Cognitive behavioural therapy for anxiety disorders in Parkinson's disease

Citation for published version (APA):

Mulders, A. E. P., Moonen, A. J. H., Dujardin, K., Kuijf, M. L., Duits, A., Flinois, B., Handels, R. L. H., Lopes, R., & Leentjens, A. F. G. (2018). Cognitive behavioural therapy for anxiety disorders in Parkinson's disease: Design of a randomised controlled trial to assess clinical effectiveness and changes in cerebral connectivity. *Journal of Psychosomatic Research*, 112, 32-39.
<https://doi.org/10.1016/j.jpsychores.2018.04.002>

Document status and date:

Published: 01/09/2018

DOI:

[10.1016/j.jpsychores.2018.04.002](https://doi.org/10.1016/j.jpsychores.2018.04.002)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Cognitive behavioural therapy for anxiety disorders in Parkinson's disease: Design of a randomised controlled trial to assess clinical effectiveness and changes in cerebral connectivity

A.E.P. Mulders^{a,1}, A.J.H. Moonen^{a,1}, K. Dujardin^{b,e}, M.L. Kuijff^c, A. Duits^a, B. Flinois^e, R.L.H. Handels^a, R. Lopes^{b,d}, A.F.G. Leentjens^{a,*}

^a Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, Maastricht, The Netherlands

^b Degenerative & Vascular Cognitive Disorders, University of Lille, Lille, France

^c Department of Neurology, Maastricht University Medical Centre, Maastricht, The Netherlands

^d Neuroimaging Department, CHU Lille, Lille, France

^e Neurology and Movement Disorders Department, CHU, Lille, France

ARTICLE INFO

Keywords:

Anxiety
Cognitive behavioural therapy
Design
Protocol
Randomised Controlled Trial
Parkinson's disease

ABSTRACT

Background: Anxiety disorders occur in up to 35% of patients with Parkinson's disease (PD) and have a negative effect on motor symptoms and quality of life. To date, no clinical trials specifically targeting anxiety in PD patients have been published.

Objective: To describe the rationale and methodology of a randomised controlled trial (RCT) that aims to study the clinical effectiveness, alterations in brain circuitry, and cost-effectiveness of cognitive behavioural therapy (CBT) for anxiety in PD.

Methods: This study is a prospective, two-centre RCT in which sixty PD patients with anxiety will be randomised to CBT treatment and clinical monitoring (intervention group) or to clinical monitoring only (control group). The CBT module used in this study was specifically developed to address symptoms of anxiety in PD patients. Participants will undergo standardised clinical, cognitive and behavioural assessment at baseline and at 2 follow-up measurements, as well as resting-state fMRI and DTI scanning before and after the intervention. The primary outcome measure is changes in severity of anxiety symptoms. Secondary outcome measures involve long-term changes in anxiety symptoms, changes in functional and structural connectivity between limbic and frontal cortices, and cost-effectiveness of the treatment. The study is registered at the [ClinicalTrials.gov](https://clinicaltrials.gov) database under registration number NCT02648737.

Conclusion: This study is the first that evaluates both the clinical effectiveness, cost-effectiveness, as well as the biological impact of CBT for anxiety in PD patients that, if proven effective, will hopefully contribute to a better and evidence-based approach for these non-motor symptoms.

1. Background

Anxiety disorders occur in up to 35% of patients with Parkinson's disease (PD) and have a negative effect on several motor symptoms including tremor, gait, dyskinesias, freezing, on/off fluctuations, and on

quality of life in general [1–3]. However, anxiety disorders in PD patients are often not recognized and consequently not treated [4, 5].

Neurobiological studies of affective processing have demonstrated the involvement of an extensive frontal-subcortical limbic network [6], which mainly depends on intact dopaminergic neurotransmission [7].

List of abbreviations: Rs-(f)MRI, Resting-state – functional Magnetic Resonance Imaging; CBT, Cognitive Behavioural Therapy; DTI, Diffusion Tensor Imaging; GAD, Generalized Anxiety Disorder; GCP, Good Clinical Practice; HAMD, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; HRQoL, Health-Related Quality of Life; ICD, Impulse Control Disorder; ICECAP-O, Icepop Capability measure for older people; LARS, Lille Apathy Rating Scale; MDD, Major Depressive Disorder; MDS-UPDRS, Movement Disorder Society – Unified Parkinson's disease Rating Scale; METC, Medical research ethics committee (MREC) (in Dutch: Medisch Ethische Toetsing Commissie (METC)); MINI, Mini International Neuropsychiatric Inventory; MoCa, Montreal Cognitive Assessment; MRI, Magnetic Resonance Imaging; PAS, Parkinson Anxiety Scale; PD, Parkinson's disease; PDSS, Parkinson's Disease Sleep Scale; PDQ, Parkinson's Disease Questionnaire; RCT, Randomised Controlled Trial; OVX, Recognize, Evaluate, Alternative thoughts, Coping, Thought stopping; SAD, Social Anxiety Disorder; TCQ, Thought Control Questionnaire; WMO, Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen); ZBI, Zarit Burden Interview

* Corresponding author at: Department of Psychiatry, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.

E-mail address: a.leentjens@maastrichtuniversity.nl (A.F.G. Leentjens).

¹ These authors are dual first author.

<https://doi.org/10.1016/j.jpsychores.2018.04.002>

Received 9 February 2018; Received in revised form 3 April 2018; Accepted 5 April 2018
0022-3999/ © 2018 Published by Elsevier Inc.

PD is primarily characterized by the progressive degeneration of dopaminergic systems and anxiety is believed to originate, at least in part, from the underlying pathological process of PD [8, 9]. Indeed, anxiety often appears prior to the appearance or recognition of motor symptoms [9], and even non-anxious PD patients already show altered emotion regulation compared to healthy adults [10]. However, the fact that anxiety symptoms do not reliably improve by L-DOPA replacement therapy suggests that other mechanisms besides dopamine deficiency are involved in the aetiology of anxiety symptoms in PD [11, 12], such as the noradrenaline and serotonin systems. Both these systems are implicated in affective processes and known to be substantially affected in the PD process [13–15]. On the other hand, both fears and social implications associated with motor symptoms of PD can provoke or exacerbate anxiety symptoms in PD [16]. Given this complex interaction between physiological and psychological factors and the diversity of the disease, psychotherapeutic treatment of anxiety requires adaptations that are tailored to the specific needs of PD patients [17, 18].

