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Cognition in Movement Disorders: Where Can We Hope to be in Ten Years?

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Abstract

Cognitive impairment and dementia associated with movement disorders represent a major management challenge and area of unmet need. This article has focused upon Parkinson's disease as an exemplar condition, but many of the roadblocks and efforts to overcome these are applicable, in a general sense, to other disorders. Short of a "penicillin moment"—a chance discovery or piece of unintended good fortune—progress is likely to be incremental. Cognitive therapies may end up being multiple and possibly multimodal, parallel with the cancer therapy field. Ultimately, benefit for one condition may extend to others as commonality in protein aggregation, synergistic pathological effects between proteins, and pathological spread emerges.

Keywords

Parkinson's disease; dementia; cognitive testing; biomarkers; therapeutics

Despite a greater knowledge of the pathophysiology underpinning several movement disorders, this has not yet translated into major improvements in our clinical management of the devastating cognitive problems associated with these conditions. Cholinesterase inhibitors probably represent the most notable therapeutic step forward in the field over the past decade, based upon neurotransmitter augmentation, a conceptually simple principle. Yet, the failure of such agents to improve cognitive dysfunction in four-repeat tauopathies such as PSP, where there is profound cholinergic deficiency (and even, in some cases, to have counterproductive effects), highlights that even the benefits of manipulating neurotransmitter function cannot be generalized.

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Unfortunately, more fundamental approaches of disease modification have, as yet, failed to yield benefit. There are, undoubtedly, several reasons behind this failure, including lack of understanding of disease pathophysiology and/or inability to identify tractable targets, inadequate animal models, disease heterogeneity, and an absence of robust biomarkers for disease progression.

In 10 years, a breakthrough could come from discovering a tractable target and drug development that tackles basic disease progression; in other words, both motor and cognitive deficits could both be delayed or favorably modified. Alternatively, identifying people at high risk of dementia, for example, in association with Parkinson's disease (PD), might lead to the use of transferrable technologies or drugs from other disease areas, such as Alzheimer's disease (AD), that may also have efficacy in PD.

This article adopts a "blue skies" approach to where we might be in 10 years, addressing how we might assess the patient, trial design, new drugs in the pipeline, and alternative nonpharmacological approaches. We will focus upon PD as an exemplar condition.

Where Can We Hope to be in Assessment of the Patient's Cognition?

Prioritizing Serial, Long-Term Cognitive Testing for Clinical Care and Research

Ideally, results from neuropsychological testing administered before PD onset would be available for comparison, but this is rarely the case. When available, recent and previous performance can be compared informally or by using a reliable change index, which takes into account measurement error and practice effects, when longitudinal group-level data are available. Given demographic trends and the current emphasis on identifying neurodegenerative diseases at the earliest stage possible, a case can be made that, moving forward, everyone should receive brief, global neuropsychological testing on a regular basis starting in midlife. Such testing could be done in the context of routine primary care, need only occur every 3 to 5 years, and could utilize tests that only take 10 minutes to complete (e.g., the Montreal Cognitive Assessment; MoCA). If this is not realistic, then the next-best option is to have all PD patients undergo some form of cognitive evaluation annually, starting at the time of diagnosis. Given that 80% to 85% of PD patients have normal cognition at diagnosis, this will allow a reasonable cognitive baseline to be established for future reference.

Emergence of Performance-Based Assessment of Functional Abilities That Are Sensitive and Specific to Cognitive Performance

Another criterion for a diagnosis of cognitive disorder is assessment of cognition-related functional abilities. Currently, there is no consensus on what constitutes significant functional impairment. Complicating the issue in PD is the impact of motor deficits on task completion, whether or not to consider "slowness," but otherwise normal performance a cognitive deficit, and the broad age range for PD (compared with AD) that contributes to significant interindividual variability in everyday functional demands that makes comparisons across individuals problematic.

