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Cognitive functioning and psychiatric symptoms in parkinson's disease

Boel, J.A.

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Chapter 8

SUMMARY AND GENERAL DISCUSSION

SUMMARY AND GENERAL DISCUSSION

The objective of this thesis was to gain more insight into cognitive and emotional functioning in patients with Parkinson's disease (PD). More specifically, the objectives were 1) to investigate whether either deep brain stimulation (DBS) of the globus pallidus internal segment (GPi) or the subthalamic nucleus (STN) is associated with more cognitive, psychiatric, and psychosocial side effects after surgery, 2) to investigate the relationship between preoperative cognitive functioning and outcome on cognitive decline, functional health, and quality of life after DBS, and 3) to investigate the prognostic validity of various applications of the recently proposed criteria for mild cognitive impairment in PD (PD-MCI) for the development of PD dementia (PDD).

GPI DBS VS. STN DBS AND PREDICTORS FOR OUTCOME AFTER SURGERY

DBS is an effective treatment option for patients with advanced PD who experience medication related motor response fluctuations [1]. The effectiveness of DBS on motor outcome and quality of life has been widely documented [2, 3]. There was controversy, however, whether either the GPi or the STN is the superior target.

The Netherlands SubThalamic And Pallidal Study (NSTAPS) was initiated to compare GPi DBS and STN DBS on functional outcome and various cognitive, psychiatric, and psychosocial outcomes. The hypothesis of this study was that GPi DBS would result in greater improvement in disability with similar improvement of motor symptoms compared to STN DBS, and that GPi DBS would have fewer cognitive, psychiatric, and psychosocial side effects. However, regarding functional outcome, the NSTAPS results indicated significantly more improvement in off-drug phase motor symptoms 1 and 3 years after STN DBS [4, 5]. The findings described in *chapter 5* indicate that this persists up to 5 years after surgery: STN DBS showed more improvement in off- and on-drug phase motor symptoms and in off-drug phase activities of daily living than GPi DBS.

This is in contrast with two other trials. A small randomized controlled trial, conducted by Anderson and colleagues, indicated that there was no significant difference between GPi DBS and STN DBS regarding improvement of motor symptoms (GPi DBS 39% and STN DBS 48%, respectively) [6]. This could, however, have been influenced by the limited sample size (GPi n=10, STN n=10). Researchers of the Veterans Affairs (VA) trial, a large RCT, also reported no significant difference between GPi DBS and STN DBS in improvement of motor symptoms up to 3 years after surgery [7, 8]. However, experts question the much smaller improvement in

both targets compared to previous studies and, consequently, the generalizability of the results from this RCT [9, 10].

Both trials investigated non-motor symptoms and reported more cognitive and behavioral side effects after STN DBS [6, 8]. In the trial by Anderson et al., non-motor symptoms are solely based on frequencies of perioperative complications. Additionally, various case-reports and cohort studies suggested that STN DBS is associated with more cognitive, psychiatric, and psychosocial side effects [11, 12]. Noteworthy, there is a much larger amount of such studies (case reports or small cohort studies) published on STN DBS than on GPi DBS. The often reported cognitive, psychiatric, and psychosocial side effects after STN DBS might therefore be partly explained by this publication bias [10, 13]. Altogether, motor as well as non-motor symptoms have to be taken into account when deciding on DBS target. Our RCT, a head-to-head comparison of GPi DBS and STN DBS, adds valuable information to the debate of which target is superior.

In the NSTAPS trial, a composite score for cognitive, psychiatric, and social side effects indicated no significant difference between GPi DBS and STN DBS 1 and 3 years after surgery [4, 5]. Various cognitive and psychiatric measures were dichotomized for this composite score thereby limiting the amount of data presented but also limiting the detection of possible differences between the groups on, for example, a certain cognitive domain instead of overall cognitive functioning. Detailed neuropsychological and psychiatric assessment was therefore further evaluated in *chapter 2*, *3*, and *4*.

Cognitive functioning after DBS: comparing GPi DBS and STN DBS

In *chapter 2* GPi DBS and STN DBS were compared on a large neuropsychological battery including 12 tests 1 year after surgery [14]. Results indicated group differences only on mental speed (Stroop word-reading and Stroop color-naming), attention (Trail Making Test B), and language (WAIS similarities), with STN DBS showing greater negative change than GPi DBS. These differences were all small (within 0.5 SD) and were not consistently found across all tests for mental speed, attention, and language.