Cognitive behavioural therapy (CBT) is considered the gold standard in psychotherapeutic treatment of anxiety in the general population [19, 20]. CBT is defined as ‘An amalgam of behavioural and cognitive problem-based interventions guided by principles of applied science. The behavioural interventions aim to decrease maladaptive behaviours and increase adaptive ones by modifying their antecedents and consequences and by behavioural practices that result in new learning. The cognitive interventions aim to modify maladaptive cognitions, self-statements, or beliefs’ [21, 22]. In PD, CBT has been proven to be an effective treatment for depression and impulse control disorders (ICD) [23–25]. PD patients who received CBT for depression in a randomised controlled trial reported not only a reduction in depression and comorbid anxiety, but also a beneficial influence on coping and quality of life, compared to PD patients who only received clinical monitoring [23]. To date, no clinical trials specifically targeting anxiety in PD patients have been published. However, there have been several pilot studies for CBT and internet-based CBT in PD patients with mixed depressive and anxiety symptoms or mild to moderate depression or anxiety symptoms, respectively [25–27]. Both studies reported significant reductions in depressive symptoms, but not in anxiety symptoms, which may have been due to small sample sizes and lack of power [26, 27]. Another uncontrolled study investigating the use of a tailored CBT module for anxiety in 12 PD patients showed that CBT can reduce anxiety levels with persisting benefits at 3 and 6 month follow-up [28]. Although the previous studies are limited by their small sample size, and/or uncontrolled nature, they warrant further exploration of CBT for anxiety in PD patients [25].

In addition to clinical effectiveness, several imaging studies have demonstrated that psychotherapeutic interventions, including CBT, can modify neural correlates of affective processing [29–32]. CBT-induced increases in both functional [30, 33] and structural connectivity [34] between limbic and frontal cortices have been demonstrated in patients with social anxiety disorder (SAD), one of the most common anxiety disorders in PD [1].

Here, we describe the design of the study *Cognitive Behavioural Therapy for Anxiety Disorders in Parkinson's Disease*, a two-centre randomised controlled trial (RCT) that aims to examine the clinical effectiveness, cost-effectiveness as well as changes in cerebral connectivity following CBT for anxiety in PD.

The main research questions are:

- 1) Is CBT treatment of anxiety in PD patients more effective than clinical monitoring in terms of change in anxiety levels, quality of life and well-being?
- 2) Is CBT treatment cost-effective, compared to clinical monitoring?
- 3) Does successful CBT treatment lead to changes in functional and structural brain connectivity between the frontal and prefrontal cortex and limbic structures such as the amygdala, cingulate gyrus and hippocampus?

2. Methods

2.1. Study design

This study is a prospective, open RCT with PD patients recruited in two centres in Europe (Maastricht University Medical Centre, Maastricht, the Netherlands and Lille University Hospital, Lille, France). Sixty PD patients with anxiety and their caregivers (optional) will be randomised to CBT and clinical monitoring (intervention group) or clinical monitoring only (control group). A randomised block design with 6 blocks of 10 participants will be applied. All participants will undergo standardised clinical, cognitive and behavioural assessment at baseline ($t = 0$), at the end of the intervention ($t = 1$) as well as 3 months after the intervention ($t = 2$). Moreover, participants randomised to the intervention group will receive an additional full assessment at 6 month follow-up ($t = 3$). At baseline ($t = 0$) and at the end of the intervention ($t = 1$) participants will undergo Magnetic Resonance Imaging (MRI) scanning, except in case of contraindications for undergoing MRI (e.g., deep brain stimulation, claustrophobia). The duration of the intervention will be approximately 10–12 weeks. Participants randomised to the control group will be given the option to receive CBT after the 3 month follow-up assessment. This will be done as clinical care and not be part of the study.

2.2. Study population

2.2.1. In- and exclusion criteria

Sixty patients with idiopathic PD according to the Queens Square Brain Bank criteria [35] and their caregivers (optional) will be prospectively enrolled. In- and exclusion criteria are listed in Table 1.

In order to achieve a representative study sample, participants will be included irrespective of their disease stage or their current anti-parkinsonian medication, provided a stable situation is present. In case a caregiver is involved, the caregiver should have daily contact with the

Table 1
In- and exclusion criteria.

Inclusion criteria	<ul style="list-style-type: none"> - Idiopathic PD according to the Queens Square Brain Bank diagnostic criteria [35] - Presence of clinically relevant anxiety symptoms, as operationalized by a Parkinson Anxiety Scale (PAS) [3] persistent score > 9 and/or PAS avoidance score > 3 - Using a stable dose of levodopa or other antiparkinsonian medication for at least 1 month - No other current psychological treatment for anxiety; psychopharmacotherapy is allowed if a stable dose is used at least 2 months prior to participation and the patient still meets inclusion criteria. During the trial the dosage should not be changed. Medication use and mental health care will be tracked throughout the study. - Age between 35 and 80 years old
Exclusion criteria	<ul style="list-style-type: none"> - Parkinsonian syndromes or neurodegenerative disorders other than PD - Dementia or severe cognitive decline, operationalized as a Montreal Cognitive Assessment (MoCa) [36] score < 24 - Major depressive disorder (MDD) as defined by the DSM 5 criteria [37] - Abuse of alcohol, drugs or benzodiazepines

PD = Parkinson's disease, PAS = Parkinson Anxiety Scale, MoCa = Montreal Cognitive Assessment, MDD = Major Depressive Disorder; DSM 5 = Diagnostic and Statistical Manual of mental disorders, 5th edition.

Fig. 1. Study flow chart.

study participant and have no serious medical or psychiatric conditions.

2.2.2. Recruitment

Patients will be recruited from the Movement Disorders clinics in the two participating centres. The treating neurologists will evaluate initial eligibility of the patients. Moreover, flyers with general information about the study and contact details of the researchers will be distributed in Movement Disorders clinics in other hospitals in the region and at several Parkinson support groups. After patients have been informed about the study and agreed to participate, a baseline assessment will take place, in which participants will be further screened to evaluate whether they meet all in- and exclusion criteria. A flowchart of the inclusion procedure is presented in Fig. 1.

