DTI for Parkinson's Disease: A Protocol for Systematic Review and Meta-Analysis

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Protocol

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Abstract

**Background:** There is no robust biological marker for the diagnosis of Parkinson's disease, and most of them are diagnosed until motor symptoms develop, which may affect the early intervention and prognosis.

**Objective:** To evaluate the diagnostic value of different parameter values of DTI in PD.

**Methods and analysis:** We will systematically search the cochrane, pubmed, and embase databases, but we only consider observational studies and English studies. The main outcomes are DTI parameters, including FA, MDC, and ADC. We will evaluate the quality of the included studies through the NOS scale, and the data synthesis will be analyzed by revman5.3.

**Discussion:** This systematic review will integrate all relevant DTI observation results on PD imaging, and evaluate whether DTI can be used as a biological marker for the diagnosis of PD. The review results will provide a useful reference for the diagnosis of PD.

**Systematic review registration:** The protocol has been registered at the International Platform of Registered Systematic Review and Meta-analysis Protocols(INPLASY202070098).

**Background**

Parkinson's disease (PD) is a neurodegenerative disease, common in elderly people, insidious onset and slow progress. Its characteristic pathological changes are reduction of substantia nigra dopaminergic neurons and the formation of Lewy bodies, leads to a decrease in dopamine transmitters in the striatum area. Resulting in clinical symptoms such as bradykinesia, resting tremor, muscle rigidity, and postural instability [1], accompanied by various non-motor symptoms [2], Such as olfactory dysfunction [3, 4], cognitive and emotional disorders, sleep disorders, abnormal stools, gastrointestinal dysfunction [5, 6], pain and sensory disturbances [7, 8, 9], etc. Seriously affect the patient's daily life, reduce life quality and loss work ability.

PD is the second largest neurodegenerative disease after Alzheimer's disease [10], about 1.2 million people in Europe suffer from PD[11], PD usually develops at the age of 65 years and older age, and overall incidence rate of 17 per 100,000 persons per year has been reported [12]. The incidence of PD has increased by more than double over the past 26 years, from 2.5 million patients in 1990 to 6.1 million patients in 2016 [13], the prevalence of PD will double from 6.9 million in 2015 to 14.2 million in 2040 [14]. Affected by the aging of the population, the PD population continues to increase, which will bring huge challenges in medical and socio-economic care [15].

PD is generally considered to be the result of the profound loss of dopamine (DA) neurons in the substantia nigra compacta (SNC) reaching the putamen [16]. Neurons in this area and other brain areas
develop abnormal intracellular deposits known as Lewy bodies that contain aggregated α-synuclein [17], and motor symptoms associated with PD have been primarily attributed to this process[18].

The diagnosis of PD depends primarily on clinical signs and symptoms [19], although non-motor manifestations including depression, sleep problems and anosmia, typically begin years earlier, it is not diagnosed until the onset of motor symptoms [20]. In this context, reliable early prediction of disease would be essential for appropriate interventions and prognosis. Unfortunately, reliable biomarkers are still lacking. Diffuse MRI has been used to investigate the brain microstructural damage in PD patients, and it could predict the changes in bradykinesia and cognitive status over one year [21, 22]. A recent study have shown that DTI in early PD in many areas has a significant but subtle changes, such as the motor, premotor, and supplementary motor cortices, corpus callosum, and SN[23, 24, 25]. Previous studies that utilized DTI to evaluate the WM of PD patients with NCPs reported conflicting observations, such as lower fractional anisotropy (FA) and higher mean diffusivity (MDC)[26, 27, 28, 29], so we will carry out a systematic analysis to explore the diagnostic value of DTI for PD.

Methods

Protocol and registration

This systematic review protocol is being reported in accordance with the reporting guidance provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) criteria (see Additional file 1) [30]. The review protocol has been registered within the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY)—registration number INPLASY202070098.

Objective: To evaluate the diagnostic role of DTI in Parkinson's disease by systematically analyzing the values of FA, MDC, and ADC in different studies.

Patient participation: The protocol is a research that draws comprehensive conclusions based on the results of multiple clinical studies, so there is no patient participation.

Inclusion and exclusion criteria: 1. primary Parkinson's disease 2. observational study (cross-sectional, cohort and case–control studies (with a sample of at least 30)); 3. The study should use DTI technology to screen PD patients and healthy controls; 4. The study should have detailed information about FA and MDC or ADC Data (MDC and ADC are not absolutely necessary).