An additional issue relates to how best to assess function as it relates to cognitive abilities. In clinical practice, this is determined on the basis of an unstructured encounter. However, for clinical research, it is important to have validated measures to assess function not only to increase accuracy of assigned diagnoses, but also to demonstrate worsening (i.e., with disease progression) or improvement (i.e., with cognitive enhancing treatment) over time.

Currently, function in clinical research is assessed through an interview (with the patient, an informed other, or both) by inquiring about performance of higher-level instrumental activities of daily living. Instruments such as the Alzheimer's Disease Cooperative Study/ Activities of Daily Living Inventory scale have been used, but PD-related motor impairment potentially biases the rating of some activities and the different cognitive profile of PD limits the utility of instruments designed for other populations. Recently, PD cognition-specific functional instruments have been developed and validated, including the PD-Cognitive Functional Rating Scale[1] and the Penn Daily Activities Questionnaire.[2]

Ultimately, because of the subjectivity and imprecision of questionnaires, further development and testing of performance-based measures for cognition in PD is needed. Examples of measures developed in the general population, but applied in PD to assess general or specific abilities, include the Everyday Cognitive Battery (which assesses medication use, finances, nutrition, and treatment choices),[3] the Hopkins Medication Schedule,[4] the Capacity to Consent to Treatment,[5] the University of California San Diego Performance-based Skills Assessment,[6] and the MacArthur Competence Assessment Tool for Clinical Research.[7] In addition, driving safety is correlated with executive and visuospatial abilities in PD,[8] and simulated driving tests for use in clinical research are now available. In the future, having a battery of validated performance-based measures, including computerized testing, would advance the field of PD cognition research and could improve clinical practice. Such instruments can also be used set a minimum clinically important difference (MCID), which is increasingly used in clinical trials to determine the clinical significance of treatment effects. It is also likely that new APP-based tools for mobile phones and tablets will become more frequently used in the assessment and monitoring of cognitive function, whereas body-worn sensors may give objective data regarding daily activity patterns and overall levels of function. Such data may now be analyzed more rapidly and meaningfully with advanced computerized algorithms.

Consensus on Preferred Neuropsychological Tests: Is it Desirable and Achievable?

Traditional global cognitive instruments developed for non-PD populations, but often used in PD, have been largely replaced by instruments developed or validated for use in PD. In addition, a large number of individual neuropsychological tests have been used to assess executive, memory, attention, visuospatial, and language abilities specifically.

On the one hand, use of a variety of instruments provides rich detail about the relative cognitive strengths and weaknesses of PD patients. However, the plethora of tests used also limits progress. For most existing instruments, major holes regarding performance need to be filled with additional research. None, other than the MoCA for screening purposes, has gained wide acceptance in PD. Given the lack of consensus regarding current instruments, a

case can be made to assemble a neuropsychological battery for use in all aspects of PD cognitive research. A “wish list” for such a battery would include:

- Existing neuropsychological tests, sensitive to early cognitive decline in PD
- Tests with normative data to allow calculation of normed test, domain, and battery scores
- Cover comparably the five primary cognitive domains (attention-working memory, memory, executive functioning, visuospatial skills, and language)
- At least two test scores per domain to allow application of level II criteria for mild cognitive impairment associated with PD
- Assess reliability and validity for use in PD patients with normal cognition, mild cognitive impairment, and mild dementia
- Sensitive to worsening in cognitive abilities over time
- Sensitive to improvements with cognitive enhancing treatment
- To limit motor confounds (i.e., limit tests that require motor skills)
- To limit speed confounds (i.e., limit timed tests for primary cognitive domains)
- Both paper- and computer-based versions of the instrument
- Alternate versions for serial evaluation in longitudinal studies
- Appropriate for translation from English into multiple languages
- To administer to a large number of healthy elderly to generate age, education, and gender norms for this battery specifically
- Establish an MCID
- Demonstrate a correlation with measures of cognitive functioning
- Demonstrate a correlation with PD cognitive biomarkers