2.2.3. Randomisation, blinding and treatment allocation

After informed consent is obtained and the baseline measurement is performed, participants will be randomly assigned to one of two groups: the intervention group or control group. Randomisation will be performed over both centres together in order to compensate for between-centre differences in population and involves a randomised block design with 6 blocks of 10 participants. Randomisation is performed by the coordinating investigator using the website randomization.com. Assessments will be performed by a psychologist who is not involved with the treatment and blinded for the intervention. The participants will be instructed not to comment on the intervention they received.

2.3. Intervention

2.3.1. CBT Treatment

Participants randomised to the intervention group will receive CBT and clinical monitoring. The CBT consists of 10 weekly individual

sessions of 60–75 min, tailored to the preferences and needs of each patient. In each session, a registered psychologist will address specified aspects of (coping with) anxiety and related concerns with a specific focus on behaviour and thoughts associated with anxiety. Any other neuropsychiatric symptoms that are present, such as depressive symptoms or apathy, will be addressed as well, although the main focus will be on anxiety.

The content of the CBT module was based on existing literature of CBT treatment of GAD and SAD and on published existing modules for CBT in anxiety and depression. Published existing modules include amongst others: psycho-education and awareness, motivational interviewing, behaviour activation, thought monitoring and restructuring, exposure, relaxation techniques, coping and problem solving skills, exercise, and sleep hygiene [23, 26, 38–40]. We adjusted these existing modules to better serve the specific needs, concerns, and circumstances of PD patients with anxiety. The resulting module was subsequently presented to small groups of PD patients and their caregivers (in ‘focus-groups’), as well as to representatives of the scientific section of the Dutch Parkinson Patient Foundation (Parkinsonpatiëntenvereniging) and to PD experts in both countries, in order to gather patient and professional feedback, respectively. The final CBT module, which consists of a treatment manual for therapists and a workbook for patients, was originally written in English and later translated to French and Dutch.

All CBT sessions have a similar overall structure. Each session will start with setting the agenda for that particular session, after which the home assignments will be reviewed (in all but the first session). Then the new topic will be introduced and exercises related to the new topic will be practiced. Subsequently, the new home assignments for the upcoming week will be discussed as well as possible barriers or concerns for completing the new tasks and/or tasks from previous sessions.

Table 2
Overview of the cognitive behavioural therapy sessions^a.

Session	
1	Introduction and psycho-education about anxiety
2	Monitoring anxiety
3	Management of anxiety: introduction and the importance of self-management
4	Management of anxiety: diaphragmatic breathing and mindful awareness
5	Changing thoughts
6	Management of anxiety: progressive muscle relaxation and imagery
7	Problem solving
8	Changing anxiety behaviour
9	Review session
10	Self-management plan and closure
	Booster session ^b

^a A detailed treatment protocol and therapist manual have been developed. Moreover, participants will receive a workbook with handouts and worksheets.

^b Each patient will receive a booster session 1.5 month following the final treatment session. The aim of the booster session is the monitor the patient's progress, to provide clinical assistance if necessary, and to encourage continued use of coping skills.

The first and last session will have some additional components related to the introduction and termination of the therapy, respectively. An overview of the sessions is provided in Table 2.

Home assignments are an important part of CBT. In order to override dysfunctional patterns that promote anxiety and achieve change, repeated practice in daily life is necessary. Patients will receive a workbook during the first session. Each week the workbook will be supplemented with handouts and worksheets that correspond to the current topic. Even though patients with severe cognitive impairment (MoCa score < 24) will be excluded from participation, cognitive problems are common in PD patients [41], and probably a substantial proportion of the participants will experience cognitive problems to some degree. These usually relate to deficits in attention and executive function, although memory deficits and visuospatial functions are also frequent [42]. Therefore, all sessions and accompanying handouts and worksheets have a clear structure and the psychologist will always check whether the information and assignments are clear to the participant and whether there are any barriers or concerns for completing the home assignments. If necessary, the psychologists will problem-solve any issues. The therapy sessions will take place at the outpatients of the Movement Disorders Clinics of the two participating centres. In case medical or other reasons make it difficult for the patient to visit the clinics, the treating therapist can visit the participants at home.

2.3.2. Clinical monitoring

Clinical monitoring has been recommended as a control situation when exploring the clinical effectiveness of a new or adjusted psychotherapeutic intervention [43]. All patients will receive clinical monitoring; those not randomised to the intervention group will receive clinical monitoring only. Clinical monitoring involves a phone call by an independent psychologist one month following the baseline assessment to inquire about current anxiety symptoms. Moreover, participants will receive general education material on coping with anxiety, derived from the Dutch/French psychiatric association webpages. Participants in the control group will remain under the care of their personal physicians, who will also monitor their medical and psychiatric status. During the intervention and follow-up period, all participants are asked to give notice when starting with any other form of psychotherapeutic interventions or psychopharmacotherapy for their anxiety. Those patients randomised to the control condition of clinical monitoring only, will be given the opportunity to receive CBT after the 3 month follow-up assessment. This treatment will be part of regular patient care and is covered by the patient's health insurance. Hence, it will not be part of the study.

2.4. Outcome measures

The primary outcome for studying the clinical effectiveness of the CBT treatment is the difference between the intervention and control group in anxiety score changes between baseline ($t = 0$) and post-treatment ($t = 1$) as measured with the Hamilton Anxiety Rating Scale (HARS) [44]. Secondary outcome measures involve long-term clinical effectiveness, which will be assessed similarly, but then using the 3-month ($t = 2$) and 6-month follow-up anxiety scores ($t = 3$, intervention group only). Moreover, changes in functional and structural cerebral connectivity between the frontal and prefrontal cortex and limbic structures such as the amygdala, cingulate gyrus and hippocampus before and after the intervention will be studied, as measured with resting-state MRI (rs-fMRI) and Diffusion Tensor Imaging (DTI). The difference in effectiveness between CBT and clinical monitoring in terms of disease-specific quality of life, generic health-related quality of life and well-being will be assessed using the Parkinson's Disease Questionnaire-8 (PDQ-8) [45], the EQ-5D-5L [46] and Icepop Capability measure for older people (ICECAP-O) [47], respectively. Lastly, care resource utilization will be obtained by an adapted version of the Resource Utilisation in Dementia [48] questionnaire. Other study parameters involve changes in comorbid psychiatric symptoms, motor symptoms, sleep disturbance, coping, as well as caregiver burden. An overview of all questionnaires is provided in Table 3.