The results of the 3-year follow-up regarding cognitive functioning of patients in the NSTAPS trial were presented in *chapter 4* [15]. The test battery was reduced to 5 neuropsychological tests, considering the burden extensive testing has on patients. However, apart from a test for global cognitive functioning, the selected tests still covered a variety of cognitive domains: attention and working memory, language, memory, and executive functioning. No significant differences were found between GPi DBS and STN DBS patients on the neuropsychological tests and the range of

decline since baseline was between 0.3 and 1.0 SD. In *chapter 5*, in which the results of the 5-year follow-up are presented, solely a global cognitive screener was included to assess cognition. Again, there was no significant difference between GPi DBS and STN DBS.

Altogether, we found no clinically significant differences in neuropsychological outcome between GPi DBS and STN DBS up to 5 years after surgery. The VA trial also compared both targets on various neuropsychological tests [8, 16]. In their study STN DBS patients performed better on a memory task and GPi DBS did better on a task for processing speed 6 months after surgery [16]. At 3-year follow-up the results indicated superiority of GPi DBS on a global cognitive screener and a memory task, while all other tests indicated no significant differences between the targets [8]. The researchers of the VA trial concluded that overall these group differences were small and should be interpreted carefully as analyses were not adjusted for baseline differences and other covariates between the groups [8].

Two recent meta-analyses reported on neuropsychological differences between GPi DBS and STN DBS [17, 18]. One meta-analysis of many neuropsychological outcomes indicated only a significant difference on Stroop color-naming favoring GPi DBS, and overall the authors concluded that present neuropsychological evidence does not favor either target [18]. The other meta-analysis reported more cognitive declines after STN DBS than after GPi DBS, but, importantly, they also report that a smaller number of studies investigating GPi DBS were included, which may have underestimated outcome in this group [17].

Cognitive functioning after DBS: comparing pre- to post-surgery

Whether the target is the GPi or the STN, findings regarding cognitive decline post-surgery raises various questions of, for example, what is the magnitude of this cognitive decline, what are the clinical implications, and questions related to the mechanisms involved (is it an implantation and/or stimulation effect?).

In general, neuropsychological changes comparing pre- to post-surgery are small to moderate [19]. Two recent meta-analyses both convey the message that GPi DBS and STN DBS produce subtle cognitive declines, that appear to be relatively well tolerated [17, 20]. Declines in the NSTAPS trial for both targets were gradually linear over time for most tests, with a range of decline between 0.3 and 1.0 SD up to 3 years after surgery [15]. The VA trial also reported gradual decline up to 3 years after surgery for most neuropsychological measures [8].

It is challenging to understand the range of cognitive decline after DBS in comparison to the range of cognitive decline associated with natural disease progression as representative control groups, especially those with long-term follow-

up, are lacking. A meta-analysis investigating the cognitive decline associated with natural disease progression reported declines ranging from 0 to 0.4 SD over an average follow-up period of 2.5 years for PD patients with a disease duration of 7.7 years. However, the authors acknowledge the considerable loss to follow up in some studies that may have led to underestimation of the cognitive decline. Either way, a comparison with cognitive decline after DBS remains challenging. Reassuringly however, are the results from the meta-analyses indicating that cognitive decline appears to be subtle and well tolerated [17, 20]. Importantly, patients and caregivers did usually not report notice of such small changes detected on neuropsychological tests post-surgery. This may indicate limited daily impact [17, 21].

Larger decline on verbal fluency shortly after surgery is a commonly reported finding [17, 22]. In our study, we also found larger declines on verbal fluency (letter and category fluency) and Stroop interference only in the first year after surgery. An RCT comparing unilateral GPi DBS and STN DBS showed persistence of impairment in verbal letter fluency also during off stimulation [23]. A study in which patients received stimulation either immediately after device implantation or beginning 3 months after surgery, reported that only the immediate stimulation group had verbal letter fluency and Stroop task declines. However, the groups performed similar 1-year after surgery [24]. In both studies, the authors suggested a specific surgical or lesion effect, but stimulation likely had an additive effect. This may also have led to more rapid decline of verbal fluency in the first year in our study. The daily impact of larger declines in verbal fluency are not yet clear, although they have been associated with communication dissatisfaction at 12 months [24].