Use of Technology

Although concerns have been raised about reliability and validity, which still need to be addressed with additional research, there are many potential advantages to computerized testing. Because many clinical centers do not have ready access to neuropsychologists, the PD clinical population is currently underserved. The nature of the computerized instruments allows administration by health care personnel other than neuropsychologists. Computerized testing offers a clear advantage in terms of standardized administration procedures, precise timing of stimulus presentation and response time, and automated scoring and results generation. In comparison with traditional neuropsychological assessment instruments, computerized tests may also represent a potential cost savings not only with regard to materials and supplies, but also in the time required of the test administrator. In addition, testing can occur in variety of environments, and alternate versions can be easily developed.

Will Trial Design Have Changed?

Will Better Animal Models Inform Trial Design and Size?

Therapeutic trials using better animal models could help accelerate identification of effective interventions and could provide information that would be more realistic for designing clinical trials in humans, including estimating sample size and trial duration. At minimum, using better animal models could help advance our understanding of the underlying neural mechanisms influencing cognitive decline in patients with movement disorders. Currently, animal trials of movement disorders are usually conducted in rodent models using suboptimal methodologies, including small sample size and nonstandardized tests. There are significant limitations in testing complex human cognitive functions using current animal models, although there are some human tests that could have an comparable equivalents in animal models.[9] For example, human executive function set shifting and inhibition of behavior tasks could relate to delayed alternation tests and stop task tests in animals, but planning and multitasking have no analogous animal model test. Moreover, at present, most therapeutic preclinical studies conducted in animal models test therapeutic agents at preclinical disease stages, rather than when diseases are clinically manifest or even at advanced stages as they are evaluated in humans. Thus, to date, results of neurotransmitter replacement and biological therapies, shown to be very successful in animal models, have not been of demonstrable benefit in humans. After so many therapeutic failures, one would hope that in 10 years industry and academia would be conducting studies in nonhuman primates (e.g., macaques, monkeys, and marmosets), in which cognition could be better tested and in which pharmacokinetics, pharmacodynamics, and cerebrospinal fluid (CSF) brain penetration and drug brain levels may be similar to those in humans.[10,11]

Future animal model trials will hopefully apply the same meticulous methodology used in human clinical trials, including sample-size estimation, standardization of tests, blinded evaluations, and administration of therapies at clinical disease stages. These studies will be more expensive, but higher costs up front may allow cost cutting at later stages of development and increase chances of success. However, even if animal models and methodology improve, we should be aware that studies in such models will not capture the heterogeneity observed in humans who also exhibit a variety of comorbidities as well as lifestyle, genetics, and environmental exposures.

Toward Improved Biomarkers

Well-defined populations are critical for clinical trials, but there are no disease-specific biomarkers for the diagnosis of nongenetic movement disorders. To evaluate targeted interventions and prevention therapies designed to delay the cognitive decline observed in these disorders, we need biomarkers that could increase diagnostic accuracy, predict cognitive decline, and accurately track progression of this decline.

Diagnostic biomarkers that quantify levels of CSF beta-amyloid, tau and phosphorylated tau, and PET imaging tracers that have high affinity for beta-amyloid are useful in the diagnosis of AD *in vivo*, for which they have been recently incorporated to improve its diagnostic criteria.[12] However, whereas quantification of CSF alpha-synuclein (α-Syn) levels is a

promising biomarker for the diagnosis of PD,[13] higher specificity and sensitivity are needed to allow its adoption to refine extant diagnostic criteria. Furthermore, CSF tau levels are not helpful for diagnosing tauopathies presenting with parkinsonism, such as PSP and corticobasal degeneration. However, the recent development of two PET imaging tracers targeting paired helical filament-tau, phenyl/pyridinyl-butadienyl-benzothiazoles/ benzothiazoliums (PBBs) and [(18)F]T807, that have high affinity *in vitro*, in animal models and in patients with AD are encouraging and may help increase the accuracy in diagnosing these disorders.[14–16] Validation of these biomarkers in AD is in progress. Evidence that these biomarkers will be helpful to diagnose patients with other tauopathies is not yet available, although one report describes increased [^{11}C]PBB signal in areas typically affected of a patient with a corticobasal syndrome.