The demographic and disease-related variables that will be collected during baseline include sex, date of birth, years of formal education, year of PD onset, side of onset, year of PD diagnosis, details on Parkinson medication (i.e., drug name, dose, frequency, levodopa equivalence) and other medication including psychopharmacology, alcohol use, medical history (i.e., cerebrovascular diseases, psychiatric disorders) and family medical history (i.e., PD, other neurological disorders, dementia, psychiatric disorders). Any change in Parkinson medication will be tracked during the whole study period.

2.4.1. MRI scan

MRI will be acquired using a 3 T whole-body scanner (Achieva TX,

Table 3

Questionnaires administered at $t = 0$, $t = 1$, $t = 2$ and $t = 3$ ^a.

	Instrument
Anxiety	Hamilton Anxiety Rating Scale [44] Parkinson Anxiety Scale [3] Liebowitz Social Anxiety Scale [49] Mini International Neuropsychiatric Inventory section G and O [50]
Global cognitive status	Montreal Cognitive Assessment [36]
Depression	Hamilton Depression Rating Scale [51]
Apathy	Lille Apathy Rating Scale [52]
Health-related quality of life	Parkinson's Disease Questionnaire [45] EQ-5D-5L ^b [46]
Well-being	ICECAP-O ^b [47]
Sleep and nocturnal disturbances	Parkinson's Disease Sleep Scale 2 [53]
Coping strategies	Brief Cope scale [54], Thought Control Questionnaire [55]
Health-related costs, patient and family related costs	Adapted version of the Resource Utilisation in Dementia ^c [48]
Motor symptom severity	MDS-UPDRS [56]
PD disease stage	Hoehn & Yahr staging [56]
Caregiver burden	Zarit burden interview [57]

EQ-5D-5L = Euroqol quality of life scale - 5 dimensions - 5 levels, ICECAP-O = Icepop Capability measure for older people, MDS-UPDRS = Movement Disorder Society - Unified Parkinson's Disease Rating Scale.

^a $t = 0$: baseline measurement, $t = 1$: post-intervention measurement, $t = 2$: 3-month follow up, $t = 3$: 6-month follow-up for intervention group only.

^b Will be administered to both participants and caregivers.

^c In this version the formulation of items has been adjusted to Parkinson's disease instead of dementia and two questions regarding use of speech therapy and home aids were added.

Table 4
Brain MRI scanning protocol.

Sequences	3D T1-weighted MP-RAGE	Resting-state fMRI	Diffusion tensor imaging (DTI)	B0 Field map
Field of view (mm)	240 × 240	192 × 192	256 × 256	256 × 256
Matrix	256 × 256	64 × 64	128 × 128	128 × 128
Slices	231	40	66	66
Inter-slice gap (mm)	0	0	0	0
Voxel (mm ³)	0.65 × 0.65 × 0.65	3x3x3	2x2x2	2x2x2
TR/TE (ms)	12/3.3	2400/30	12,000/56	660/4
Flip angle	9°	90°	90°	80°
B value (ms/mm ²)		1000		
Nr of directions		32		

MP RAGE = magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo, fMRI = functional Magnetic Resonance Imaging.

Philips Healthcare, Best, the Netherlands) using a 32-channel head coil for signal reception. The MRI protocol includes an anatomical scan, rs-fMRI, DTI and B0 field map. The total MRI scan will take about 45 min. Details of the brain MRI protocol can be found in Table 4. Imaging will be performed at the Department of Radiology of Maastricht University Medical Centre and at the Department of Radiology of Lille University Hospital.

2.4.2. Data collection and management

All personnel involved in the data collection will review the standard operating procedures (SOP) and manuals. Assessors are certified in Good Clinical Practice (GCP) and in performing the MDS-UPDRS part III [56]. Data will be collected on paper forms and entered into a web-based data entry portal of which a back-up will be stored electronically on a daily basis. The data of all participants will be handled confidentially. A subject identification code list will be used to trace data to an individual subject. The coordinating investigator will provide all data of subjects with a number that is not based on the patient's initials and birth-date. The key to the code will be safeguarded by the coordinating investigator. All data will be stored for 15 years as required by law.

2.4.3. Power and sample size calculation

Power calculation was based on a standardised difference of 0.8 in HARS total score, with alpha set at 0.05 and power set at 0.80, and a predicted effect size of Cohen's *d* (0.95), based on a previous RCT with CBT in PD [23]. The standardised difference is defined as the ratio of the difference of interest to the standard deviation in scores of the sample. The difference of interest was set 3 points on the HARS (being the difference in average scores between patients without anxiety and with mild anxiety [2]; standard deviation was estimated at 5 [2, 23]. Based on these quantities, the required number of patients to be included is 40 (20 per group). Including 30 patients per group would allow for a drop-out of approximately 30%. This is a conservative sample size calculation since, based on the only published RCT of CBT in depression in PD [23], we expect that the effect size will be larger (> 5 points) and drop-out will be lower (< 10%). If subjects decide to leave the study prematurely they will not be replaced by new participants. The dropped out participants will be included in the analysis according to the intention-to-treat principle (ITT).

No sample size calculation was made for the MRI analyses specifically, since longitudinal data to determine the sensitivity of different DTI parameters to change over time are lacking. However, taking the

sample size of published studies in this area as reference [32, 34, 58, 59], we expect to be overpowered for these analyses using the same sample size as for the analysis of clinical efficacy.

2.5. Statistical analyses

Unless indicated otherwise, analysis will be performed using IBM SPSS statistics 24.0, Stata 13, or more recent versions if available. Significance level of 0.05 will be used. The numerical variables will be described as means, median, standard deviations and ranges. Categorical variables will be described as frequencies and percentages. Data analyses of primary and secondary outcomes will be conducted using relevant univariate, multivariate and multilevel techniques. For the primary study parameter, between-group comparisons will be conducted on post-treatment data and 3 month follow-up data in order to compare within-subject changes in anxiety scores (HARS) relative to baseline between the intervention and control group. This will be done using separate repeated measures Analysis of Covariance (rm-ANCOVA) for each of the two outcomes. Covariates include the use of benzodiazepines and antidepressants, Parkinson medication, which will be converted into levodopa equivalents using the algorithm of Tomlinson et al. [60], as well as significant differences in other relevant parameters. For the secondary parameters, between-group comparisons will be likewise conducted on post-treatment data and 3 month follow-up data to assess differences in changes relative to baseline between the intervention- and control group. To compare changes in anxiety scores and the secondary parameters between baseline and 6 month follow-up in the intervention group, within-subject comparisons will be performed.