Concluding, based on the results presented in this thesis and on the current literature, there is no indication that either target, the GPi or the STN, is safer than the other regarding cognitive outcome after surgery. Pre- to post-surgery data indicate subtle gradual cognitive decline over time for both targets, which appears to be well tolerated and is often not noticed by patients and caregivers. The larger declines shortly after surgery on only a few tests, such as verbal fluency, indicate a specific surgical or lesion effect, with probably an additive effect of stimulation.

Psychiatric symptoms and psychosocial functioning after DBS: comparing GPi DBS and STN DBS

The NSTAPS trial included a large battery of standardized psychiatric and social questionnaires. In *chapter 3* the 1-year results indicated no differences between GPi DBS and STN DBS on measures of depression, anxiety, mania, positive and negative affect, and personality [25]. Within-group comparisons showed statistically significant changes on several of these measures in both groups but these changes

seemed of minor clinical relevance, since scores at baseline as well as at 1-year were not indicative for, for example, mania or depression. The Mini International Neuropsychiatric Interview (MINI) indicated no increase in psychiatric disorders. There were no suicide attempts, and marital satisfaction of patients and partners remained relatively stable after both GPi DBS and STN DBS.

In *chapter 4*, psychiatric symptoms and psychosocial functioning 3 years after surgery was discussed [15]. There were no significant differences between GPi DBS and STN DBS on measures of mania, depression, and anxiety. The MINI did not indicate a substantial number of psychiatric diagnoses, and social functioning and marital satisfaction were again comparable in both groups. There were no suicide attempts. In *chapter 5* we reported on measures of depression and anxiety, which also did not indicate differences between GPi DBS and STN DBS 5 years after surgery.

Altogether, the results from the NSTAPS trial did not indicate differences in psychiatric symptoms and social functioning between GPi DBS and STN DBS up to five years after surgery. Our results are similar to those from the VA trial and a randomized study comparing unilateral GPi DBS and STN DBS [8, 26]. The VA trial reported a significant difference in depression scores between the targets 2 years after surgery (slight improvement for the GPi group and slight worsening in the STN group), but there were no significant differences 3 years after surgery [8, 27]. The study on unilateral surgery reported no significant difference between the two targets in mood outcomes [26].

Psychiatric symptoms and psychosocial functioning after DBS: comparing pre- to post-surgery

Regarding pre- to post-surgery differences, results from the NSTAPS trial did not indicate any relevant within-group differences up to five years after surgery.

An important finding here is that our results regarding suicide rates post-surgery are reassuring, especially since a higher suicide rate after STN DBS has been reported before [28]. Results of the VA trial also reported no elevated suicide ideation and behaviors in the 6-month period post-surgery [29]. Additionally, contrary to earlier rather alarming reports [30], another reassuring finding is the relative stable marital satisfaction post-surgery.

The VA trial reported on depression up to 3 years post-surgery, at which they didn't find differences compared to baseline [8]. The study comparing unilateral GPi DBS and STN DBS also investigated psychiatric diagnoses by DSM-IV criteria and they reported no changes in diagnoses 1 year post-surgery. They did report few statistically significant but small changes in anxiety, depression, and mania (worsened scores 1 year post-surgery). Additionally, the authors mentioned specifically that

medication reduction should be gradual to reduce risks for adverse effects [26]. Reduction in dopaminergic drugs post-surgery could potentially lead to a dopamine withdrawal syndrome in which patients experience negative psychiatric side effects, for example, apathy, depression, or anxiety [31].

Concluding, as with cognitive outcome after surgery, the results discussed in this thesis and the current literature do not indicate either target, GPi DBS or STN DBS, to be safer with regard to psychiatric symptoms and psychosocial functioning after surgery. Pre- to post-surgery results indicated a low number of psychiatric diagnoses, suicides, and marital problems.