This new development increases the likelihood of finding tracers that could label α-Syn because this shows us that imaging radiotracers can feasibly label intracellular protein inclusions such as those found in PD.[17] Improved biomarkers not only will increase diagnostic accuracy, but will also allow the diagnosis of patients at earlier disease stages, thereby improving the chances of finding successful biological therapies. PET tau and α-Syn biomarkers may also serve as surrogate markers of disease progression. It is unlikely that PET ligands will become inexpensive and accessible world-wide, but they could pave the way for the identification of other less-costly, more-ubiquitous imaging approaches (e.g. single-photon emission CT), as well as less-invasive blood or urine biomarkers that could allow an early diagnosis of movement disorders.

Moreover, in the coming years, we may also be able to use genetics to design therapeutic trials that will target specific populations more likely to respond to therapy or with similar disease progression, which, in turn, will increase the likelihood of finding successful therapies. For example, if apolipoprotein E4 (ApoE4), the H1/H1 haplotype, or the α-Syn gene predispose to the conversion of PD patients with mild cognitive impairment to dementia, stratifying or selecting patient samples with these genes will decrease the sample size needed and may more readily identify successful therapies.

Adaptive Design/Fast Tracking

In an attempt to increase the efficiency and likelihood of success, there is a growing interest among drug developers in using adaptive design approaches, defined as an *a priori* plan to modify aspects of a study based on interim data analyses performed at preplanned time points.[18] This approach could lead to fundamental “in flight” changes that include total sample size, dose level, concomitant treatments, changes in primary or secondary outcomes, and study duration (e.g., early termination). There are concerns, however, that this approach could introduce bias and increase the possibility of type 1 errors (incorrect conclusions). Adjustment of the sample size during the course of a clinical trial has become a popular strategy lately.[19]

Drugs in the Pipeline: Hope or hype?

Therapeutic efforts in PD will increasingly focus on cognitive decline over the next decade. This will be driven by the high unmet need and growing understanding of the

pathophysiology and clinical course of cognitive decline. It appears that cognitive impairment is multifactorial,[20] and progress will therefore be incremental. The biology of cognitive impairment and an appreciation of overlapping features with AD may allow the field to leverage biomarkers and interventions from the AD field. This could accelerate the pace at which new interventions are tested.

Clinical trials of agents for cognitive impairment may be aimed at enhancing cognition or slowing decline. Pharmacological or biological interventions may focus on a range of targets, from fundamental disease processes to resulting neurotransmitter deficits, such as acetylcholinesterase (AChE) inhibitors. Near-term successes are likely to build on the modest, but real, progress in alleviating neurotransmitter deficits. Though treatment effects are small, and similar in magnitude to AD, successful AChE inhibitor trials validate the concept of enhancing cholingergic transmission as a therapeutic approach.[21–23] They also suggest that trials in AD may be predictive for PDD, at least for certain mechanisms.

Selective cholinergic agonists may provide additional benefit beyond the cholinesterase inhibitors. EVP-6124, a selective nicotinic alpha 7 coagonist, showed significant improvement on an abbreviated version of the Alzheimer's Disease Assessment Scale, as well as the clinical dementia rating scale sum of boxes. As a coagonist, the agent works in combination with acetylcholine (ACh), making it possible for smaller amounts of naturally occurring ACh to be effective in activating the alpha 7 receptor and possibly improving the tolerability, as compared with previous nicotinic agonists.[24] There have been other promising alpha 7 clinical trials in the AD population and in subjects with cognitive impairment in the setting of schizophrenia. Partial agonists of the alpha 4/beta 2 receptor and other mechanisms of targeting cholinergic pathways have also shown some promise. If the effects are confirmed, the prominent cholinergic deficits would make PD with dementia (PDD) a natural next step for clinical trials with these agents.