For MRI scan analyses, between-group analyses using paired-sample and two-sample *t*-tests will be conducted to calculate differences in changes in cerebral connectivity pre- and post-intervention. Functional connectivity measures and graph topology indices will be extracted from rs-fMRI data [61]. Diffusion metrics (fractional anisotropy, radial and axial diffusivity) and structural connectivity computed from DTI data will be also used as descriptive variables in the statistical comparisons [62].

The economic evaluation will be performed following the Dutch guideline for economic evaluations in healthcare. The incremental cost-effectiveness ratio (ICER) will be calculated using standard unit price based costs in combination with the adapted RUD and EQ-5D-5 L utility based QALYs. An ITT analysis, a 3-month time horizon and a societal perspective will be adopted. A bootstrap analysis will be used to reflect the uncertainty in this ICER.

3. Drop-outs, missing values and adverse events

Participants can leave the study at any time for any reason or no reason at all if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. If subjects decide to leave the study prematurely they will not be replaced by new participants. The dropped out participants will be included in the analysis according to the ITT. For the ITT analyses, missing values on the primary outcome will be imputed using multiple imputations. For this, ten imputed datasets will be generated using multivariate multiple imputation by chained equations (MICE) [63] with demographic, clinical and baseline values of the primary outcome as predictors of the missing outcome values as well as variables predicting missingness (e.g. age, illness severity, morbidity). This technique yields better (i.e. less biased) estimates for outcome analyses in RCTs than single imputation or complete case analysis with covariate adjustment for missingness, especially if data are not-missing-at-random (i.e. missingness is related to unobserved variables) [64]. Subsequent analyses on imputed datasets will be performed in state 13 or higher [65].

Adverse events are defined as any undesirable experience occurring

to a subject during the study, which may or may not be related to the trial procedure or experimental intervention. All spontaneously reported study-related adverse events by the subject or observed by the investigator or his staff will be recorded according to section 10, [subsection 1](#) of the Dutch Research Involving Human Subjects Act (WMO). In case of a serious adverse event the sponsor, the Ethics committee and other relevant authorities such as the principal investigator and Toetsingonline will be notified immediately. A liability insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO) and France has been signed.

3.1. Medication adjustments

Preferably, Parkinson medication is kept stable during the study. Nonetheless, if medication changes are presumed necessary by the treating neurologist, they are allowed to do so. Any changes in medication will be tracked during the intervention period and follow-up moments. Psychopharmacotherapy is allowed if, by the start of the study, a stable dose is used at least 2 months prior to participation and the patient still meets the inclusion criteria.

3.2. Ethical approval, trial registration and monitoring

The study is carried out in compliance with the Helsinki Declaration. The local ethics committee of Maastricht University Medical Centre (July 2016) and Lille University Hospital (September 2016) have approved the study protocol. Written informed consents will be obtained from all participants. The study is registered at the [ClinicalTrials.gov](#) database under registration number NCT02648737, as well at FoxTrialFinder under ID number 004701. The study will be monitored in both centres by Clinical Trial Center Maastricht according to the international ICH-GCP guidelines.

4. Discussion

The overall aim of this open, two-centre RCT is to evaluate the clinical effectiveness of a CBT module for the treatment of anxiety in patients with PD and provide additional information on cost-effectiveness and the underlying changes in functional and structural brain connectivity that occur during this treatment. The treatment module is specifically designed to serve the needs, concerns, and circumstances of PD patients with anxiety and is based on the knowledge and experience of PD experts. CBT will, if proven effective, provide PD patients with behavioural and anxiety management techniques that may give lasting benefits on anxiety symptoms, well-being, quality of life, and possibly on motor symptoms. In this multinational RCT design patients are recruited in two countries at both outpatient clinics and informal meeting points for PD patients. This way of recruiting facilitates generalizability, as a broader range of patients can be reached instead of solely patients with more severe PD symptoms that come from the Movement Disorders Clinics.

While most studies investigating brain alterations following psychotherapeutic interventions use functional imaging methods, only few have examined structural brain correlates of CBT [30, 31, 34]. One study using structural and diffusion MRI measures observed reductions in parieto-occipital and prefrontal gray matter volumes, increases in fractional anisotropy in two anxiety-related white matter fiber tracts, as well as increases in structural connectivity in a frontolimbic network following a 10-week group-based CBT protocol for SAD patients [34]. Albeit in the absence of a control group and in a different patient population, this study provided insight into how the brain adapts to psychotherapeutic treatments. Our study is the first one that aims at assessing both functional and structural brain alterations following CBT in PD patients using different MRI modalities, such as rs-MRI and DTI, in the presence of a control group. Therefore, this study has an additional value to earlier CBT trials in PD patients [23, 26, 28], as it may

provide increased understanding of the underlying biological mechanisms of both anxiety and response to treatment in PD patients. Moreover, it can provide additional insight into whether CBT effects differ between different anxiety disorders and patient populations.

There are, however, also some limitations in this study design. Firstly, the follow-up duration of 3 months is relatively short to evaluate the long-term benefits of the CBT treatment. However, we agreed it was ethically not acceptable to deny the control group CBT treatment for a period longer than 6 months following the start of the intervention. Alternatively, we added an additional follow-up moment ($t = 3$) for patients randomised to the intervention group 6 months after the CBT treatment, which will give the possibility to study within-subject changes over time and provide insight into long-term benefits of the CBT treatment. Secondly, although there are no major risks associated with participation in the CBT intervention, participating in the study can be time-consuming and demanding for participants, especially considering the relatively high health care utilization in PD patients. Some PD patients might not be able to travel independently and have to rely on others, such as partners, family members, friends or other caregivers. These factors make inclusion and treatment adherence challenging. We discussed the feasibility of the number of sessions in multiple PD focus groups and none of the participants, neither in the Netherlands nor in France, perceived the frequency of the sessions as too burdensome or as a reason not to participate. In case medical or other practical reasons hinder participants to visit the outpatient clinic, the therapist can visit the participant at the site where the participant resides. We do not expect this to influence the treatment. Thirdly, with the involvement of different therapists, there is a risk of therapist effects, which refers to the tendency of different therapist to obtain differential symptomatic change in the patients [66]. However, all of our therapists have received appropriate training, and a detailed treatment protocol and therapist manual have been developed, which has shown to minimize therapist effects [67, 68]. Despite our efforts to standardise the intervention as much as possible, the involvement of a caregiver during the CBT intervention might likewise moderate treatment outcome as it is optional and not necessary for participation in the study. The purpose of their attendance is primarily to offer caregivers the opportunity to learn about the treatment in which the participant is involved and to explore strategies through which they can support the participant if necessary. This can vary from motivating the participant to do the home assignments up to assisting them to fill out the worksheets in case physical reasons make this difficult. The caregiver attendance is limited to three educational sessions.