Preoperative cognitive functioning and outcome after DBS

In *chapter 2* we investigated potential predictors for cognitive decline 1 year after surgery [14]. Cognitive decline was defined as at least three significant reliable change indices (RCI's) on 15 test scores. Since there were no significant differences in cognitive decline between GPi DBS (29.3% decliners) and STN DBS (39.3% decliners), these groups were combined for the analyses. Baseline cognitive tests were combined into domain scores and various clinical and demographic baseline characteristics were included in the model when univariate analyses indicated an association of $p<0.20$ with cognitive decline. Older age and a higher semantic fluency score at baseline were significant predictors for cognitive decline. No satisfactory explanation can be provided for the predictive value of baseline semantic fluency, while older age seems a plausible predictor for cognitive outcome after surgery and has been reported before [32]. We couldn't replicate results regarding a previous predictive model by our group [32]. This could be due to differences in the assessment of cognitive decline as we used RCI, whereas the study by Smeding et al. used multivariate normative comparison with a PD control group. We also investigated the relation between quality of life and cognitive decline 1-year after surgery. The results indicated that both the decliners and non-decliners improved on quality of life and this was not significantly different between the groups.

In *chapter 6* we investigated preoperative cognitive status in relation to quality of life and functional health 3 years after DBS. The patients receiving GPi DBS and STN DBS from the NSTAPS trial were combined. Patients were grouped according to MDS PD-MCI criteria at baseline into patients with MCI (PDmci) and patients with normal cognition (PDnc). Results indicated that there were no differences between PDmci and PDnc on quality of life and functional health 3 years after DBS. Significantly more PDmci patients had dropped out. When investigating predictors for dropout using a multivariate analysis, only levodopa response at baseline was a significant predictor for dropout. Concluding, among PDmci and PDnc patients

who completed 3-year follow-up, functional health outcomes after DBS in terms of quality of life and functional health were similar. MCI was not a significant predictor for dropout.

The analyses in this thesis did not indicate reliable predictors for outcome after surgery and are in contrast with some previous studies. In the NSTAPS as well as in the VA trial, quality of life improved for patients with and without cognitive decline, but only in the VA trial patients with cognitive decline improved significantly less regarding quality of life [7]. Quality of life can be influenced by baseline factors, for example by preoperative cognitive functioning. Witt and colleagues have shown that cognitive impairment assessed on a scale for global cognitive functioning is associated with lower quality of life after surgery [33]. We were not able to reproduce such an association when applying the MDS PD-MCI criteria using a more detailed large cognitive battery at baseline.

Concluding, based on the findings in this thesis and current literature, as of yet cognitive decline after surgery cannot be reliable predicted using baseline variables. In addition, preoperative mild cognitive impairment is not per se a contraindication for DBS.

Strengths and limitations – DBS

The NSTAPS trial is one of the largest RCTs comparing GPi DBS and STN DBS, and its main strength lays in the clinical relevance. The inclusion criteria of this study match prevailing practice for patients commonly opting for DBS. In other words: the results of this trial are generalizable to the average patient with advanced PD. In addition to the various functional outcome measures included in the NSTAPS trial, the extensive test battery including neuropsychological, psychiatric, and psychosocial measures is unique. Considering the chronic nature of PD, systematic long-term follow-up of GPi DBS and STN DBS is needed to compare these targets over time. The NSTAPS trial included a 5-year follow-up and, even though the test battery is considerably reduced, it still includes various measures of functional, cognitive, and psychiatric outcome.

With the extensive testing and multiple follow-ups comes a caveat of the trial: the amount of missing data. However, imputation analyses as well as statistical analyses robust to missing data showed similar results compared to complete case analyses. Nevertheless, the patients who completed the 3- and 5-year follow-up are likely a select group. Cognitive decline over time could be underestimated, as the patients who perform relatively well are less likely to drop out. The between group analyses comparing GPi DBS and STN DBS was probably not affected since dropout was not significantly different between the groups.

The NSTAPS trial did not include measures to assess apathy as this was less well recognized by the time the study protocol was written. Apathy is of clinical relevance, because it is reported to have overlap with cognitive impairment and mood, for example depression [34]. Additionally, impulse related disorders in PD, often associated with dopaminergic drugs, warrant further investigation [35]. Impulse related disorders can affect quality of life, and reports have indicated contrasting results thus far [36, 37].