Other neurotransmitter-based approaches may be viable in PD-related cognitive impairment. Agents that inhibit the excitotoxicity of glutamate have been challenging to develop. There is inconsistent evidence that the N-methyl D-aspartate receptor antagonist, memantine, has any benefit in PDD.[25,26] The effect of dopaminergic replacement strategies on cognition in PD remains uncertain. Exogenous dopamine replacement has variable effects, which may depend on the selectivity for dopamine receptors, particular cognitive domains assessed, and the stage of disease. However, there appears to be a clear relationship between cognition and dopamine deficiency, as measured by dopamine transporter imaging,[27,28] and dopamine metabolism, as assessed by catechol-*O*-methyltransferase polymorphisms.[29] These findings are consistent with the role of dopamine in supporting cognitive function underpinned by frontostriatal connections. Therefore, any strategy that protects or restores nigral dopaminergic neurons, and allows for more physiologic dopaminergic transmission than is obtained with exogenous dopamine administration, could preserve or enhance specific cognitive domains.

Treatments aimed at the underlying etiology may slow, delay, or even prevent cognitive decline. There is a strong case to be made for α-Syn-related pathology in the development of cognitive impairment. Human genetics,[30] clinical pathological correlations,[31] and

experimental models[32] all support the role of α-Syn pathology as a driver of PDD. Therefore, approaches to reducing aggregation or limiting the spread of Lewy pathology may slow cognitive decline. These are early days for such approaches and little is known about the right species or form (monomer, oligomers, or aggregates) of α-Syn to target, the safety of altering α-Syn levels, or the extent of change that is necessary for clinical benefit. However, experimental models suggest that active or passive immunotherapy approaches can reduce α-Syn levels, as measured by biochemical assays or immunohistochemistry, and are associated with improvement in cognitive behaviors.[33]

There are important challenges for any programs targeting α-Syn pathology. They must first show safety and then biological activity. This will be difficult, given that there is currently no α-Syn imaging marker. Total CSF α-Syn may be useful for this purpose. However, this has not performed particularly well as a diagnostic or prognostic marker. Several unknowns may make this biomarker difficult to use and interpret, including the uncertain relationship of extra- and intracellular α-Syn levels. The first α-Syn immunotherapy program, an active vaccination, is in early clinical testing and this first wave of clinical studies will help to determine the overall safety of such programs.

Other approaches to disease modification may be particularly important for slowing the rate of cognitive decline. Mutations in glucocerebrosidase (GCase) are the most common genetic risk factor for PD.[30] A reciprocal relationship has been proposed between reduced GCase activity and α-Syn aggregation.[34] GCase carriers with PD appear to have more cognitive impairment, and GCase mutations are associated with DLB.[35] This suggests that approaches to enhance enzyme function, from small-molecule chaperones to enzyme replacement with gene therapy, could slow disease progression and cognitive decline.

β-amyloid and tau may be important targets for cognitive impairment in PD, in addition to their role in AD. The relative contribution of AD-related pathology has been controversial: Genetics, human biomarker studies, and postmortem findings need to be considered in determining whether these targets should be pursued. The association of ApoE4 with PDD has been inconsistent, but this is likely a result of methodological issues. A recent study shows a consistent association with dementia in synucleinopathies.[36] Several postmortem studies have shown a correlation between PDD and β-amyloid pathology. Recent data suggest that both β-amyloid plaques and taucontaining neurofibrillary tangles are contributors to PDD; up to 50% of postmortem brains from patients with PDD met criteria for a secondary diagnosis of AD.[20] Studies assessing CSF amyloid β(1–42) have shown faster rates of cognitive decline in those with lower levels,[37] as well as a potential association with the postural instability gait disorder phenotype,[38] which itself is associated with a more aggressive course and faster cognitive decline. Imaging studies using primarily Pittsburgh compound B (PIB) and PET paint an inconsistent picture. It certainly appears that fibrillar β-amyloid, which is labeled by most tracers, is generally lower than it is in AD or DLB.[39] However, PD subjects with higher-than-average binding appear to have faster rates of cognitive progression.[40]