In conclusion, this low risk intervention study has great relevance for clinical practice. It evaluates the clinical effectiveness of a CBT module for anxiety in PD and contributes to a better understanding of the underlying biological mechanisms of anxiety in PD. Inclusion started March 2017 and we aim to complete the study in 2019.

Competing interest statement

The authors have no competing interests to report.

Conflict of interest statement

The authors have no competing interests to report.

Acknowledgements

This project is funded by a grant of the Michael J. Fox Foundation for Parkinson's Research, a non-profit organization supporting Parkinson's research worldwide, grant ID 11169.

References

- [1] M.P. Broen, N.E. Narayan, M.L. Kuijff, N.N. Dissanayaka, A.F. Leentjens, Prevalence

- of anxiety in Parkinson's disease: a systematic review and meta-analysis, *Mov. Disord.* 31 (8) (2016) 1125–1133.
- [2] A.F.G. Leentjens, K. Dujardin, L. Marsh, I.H. Richard, S.E. Starkstein, P. Martinez-Martin, Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale, *Mov. Disord.* 26 (3) (2011) 407–415.
 - [3] A.F.G. Leentjens, K. Dujardin, G.M. Pontone, S.E. Starkstein, D. Weintraub, P. Martinez-Martin, The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale, *Mov. Disord.* 29 (8) (2014) 1035–1043.
 - [4] G.M. Pontone, J.R. Williams, K.E. Anderson, G. Chase, S.A. Goldstein, S. Grill, E.S. Hirsch, S. Lehmann, J.T. Little, R.L. Margolis, P.V. Rabins, H.D. Weiss, L. Marsh, Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease, *Mov. Disord.* 24 (9) (2009) 1333–1338.
 - [5] J.S. Reijnders, U. Ehrt, W.E. Weber, D. Aarsland, A.F.G. Leentjens, A systematic review of prevalence studies of depression in Parkinson's disease, *Mov. Disord.* 23 (2) (2008) 183–189 (quiz 313).
 - [6] M.L. Phillips, W.C. Drevets, S.K. Rauch, R. Lane, Neurobiology of emotion perception I: the neural basis of normal emotion perception, *Biol. Psychiatry* 54 (5) (2003) 504–514.
 - [7] A.J.H. Moonen, A. Wijers, K. Dujardin, A.F.G. Leentjens, Neurobiological correlates of emotional processing in Parkinson's disease: a systematic review of experimental studies, *J. Psychosom. Res.* 100 (2017) 65–76.
 - [8] G.M. Pontone, Anxiety in Parkinson's: a complex syndrome of non-dopaminergic and dopaminergic etiology, *Eur. J. Neurol.* 24 (4) (2017) 541–542.
 - [9] A. Djamasshidian, J.H. Friedman, Anxiety and depression in Parkinson's disease, *Curr. Treat. Options Neurol.* 16 (4) (2014) 285.
 - [10] A.J.H. Moonen, P.H. Weiss, M. Wiesing, R. Weidner, G.R. Fink, J. Reijnders, W.M. Weber, A.F.G. Leentjens, An fMRI study into emotional processing in Parkinson's disease: Does increased medial prefrontal activation compensate for striatal dysfunction? *PLoS One* 12 (5) (2017) e0177085.
 - [11] H.J. Kim, S.Y. Park, Y.J. Cho, K.S. Hong, J.Y. Cho, S.Y. Seo, D.H. Lee, B.S. Jeon, Nonmotor symptoms in de novo Parkinson disease before and after dopaminergic treatment, *J. Neurol. Sci.* 287 (1–2) (2009) 200–204.
 - [12] K.L. Eskow Jaunarajs, M. Angoa-Perez, D.M. Kuhn, C. Bishop, Potential mechanisms underlying anxiety and depression in Parkinson's disease: consequences of L-DOPA treatment, *Neurosci. Biobehav. Rev.* 35 (3) (2011) 556–564.
 - [13] A. Maillet, P. Krack, E. Lhommee, E. Metereau, H. Klinger, E. Favre, D. Le Bars, E. Schmitt, A. Bichon, P. Pelissier, V. Fraix, A. Castrioto, V. Sgambato-Faure, E. Broussolle, L. Tremblay, S. Thobois, The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease, *Brain* 139 (Pt 9) (2016) 2486–2502.
 - [14] P. Remy, M. Doder, A. Lees, N. Turjanski, D. Brooks, Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system, *Brain* 128 (Pt 6) (2005) 1314–1322.
 - [15] A.H.V. Schapira, K.R. Chaudhuri, P. Jenner, Non-motor features of Parkinson disease, *Nat. Rev. Neurosci.* 18 (8) (2017) 509.
 - [16] S. Coakeley, K.E. Martens, Q.J. Almeida, Management of anxiety and motor symptoms in Parkinson's disease, *Expert. Rev. Neurother.* 14 (8) (2014) 937–946.
 - [17] N.A. Pachana, S.J. Egan, K. Laidlaw, N. Dissanayaka, G.J. Byrne, S. Brockman, R. Marsh, S. Starkstein, Clinical issues in the treatment of anxiety and depression in older adults with Parkinson's disease, *Mov. Disord.* 28 (14) (2013) 1930–1934.
 - [18] N.N. Dissanayaka, E. White, J.D. O'Sullivan, R. Marsh, P.A. Silburn, D.A. Copland, G.D. Mellick, G.J. Byrne, Characteristics and treatment of anxiety disorders in Parkinson's disease, *Movement Disord. Clin. Practice* 2 (2) (2015) 155–162.
 - [19] P. Cuijpers, M. Sijbrandij, S. Koole, M. Huibers, M. Berking, G. Andersson, Psychological treatment of generalized anxiety disorder: a meta-analysis, *Clin. Psychol. Rev.* 34 (2) (2014) 130–140.
 - [20] C. Otte, Cognitive behavioral therapy in anxiety disorders: current state of the evidence, *Dialogues Clin. Neurosci.* 13 (4) (2011) 413–421.
 - [21] J.J. Arch, M.G. Craske, First-line treatment: a critical appraisal of cognitive behavioral therapy developments and alternatives, *Psychiatr. Clin. N. Am.* 32 (3) (2009) 525.
 - [22] M. Craske, *Cognitive-behavioral Therapy*, APA Books, New York, NY, 2010.
 - [23] R.D. Dobkin, M. Menza, L.A. Allen, M.A. Gara, M.H. Mark, J. Tiu, K.L. Bienfait, J. Friedman, Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial, *Am. J. Psychiatry* 168 (10) (2011) 1066–1074.
 - [24] D. Okai, M. Samuel, S. Askey-Jones, A.S. David, R.G. Brown, Impulse control disorders and dopamine dysregulation in Parkinson's disease: a broader conceptual framework, *Eur. J. Neurol.* 18 (12) (2011) 1379–1383.
 - [25] I. Koychev, D. Okai, Cognitive-behavioural therapy for non-motor symptoms of Parkinson's disease: a clinical review, *Evidence Based Mental Health* 20 (1) (2017) 15–20.
 - [26] J.S. Calleo, A.B. Amspoker, A.I. Sarwar, M.E. Kunik, J. Jankovic, L. Marsh, M. York, M.A. Stanley, A pilot study of a cognitive-behavioral treatment for anxiety and depression in patients with parkinson disease, *J. Geriatr. Psychiatry Neurol.* 28 (3) (2015) 210–217.
 - [27] M. Kraepelien, P. Svenningsson, N. Lindefors, V. Kalso, Internet-based cognitive behavioral therapy for depression and anxiety in Parkinson's disease — a pilot study, *Internet Inter.* 2 (1) (2015) 1–6.