Prospects for future research – DBS

In a recent editorial, the bright future of DBS for many other diseases aside PD was discussed [38]. The author stated that 'Optimism, however, needs to be tempered by reflection and caution', not to slow progress or creativity but to critically evaluate all aspects of DBS research designed to improve knowledge of DBS for current indications. The studies included in the current thesis have clarified some important research questions but also indicate various future research options within the field of DBS for PD.

The NSTAPS trial showed no clinically relevant differences between GPi DBS and STN DBS. Prediction models did not indicate PD-MCI as a significant predictor for outcome after surgery. However, there are a few reports of patients with significant decline after DBS. To investigate whether these rare individual cases can be predicted pre-surgery, studies including large numbers of patients are needed. In general, it is challenging to include such large numbers, and an option would be to merge data from various studies. Merging data poses various challenges in that often different neuropsychological tests are used. Another, perhaps more realistic option, would be to retrospectively investigate all DBS patients within a center. An example here is our recent retrospective study investigating psychiatric symptoms in the medical files of 236 PD patients treated with STN DBS [39].

Another important remaining question is related to the actual cognitive decline as a consequence of DBS. This question cannot be simply answered by a comparison of neuropsychological testing pre- and post-surgery. This is because the effects of the DBS, either the surgery itself, stimulation effects, medication changes, and interactions between these DBS related factors, cannot easily be disentangled from the cognitive decline that is associated with natural disease progression. Assessing whether changes from pre- to post-surgery are clinically meaningful also remains to be investigated by further studies. RCI is an often used approach, but multivariate normative comparisons (MNC) might be more sensitive in identifying slight changes over many tests [40]. For the latter approach, but also for disentangling DBS effects from the natural disease progression, a large, representative control group is needed. Ideally, a

trial should compare DBS vs. best medical treatment over a long follow-up period, but such a design poses ethical challenges. Currently a study comparing STN DBS vs. continuous levodopa infusion therapy is ongoing in the AMC (INfusion VErsus STimulation, INVEST, study). This study includes extensive neuropsychological assessment 1 and 3 years after surgery and the effects of DBS on cognitive decline can be compared to cognitive decline associated with natural disease progression in PD represented by patients randomized to continuous levodopa infusion therapy.

Informed shared decision making prior to surgery, in which the healthcare professional provides the patient with all relevant information and discusses expectations of outcome after DBS, is common practice. Additionally, it has become of more interest to researchers. A recent review article reporting on a multidisciplinary symposium underlines the need for patients and caregivers to receive information on various disease aspects in PD at diagnosis, such as cognition and mood [41]. This likely extends to receiving information throughout the whole course of the disease and researchers should investigate the process of informed shared decision making, more specifically, the influence of pre-operative expectations on outcome after surgery.

The DBS surgery and materials such as the electrodes are also subject to various research advances. 'Awake' surgery is now compared to DBS under full anesthesia to minimize the impact of the surgery on patients, as many of them experience perioperative discomfort [42]. First reports indicated similar motor functioning [43], but a randomized controlled trial is needed to systematically compare the two types of surgery and its possible side effects, for example on cognition. The General Anesthesia vs. Local Anesthesia in stereotaXY (GALAXY) study is an ongoing RCT in the AMC comparing 'awake' surgery and DBS under full anesthesia. Another advancement is the use of directional steering electrodes to minimize side effects by more specific located current spread. Again, only limited studies have been performed, and the reduction of sides effects while maximizing motor functioning have still to be investigated [19].

Implications for clinical practice – DBS

The results of the NSTAPS trial indicated that the STN is the preferred DBS target over the GPi based on better functional outcome in off-drug phase without clinically relevant group differences on cognitive, psychiatric, and psychosocial side effects. Regarding clinical practice, in our hospital and various other centers, the STN is the preferred target for patients with advanced PD. More specific clinical implications regarding cognitive, psychiatric, and psychosocial outcome after DBS are presented in box 1.

The choice of the target remains a complex process in which DBS-teams consisting of specialists across various disciplines (neurologists, neurosurgeons, psychiatrists, neuropsychologists, and nurses) make a well weighted decision based on individual characteristics of a patient. The main role of the neuropsychologist involves direct patient care by assessing preoperative cognition and, with that, excluding patients with severe cognitive impairment as dementia is a contraindication for DBS. The neuropsychologist makes a contribution to the assessment, selection, and postoperative (for example cognition or mood related) care of patients [44].