There are several anti-β-amyloid immunotherapies in clinical development for AD. The right species or form to target remains unclear. The tau biology field is at an earlier stage of

development than β-amyloid. However, a similar case can be made for the role of tau based on genetics and pathology. The question will remain of how important these AD-related pathologies are for PDD, and the only way to answer this will be with natural history studies using relevant imaging and CSF biomarkers. Because of the more evolved imaging tools, β-amyloid and tau may be more-testable protein aggregates to pursue in the near future, rather than α-Syn-based therapies.

Although the progression of cognitive dysfunction is relatively slow, cognitive decline may be a valuable paradigm for testing a range of putative disease-modifying agents. There is a general need for new clinical trial paradigms in PD. The traditional design has focused on *de novo* subjects and motor progression. This is becoming more difficult with earlier use of dopaminergic therapy, and the *de novo* period is the one in which our current therapies are most efficacious. There is considerable interest in conversion from premotor PD to manifest motor PD as a clinical trial paradigm. Low predictive value of premotor features and long timelines for conversion are likely to make this a difficult challenge for drug developers. This approach may only be feasible in select, genetically at-risk cohorts, such as leucine-rich repeat kinase 2 carriers or GCase mutation heterozygotes, in whom disease onset starts at a specific age. In contrast, cognitive decline is a common feature of PD that progresses relentlessly and is relatively unaffected by existing therapies, making it a good marker for disease progression. Diagnostic criteria for mild cognitive impairment, PDD, and natural history studies that focus on the course of cognitive decline and specific cognitive domains will pave the way for using cognitive decline as a key measure of disease progression in disease modification clinical trials with a range of relevant agents.

Alternative Approaches

The potential benefit of exercise and “brain training” on cognitive decline and dementia in PD needs to be better established. The level of mid-life cardiorespiratory fitness has been associated with lower risk of developing all-cause dementia in later life.[41] In cognitively normal older adults, exercise engagement has been associated with reduced PIB binding, as well as higher cerebrospinal amyloid Aβ42 levels,[42] whereas greater levels of physical activity may be associated with higher cerebral white matter integrity[43] and increased gray matter volumes. These effects may be modified, in part, by APO ε4 status.[44]

A recent systematic review studied evidence for efficacy of nonpharmacological therapies in managing cognitive impairment and dementia in PD.[45] Cognitive rehabilitation, physical rehabilitation, exercise, and brain stimulation techniques were considered in this review. The researchers concluded that research in this area is currently very limited in both quality and quantity. Despite this, there is some evidence that aerobic exercise increases executive function and spatial memory in PD.[46,47] The benefits of exercise on cognition in PD may be mediated by raised levels of brain-derived neurotrophic or other trophic factors, increased blood flow, wide-spread effects upon the immune system, neurotransmitter modulation (e.g., glutamatergic neurotransmission), increased dendritic spine density, neurogenesis, or combinations of these factors.[48] Clearly, further work is required to better elucidate the mechanism of action of exercise and the potential size and sustainability of its effect upon cognitive function in PD.

Very few studies have addressed the potential benefits of cognitive training (e.g., regular completion of Sudoku puzzles) upon mental functioning in PD, either alone or in combination with exercise training. Most have been nonrandomized or recruited small numbers of participants.[45] This needs to be addressed in future studies. As "proof of principle" that such training may have real-world effects, a recent randomized study showed that cognitive speed of processing training could improve useful field-of-view test (UFOV) performance in people with PD.[49] UFOV is a robust predictor of driving performance in aging and PD.