Exclusion criteria: Parkinson's disease, Parkinson's Overlay syndrome, case reports, submissions, qualitative studies, letters to the editor, comments, meeting minutes, reviews and meta-analyses.

Types of outcome measures

The primary outcome is fractional anisotropy (FA), secondary outcomes are mean diffusivity coefficient (MDC) and apparent diffusion coefficient (ADC).
Search methods for identification of studies

We will primarily search Cochrane, PubMed and EMBASE, studies regardless of publication date, but only English language will be included. Using the keywords “Parkinson's Disease”, “Diffusion tensor imaging”, “Fractional anisotropy (FA)”, “Apparent diffusion coefficient (ADC)”, “Mean diffusion coefficient (MDC)” (see Additional file 2 for PubMed’s search strategy).

Data extraction and management

Studies imported into EndNote V.X9 (Thompson Reuters, New York, New York, USA) after removing duplicates will be independently reviewed by two authors (XY, YL and ML) based on the exclusion and inclusion criteria. All data will be extracted and recorded independently by two reviewers (XY and YL) in an electronic database created in Microsoft Office Excel V.2010. The information including the first author’s name, date of publication, type of study (cross-sectional, cohort / case-control studies), sample size, diagnostic criteria, mean and SD for FA, MDC, ADC score, 95% CI, and other relevant data for quality evaluation and risk of bias assessment. Any unclear information from an included article will be clarified after contacting the corresponding authors and differences will be resolved by discussion with a third author.

Assessment of risk of bias in included studies

The Newcastle-Ottawa Scale will be used to evaluate the quality of studies. This scale is a non-randomised controlled trial quality evaluation instrument with scores ranging from 0 to 9; scores of 0–4 and 5–9 mean low quality and high quality, respectively[31].

Data synthesis

The RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for data analysis. Both the $\chi^2$ test and I² statistics will be used for the assessment of heterogeneity, and a fixed effect model will be used if there is no obvious heterogeneity ($I^2<50\%$ and $p>0.1$), with a random effects model being used if significant heterogeneity is found to exist ($50\% <I^2<80\%$ or $p<0.01$). For continuous data, we will calculate the mean difference (MD), and 95% confidence intervals (CI) if outcome measure scales are the same. In the case of different outcome measure scales, we will calculate the standardized mean difference (SMD) and 95% CI. If more than 10 articles are included, publication bias will be analysed by visual inspection of funnel plots.

Subgroup analysis

Subgroup analysis may eventually be carried out according to type of study (cross-sectional / cohort / case report), if appropriate we will carried out subgroup analysis according to different areas of the brain.

Sensitivity analysis
If a meta-analysis is performed, a sensitivity analysis will be conducted, excluding studies from the analysis one by one. These will be performed to examine the potential influence of each study in the pooled estimates.

Confidence in cumulative evidence assessment

The review will evaluate the confidence of the body of cumulative evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [32] approach. We will assess the strength of evidence using five criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias. We will rate the overall level of certainty for each outcome as high, moderate, low, or very low. Results will be presented in tables for each primary outcome.

Discussion

This review will synthesize the parameter of DTI on PD’s imaging observations, summarize whether different parameter values are consistent in PD patients, and whether they can be used as biological markers for PD diagnosis and prediction. It will also help discover the gaps in existing studies, provide new directions for future research and find new biological markers for PD diagnosis.

Abbreviations

PD: Parkinson's disease

DTI: Diffusion tensor imaging

FA: Fractional anisotrop

ADC: Apparent diffusion coefficient

MDC: Mean diffusion coefficient

INPLASY: International Platform of Registered Systematic Review and Meta-analysis Protocols

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols;

GRADE: Grading of Recommendations Assessment, Development and Evaluation

Declarations

Acknowledgements

Not applicable.

Authors’ contributions
DY, XC, and ML designed the study. XY, ML, SJ, and YL drafted the manuscript, and DY and XC initiated the study design. XY and YL developed the search strategy. All authors contributed to the refinement of the study protocol, reviewed, and provided feedback on the manuscript and approved the final manuscript. DY and XC serve as the guarantor of the manuscript. The authors read and approved the final manuscript.

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**Availability of data and materials**

Not applicable.

**Ethics approval and consent to participate**

Systematic review—not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

All authors report no conflicts of interest.

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