 - [28] N.N.W. Dissanayaka, D. Pye, L.K. Mitchell, G.J. Byrne, J.D. O'Sullivan, R. Marsh, N.A. Pachana, Cognitive behavior therapy for anxiety in Parkinson's disease: outcomes for patients and caregivers, *Clin. Gerontol.* 40 (3) (2017) 159–171.
 - [29] A.B. Bruhl, A. Delsignore, K. Komossa, S. Weidt, Neuroimaging in social anxiety disorder—a meta-analytic review resulting in a new neurofunctional model, *Neurosci. Biobehav. Rev.* 47 (2014) 260–280.
 - [30] K.N.T. Mansson, A. Salami, A. Frick, P. Carlbring, G. Andersson, T. Furmark, C.J. Boraxbekk, Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder, *Transl. Psychiatry* 6 (2016).
 - [31] K.N.T. Mansson, A. Salami, P. Carlbring, C.J. Boraxbekk, G. Andersson, T. Furmark, Structural but not functional neuroplasticity one year after effective cognitive behaviour therapy for social anxiety disorder, *Behav. Brain Res.* 318 (2017) 45–51.
 - [32] T. Wang, X. Huang, P. Huang, D. Li, F. Lv, Y. Zhang, L. Zhou, D. Yang, P. Xie, Early-stage psychotherapy produces elevated frontal white matter integrity in adult major depressive disorder, *PLoS One* 8 (4) (2013) e63081.
 - [33] K.N. Mansson, P. Carlbring, A. Frick, J. Engman, C.J. Olsson, O. Bodlund, T. Furmark, G. Andersson, Altered neural correlates of affective processing after internet-delivered cognitive behavior therapy for social anxiety disorder, *Psychiatry Res.* 214 (3) (2013) 229–237.
 - [34] V.R. Steiger, A.B. Bruhl, S. Weidt, A. Delsignore, M. Rufer, L. Jancke, U. Herwig, J. Hanggi, Pattern of structural brain changes in social anxiety disorder after cognitive behavioral group therapy: a longitudinal multimodal MRI study, *Mol. Psychiatry* 22 (8) (2017) 1164–1171.
 - [35] M.C. de Rijk, W.A. Rocca, D.W. Anderson, M.O. Melcon, M.M. Breteler, D.M. Maraganore, A population perspective on diagnostic criteria for Parkinson's disease, *Neurology* 48 (5) (1997) 1277–1281.
 - [36] Z.S. Nasreddine, N.A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, J.L. Cummings, H. Chertkow, The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, *J. Am. Geriatr. Soc.* 53 (4) (2005) 695–699.
 - [37] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., (2013) Washington, DC.
 - [38] M.A. Stanley, N.L. Wilson, A.B. Amspoker, C. Kraus-Schuman, P.D. Wagener, J.S. Calleo, J.A. Cully, E. Teng, H.M. Rhoades, S. Williams, N. Masozera, M. Horsfield, M.E. Kunik, Lay providers can deliver effective cognitive behavior therapy for older adults with generalized anxiety disorder: a randomized trial, *Depress Anxiety* 31 (5) (2014) 391–401.
 - [39] M.A. Stanley, N.L. Wilson, D.M. Novy, H.M. Rhoades, P.D. Wagener, A.J. Greisinger, J.A. Cully, M.E. Kunik, Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care a randomized clinical trial, *J. Am. Med. Assoc.* 301 (14) (2009) 1460–1467.
 - [40] C. Veazey, K.F. Cook, M. Stanley, E.C. Lai, M.E. Kunik, Telephone-administered cognitive behavioral therapy: a case study of anxiety and depression in parkinson's disease, *J. Clin. Psychol. Med.* 16 (3) (2009) 243–253.
 - [41] A.J. Yarnall, D.P. Breen, G.W. Duncan, T.K. Khoo, S.Y. Coleman, M.J. Firbank, C. Nombela, S. Winder-Rhodes, J.R. Evans, J.B. Rowe, B. Mollenhauer, N. Kruse, G. Hudson, P.F. Chinnery, J.T. O'Brien, T.W. Robbins, K. Wesnes, D.J. Brooks, R.A. Barker, D.J. Burn, L.-P.S. Group, Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study, *Neurology* 82 (4) (2014) 308–316.
 - [42] I. Litvan, J.G. Goldman, A.I. Troster, B.A. Schmand, D. Weintraub, R.C. Petersen, B. Mollenhauer, C.H. Adler, K. Marder, C.H. Williams-Gray, D. Aarsland, J. Kulisevsky, M.C. Rodriguez-Oroz, D.J. Burn, R.A. Barker, M. Emre, Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines, *Mov. Disord.* 27 (3) (2012) 349–356.
 - [43] T.D. Borkovec, N.J. Sibrava, Problems with the use of placebo conditions in psychotherapy research, suggested alternatives, and some strategies for the pursuit of the placebo phenomenon, *J. Clin. Psychol.* 61 (7) (2005) 805–818.
 - [44] M. Hamilton, The assessment of anxiety states by rating, *Br. J. Med. Psychol.* 32 (1) (1959) 50–55.
 - [45] C. Jenkinson, R. Fitzpatrick, V. Peto, R. Greenhall, N. Hyman, The PDQ-8: Development and validation of a short-form Parkinson's Disease Questionnaire, *Psychol. Health* 12 (6) (1997) 805–814.
 - [46] M. Herdman, C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel, X. Badia, Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), *Qual. Life Res.* 20 (10) (2011) 1727–1736.
 - [47] J. Coast, T.J. Peters, L. Natarajan, K. Sproston, T. Flynn, An assessment of the construct validity of the descriptive system for the ICECAP capability measure for older people, *Qual. Life Res.* 17 (7) (2008) 967–976.
 - [48] A. Wimo, A. Gustavsson, L. Jonsson, B. Winblad, M.A. Hsu, B. Gannon, Application of Resource Utilization in Dementia (RUD) instrument in a global setting, *Alzheimers Dement.* 9 (4) (2013) 429–435 (e17).
 - [49] M.R. Liebowitz, Social phobia, *Mod. Probl. Pharmacopsychiatry* 22 (1987) 141–173.
 - [50] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, *J. Clin. Psychiatry* 59 (Suppl. 20) (1998) 22–33 (quiz 34–57).
 - [51] M. Hamilton, A rating scale for depression, *J. Neurol. Neurosurg. Psychiatry* 23 (1960) 56–62.
 - [52] P. Sockeel, K. Dujardin, D. Devos, C. Deneve, A. Destee, L. Defebvre, The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease, *J. Neurol. Neurosurg. Psychiatry* 77 (5) (2006) 579–584.
 - [53] C. Trenkwalder, R. Kohnen, B. Hogl, V. Metta, F. Sixel-Doring, B. Frauscher, J. Hulsman, P. Martinez-Martin, K.R. Chaudhuri, Parkinson's disease sleep scale—validation of the revised version PDSS-2, *Mov. Disord.* 26 (4) (2011) 644–652.
 - [54] C.S. Carver, You want to measure coping but your protocol's too long: consider the brief COPE, *Int. J. Behav. Med.* 4 (1) (1997) 92–100.
 - [55] A. Wells, M.I. Davies, The thought control questionnaire - a measure of individual differences in the control of unwanted thoughts, *Behav. Res. Ther.* 32 (8) (1994) 871–878.
 - [56] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin,