Other potential, nonpharmacological approaches include exploring novel DBS targets. Freund et al. reported on the case of a 71-year-old man with PDD, in whom two electrodes were inserted into the cholinergic nucleus basalis of Meynert (nbM), in addition to the STN.[50] Activation of the nBM electrodes resulted in significantly improved attention, concentration, alertness, drive, and spontaneity, which reversed when the stimulator system was switched off. In AD, clinical and preclinical studies have explored the fornix, entorhinal cortex, and nbM as potential DBS targets.[51] Laxton et al. performed the first DBS study in 6 patients with AD, chronically stimulating the fornix/hypothalamus area over 12 months.[52] There was evidence for reduced rate of decline in Mini–Mental State Examination scores, as well as increased cerebral cortical metabolism in these subjects, with autonomic and cardiovascular side effects only observed at high stimulation settings. Further trials are now ongoing in AD, whereas in PDD, the nBM is being actively explored further as a DBS target, given its involvement in memory, attention, arousal, and perception.[53] Given the relative preservation of postsynaptic M1 cholinergic receptors in PDD, compared with AD, it is plausible that enhancing ACh release through nBM stimulation may be associated with significant clinical benefit.

Transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) are noninvasive techniques that may improve cognitive function in cognitively normal and demented individuals. They have not been fully evaluated in the context of PD, although a small study suggested that active tDCS of the left dorsolateral prefrontal cortex could improve working memory in PD.[54] It is conceivable that wearable neurostimulators, in conjunction with mobile EEG, may be developed to deliver tDCS when EEG signatures of confusion or hallucinosis are detected. More speculatively, in the future, optogenetically based technology may be used to target specific interneuronal populations to reduce phenomena such as visual hallucinations.

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References

1. Kulisevsky J, Fernandez de Bobadilla R, Pagonabarraga J, et al. Measuring functional impact of cognitive impairment: validation of the Parkinson's Disease Cognitive Functional Rating Scale. Parkinsonism Relat Disord. 2013; 19:812–817. [PubMed: 23773412]
2. Weintraub D, Shea J, Rubright J, et al. Psychometric properties of the brief Penn Daily Activities Questionnaire (PDAQ) for Parkinson's disease. Mov Disord. 2013; 28:308.