Box 1. Implications for clinical practice – DBS

Regarding cognitive, psychiatric, and psychosocial outcome after DBS, implications for clinical practice include that we can inform patients about:

1. the absence of clinically relevant differences between GPi DBS and STN DBS on cognitive, psychiatric and psychosocial side effects after DBS,
2. the subtle cognitive decline after DBS as changes are usually small to moderate and often not noticed by patients and caregivers,
3. that, as of yet, we have not identified reliable predictors for cognitive decline after DBS
4. that also those patients who show small to moderate cognitive declines after DBS experience improved quality of life.

MDS PD-MCI CRITERIA

While cognitive deficits in PD have been known for a long time, PD-MCI has only been recently introduced as a concept. To aid in uniform assessment, MDS PD-MCI criteria were proposed by expert consensus [45]. These criteria needed validation, and an international study group was formed, sharing individual patient data to address this issue [46].

In *chapter 7* we evaluated the prognostic validity of level I (based on an abbreviated neuropsychological assessment) PD-MCI criteria for development of PD dementia (PDD). We found that level I PD-MCI is related to the hazard of PDD with lower performance on neuropsychological assessment increasing this hazard. These findings

were corrected for demographic and clinical characteristics, such as age, motor symptoms and depression. Increasing age and disease severity also increased the hazard for PDD. Additionally, we compared level I to level II (based on a comprehensive assessment) PD-MCI criteria in a subset of the data (4 studies). Level II PD-MCI did not show added value to level I PD-MCI on the hazard of PDD. However, results did indicate that when using a cut-off of -1SD, -1.5SD, or -2SD, level II PD-MCI identified more cases as impaired.

Our current findings match results from previous studies. Progression to PDD has been associated with increased age, disease severity and PD-MCI [45, 47, 48]. Additionally, our findings are in line with PD-MCI as a progressive transitional stage between normal cognition and dementia as results indicated a pattern of increase in hazard with each successive degree of neuropsychological impairment (-1SD, -1.5SD, and -2SD) [45].

The study described in *chapter 7* is a follow-up of a recently published article on the level II PD-MCI criteria by our MDS study group [49]. When assessing PD-MCI using level II, a division can be made into single or multiple domain impairment. Multiple domain impairment was more frequent than single domain impairment in our study (92% and 8%, respectively), a finding commonly reported in the literature as well [50-52]. Additionally, when investigating which specific domains are affected, studies report all kinds of combinations and, as of yet, there is no specific cognitive profile identified [53].

Regarding level I and level II criteria, studies utilizing either of these all reported that PD-MCI is frequent, ranging between 9 to 65% of PD cohorts [54]. However, frequencies of PD-MCI vary according to the application of the criteria, for example depending on the tests used [48]. Deciding whether to use level I or level II criteria may therefore be influenced by a few factors. Level I criteria were proposed for situations in which comprehensive testing is not possible, for example when there are time constraints. Level II (more tests) increase the probability to detect cognitive impairment [50], as was also demonstrated in our study (Hoogland et al, submitted). However, there seems to be an upper limit regarding the number of tests, as Goldman and colleagues showed that using more than two test per domain added very little to the final assessment [50]. They concluded that their findings strongly support the MDS PD-MCI level II criteria, in which two tests per each of five domains are suggested. Overall, considering that cognitive deficits in PD encompass various domains, neuropsychological testing should therefore also cover all domains for both level I and level II.

The MDS PD-MCI criteria suggest using a cut-off between -1 SD and -2 SD to identify cognitive impairment. A cut-off of -1 SD might be considered too liberal

with increased frequencies of PD-MCI patients, whereas -2 SD might be too strict [48, 52]. A study investigating sensitivity and specificity of the new level II PD-MCI criteria for accurate classification of MCI as traditionally diagnosed in a more informal way (by clinical judgement) showed best sensitivity and specificity at a cut-off of -2 SD. They also reported that using -1 or -1.5 SD in order not to miss PD-MCI in high functioning individuals would sacrifice specificity [52]. Although most studies use -1.5 SD, the currently published results are contrasting. Therefore, the optimal cut-off score is yet to be defined and further research is needed [54].