- W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, U.R.T.F. Movement Disorder Society, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, *Mov. Disord.* 23 (15) (2008) 2129–2170.
- [57] S.H. Zarit, K.E. Reever, J. Bach-Peterson, Relatives of the impaired elderly: correlates of feelings of burden, *Gerontologist* 20 (6) (1980) 649–655.
- [58] X.Y. Yang, J. Sun, J. Luo, Z.X. Zhong, P. Li, S.M. Yao, H.F. Xiong, F.F. Huang, Z.J. Li, Regional homogeneity of spontaneous brain activity in adult patients with obsessive-compulsive disorder before and after cognitive behavioural therapy, *J. Affect. Disord.* 188 (2015) 243–251.
- [59] X.Y. Yang, J. Luo, J. Liu, Y. Ma, Z.-h. Guo, X.-j. Yang, Z.-j. Li, Effects of cognitive behavioral therapy on white matter fibers of patients with obsessive-compulsive disorder as assessed by diffusion tensor imaging: study protocol for a parallel group, controlled trial, *Asia Pacific J. Clin. Trials* 1 (3) (2016) 116.
- [60] C.L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, C.E. Clarke, Systematic review of levodopa dose equivalency reporting in Parkinson's disease, *Mov. Disord.* 25 (15) (2010) 2649–2653.
- [61] R. Lopes, C. Delmaire, L. Defebvre, A.J. Moonen, A.A. Duits, P. Hofman, A.F. Leentjens, K. Dujardin, Cognitive phenotypes in parkinson's disease differ in terms of brain-network organization and connectivity, *Hum. Brain Mapp.* 38 (3) (2017) 1604–1621.
- [62] S. Galantucci, F. Agosta, E. Stefanova, S. Basaia, M.P. van den Heuvel, T. Stojkovic, E. Canu, I. Stankovic, V. Spica, M. Copetti, D. Gagliardi, V.S. Kostic, M. Filippi, Structural brain connectome and cognitive impairment in parkinson disease, *Radiology* 283 (2) (2017) 515–525.
- [63] I.R. White, P. Royston, A.M. Wood, Multiple imputation using chained equations: issues and guidance for practice, *Stat. Med.* 30 (4) (2011) 377–399.
- [64] R.H.H. Groenwold, A.R.T. Donders, K.C.B. Roes, F.E. Harrell, K.G.M. Moons, Dealing with missing outcome data in randomized trials and observational studies, *Am. J. Epidemiol.* 175 (3) (2012) 210–217.
- [65] P. Royston, Multiple imputation of missing values: update, *Stata J.* 5 (2) (2005) 188–201.
- [66] L.P. Goldsmith, G. Dunn, R.P. Bentall, S.W. Lewis, A.J. Wearden, Therapist Effects and the Impact of Early Therapeutic Alliance on Symptomatic Outcome in Chronic Fatigue Syndrome, *PLoS One* 10 (12) (2015) e0144623.
- [67] P. Crits-Christoph, J. Mintz, Implications of therapist effects for the design and analysis of comparative studies of psychotherapies, *J. Consult. Clin. Psychol.* 59 (1) (1991) 20–26.
- [68] P. Crits-Christoph, K. Baranackie, J. Kurcias, A. Beck, K. Carroll, K. Perry, L. Luborsky, A. Mclellan, G. Woody, L. Thompson, D. Gallagher, C. Zithrin, Meta-Analysis of Therapist Effects in Psychotherapy Outcome Studies, *Psychother. Res.* 1 (2) (1991) 81–91.