattern of emergence in PD patients. Thus, prodromal clinical signs of PD might point to depressive or apathetic symptoms present at the time or prior to the diagnosis of PD. These early symptoms might herald the initiation of PD by years and subside upon initiation of dopaminergic therapy and finally might reemerge later in the course of the disease [33]. Results of the mentioned studies thereby shed light over neural disruptions associated with prodromal signs rather than late ones.

Finally, PLIC plays a pivotal role in movement regulation with pyramidal and extrapyramidal motor pathways passing through [34]. Damage to the PLIC as a white matter tract comprising corticofugal fibers might mirror early disruptions in motor function and anticipate a more severe motor decline in later PD stages, as it has been linked to poor motor outcomes in PD or other movement disorders [35, 36].

Besides minor clinical signs, PD patients in this study, except one, did not hit the cutoff point for the diagnosis of anxiety or depression as measured by HADS score, nor did they have signs of severe motor impairment by the part three UPDRS score. Mild cognitive disturbances, but not any evidence of dementia, were demonstrated in these patients.

Diffusion MRI connectometry is a novel approach to investigate connectivity patterns of fiber bundles. This method empowers the analysis by using the notion of "local connectomes" and probing only the significantly associated fiber bundle to the study variable instead of pre-allocating regions or tracks unavoidably encompassing unrelated branches [15]. Furthermore, connectometry measures the density of water diffusion for any given direction of a voxel, which represents the "local connectome fingerprint" of each individual [37], reflecting its higher sensitivity and specificity than conventional diffusivity indices [15]. Association of PLIC with poor QoL in this group of PD patients may, therefore, shed light on signature tract disruptions as possible biomarkers to predict exacerbation of psychomotor and cognitive symptoms later in the course of the disease.

A limited number of patients and slight deviation toward patients with advanced motor impairments—11 patients with H and Y stage 2 or above—prevents extrapolation

of these results to early Parkinson's disease. Longitudinal studies investigating a larger number of prodromal or early PD patients with other anatomical and functional imaging techniques are needed to explore whether these results are reproducible and further explain our findings in related to motor and non-motor symptoms of PD.

Conclusions

White matter microstructural disruption of the posterior limb of the internal capsule in correlation with quality of life impairment in PD patients is in line with previous studies investigating major determinants of poor quality of life in these patients; anxiety, depression, apathy and motor impairment. Results in our sample of PD patients with relatively mild motor impairment and no apparent sign of depression/anxiety identify a unique and inexplicable association of the PLIC to the QoL in PD patients.

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Author contributions FGS and MHA contributed to the conception and design of the study; MHA, FGS, MMZ and MH contributed to data collection and analysis. FGS and MHA contributed to writing the manuscript.

Compliance with ethical standards

Ethics approval and consent to participate All procedures performed here including human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Availability of data and material Data used in this study is accessible via: https://www.nitrc.org/ir/data/projects/parktdi.

Conflict of interests The authors declare that they have no competing interests.

Informed consent Informed consent was obtained from all individual participants included in the study.

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