Concluding, the efforts of our MDS study group evaluating the prognostic validity of the MDS PD-MCI criteria for the development of PDD are a first step towards uniform criteria. Based on our studies and current literature, we know that PD-MCI is a risk factor for PDD, with increased cognitive impairment associated with a higher risk for PDD. In addition, PD-MCI assessed by either level I or level II criteria is frequent and frequencies depend on application of the criteria. Level II showed greater sensitivity [52] compared to level I using a cut-off of -2 SD, but the decision for either level of the criteria and the specific cut-off to use remains an issue of investigation.

Strengths and limitations – PD-MCI

One of the main strengths of the current study investigating the MDS PD-MCI criteria is that it consists of a large multicenter international sample. Patients are followed for an extensive period, and side by side comparison of level I and Level II PD-MCI criteria was possible in the same data. We performed uniform application of the MDS PD-MCI criteria across studies based on all cognitive domains.

A few limitations of the current study are related to the retrospective nature. For example, the specific influence of the variability in methods across the included studies (different methods for patient recruitment, neuropsychological evaluation, assessment of motor symptoms, and evaluation of the endpoint of interest) could not be quantified. Additionally, cognitive decline on serial testing as well as a decline from premorbid level could not be addressed in the current study. Only relatively few patients developed PDD, and statistical power may thus have been an issue in our analyses. A limitation of longitudinal research in general is related to dropout [49], as patients who drop out are likely to represent a specific group. Information on dropout was not available in our study.

Prospects for future research – PD-MCI

In contrast to motor function, cognition is not always assessed when PD patients visit the hospital. However, serial cognitive testing is needed to map the full spectrum

of cognition in PD [41] and repeated testing improves predictions of an outcome, for example, conversion to PDD [55]. Ideally, neuropsychological testing should be included in standard clinical care.

To address the issue of which neuropsychological tests should be administered one should consider that PD-MCI and its associated cognitive deficits are heterogeneous [54]; a profile based on specific (multiple) domain impairment has not yet been identified [49]. A neuropsychological test battery should therefore cover a broad range of cognitive domains. One of the conclusions of research efforts by our MDS PD-MCI study group attempting to specify a neuropsychological battery was that there was a high between-study variability when using published norms [56]. This is likely a reflection of the diversity in testing procedures across the world. These findings highlight the need for a PD-specific battery available for use across multiple languages and cultures. To improve interpretation and generalization of results across studies, experts could propose a specific neuropsychological test battery.

To investigate whether there is a specific cognitive profile (or various specific cognitive profiles for that matter), a large prospective study, including neuropsychological tests covering all domains, with a long-term follow-up could provide important information regarding the course of PD-MCI. That way operational aspects of the criteria, for example on the indication for when to use level I or level II criteria, defining optimal cut-off scores, and how to incorporate changes from premorbid cognitive functioning could be further investigated as well. Subsequently, with more knowledge regarding the course of PD-MCI, subgroups of patients can be identified to investigate potential treatment interventions, and PD-MCI can be used as an outcome to assess the effects of interventions [57]. Lastly, combining neuropsychological assessment with neuroimaging or neurochemical biomarker data might improve assessment of a patient's current status and improve prediction of future cognitive decline [48].

Implications for clinical practice – PD-MCI

PD-MCI has become increasingly recognized but cognitive impairment in PD remains a large and unmet challenge to the research, patient communities and funding sources [58]. Greater understanding of the course of PD-MCI is important for appropriate information sharing with patients and caregivers [54]. Additionally, it is important for the identification of subgroups of PD patients to investigate potential treatment interventions, and to use PD-MCI as an outcome measure to assess the effects of such interventions [57]. With the current knowledge on PD-MCI, there is already valuable information we can share with patients and caregivers. Clinical implications are summarized in box 2.

Box 2. Implications for clinical practice – PD-MCI

Based on our study and published literature on PD-MCI, we can inform patients about:

1. PD-MCI being variable in its course as reversion to normal cognition (however, only in a minority of cases), stable MCI, and progression to PDD have been reported,
2. PD-MCI being a risk factor for PDD, with increased cognitive impairment associated with a higher risk for PDD,
3. the time span of progression of cognitive decline cannot yet be reliably determined,
4. multiple domain impairment is much more common than single domain impairment indicating clinical heterogeneity.

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