3. Young TL, Granic A, Chen TY, et al. Everyday reasoning abilities in persons with Parkinson's disease. Mov Disord. 2010; 25:2756–2761. [PubMed: 20939079]
4. Manning K, Clarke C, Lorry A, et al. Medication management and neuropsychological performance in Parkinson's disease. Clin Neuropsychol. 2012; 26:45–58. [PubMed: 22150514]
5. Martin RC, Okonkwo OC, Hill J, et al. Medical decision-making capacity in cognitively impaired Parkinson's disease patients without dementia. Mov Disord. 2008; 23:1867–1874. [PubMed: 18759361]
6. Pirogovsky E, Martinez-Hannon M, Schiehser D, et al. Predictors of performance-based measures of instrumental activities of daily living in nondemented patients with Parkinson's disease. J Clin Exp Neuropsychol. 2013; 9:926–933. [PubMed: 24074137]
7. Karlawish J, Cary M, Moelter S, et al. Cognitive impairment and PD patients' capacity to consent to research. Neurology. 2013; 81:801–807. [PubMed: 23892706]
8. Amick MM, Grace J, Ott B. Visual and cognitive predictors of driving safety in Parkinson's disease patients. Arch Clin Neuropsychol. 2007; 22:957–967. [PubMed: 17851032]
9. Alexander GE, Ryan L, Bowers D, et al. Characterizing cognitive aging in humans with links to animal models. Front Aging Neurosci. 2012; 4:21. [PubMed: 22988439]
10. Hoshi Y, Uchida Y, Tachikawa M, Inoue T, Ohtsuki S, Terasaki T. Quantitative atlas of blood-brain barrier transporters, receptors, and tight junction proteins in rats and common marmoset. J Pharm Sci. 2013; 102:3343–3355. [PubMed: 23650139]
11. Syväanen S, Lindhe O, Palner M, et al. Species differences in blood-brain barrier transport of three positron emission tomography radioligands with emphasis on P-glycoprotein transport. Drug Metab Dispos. 2009; 37:635–643. [PubMed: 19047468]
12. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:257–262. [PubMed: 21514247]
13. Wang Y, Shi M, Chung KA, et al. Phosphorylated α-synuclein in Parkinson's disease. Sci Transl Med. 2012; 4:121ra20.
14. Maruyama M, Shimada H, Suhara T, et al. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. Neuron. 2013; 79:1094–1108. [PubMed: 24050400]
15. Xia CF, Arteaga J, Chen G, et al. [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. Alzheimers Dement. 2013; 9:666–676. [PubMed: 23411393]
16. Blagbrough IS, Zara C. Animal models for target diseases in gene therapy—using DNA and siRNA delivery strategies. Pharm Res. 2009; 26:1–18. [PubMed: 18841450]
17. Fodero-Tavoletti MT, Mulligan RS, Okamura N, et al. In vitro characterisation of BF227 binding to alpha-synuclein/Lewy bodies. Eur J Pharmacol. 2009; 617:54–58. [PubMed: 19576880]
18. Wang SJ, Hung HM, O'Neill R. Paradigms for adaptive statistical information designs: practical experiences and strategies. Stat Med. 2012; 31:3011–3023. [PubMed: 22927234]
19. G, Shih WJ, Xie T, Lu J. A sample size adjustment procedure for clinical trials based on conditional power. Biostatistics. 2002; 3:277–287. [PubMed: 12933618]
20. Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol. 2012; 72:587–598. [PubMed: 23037886]
21. Ravina B, Putt M, Siderowf A, et al. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. J Neurol Neurosurg Psychiatry. 2005; 76:934–939. [PubMed: 15965198]
22. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004; 351:2509–2518. [PubMed: 15590953]
23. Dubois B, Tolosa E, Katzenschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord. 2012; 27:1230–1238. [PubMed: 22915447]
24. Prickaerts J, van Goethem NP, Chesworth R, et al. EVP-6124, a novel and selective α7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of α7 nicotinic acetylcholine receptors. Neuropharmacology. 2012; 62:1099–1110. [PubMed: 22085888]

25. Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2009; 8:613–618. [PubMed: 19520613]
26. Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010; 9:969–977. [PubMed: 20729148]
27. Arnaldi D, Campus C, Ferrara M, et al. What predicts cognitive decline in de novo Parkinson's disease? Neurobiol Aging. 2012; 33:1127.e11–1127.e20. [PubMed: 22226489]
28. Ravina B, Marek K, Eberly S, et al. Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease. Mov Disord. 2012; 27:1392–1397. [PubMed: 22976926]
29. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the Cam-PaIGN cohort. Brain. 2009; 132:2958–2969. [PubMed: 19812213]
30. Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. Mov Disord. 2013; 28:14–23. [PubMed: 23389780]
31. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Ann NY Acad Sci. 2010; 1184:188–195. [PubMed: 20146698]
32. Lim Y, Kehm VM, Lee EB, et al. α-Syn suppression reverses synaptic and memory defects in a mouse model of dementia with Lewy bodies. J Neurosci. 2011; 31:10076–10087. [PubMed: 21734300]
33. Masliah E, Rockenstein E, Mante M, et al. Passive immunization reduces behavioral and neuropathological deficits in an alphasynuclein transgenic model of Lewy body disease. PLoS One. 2011; 29(6):e19338. [PubMed: 21559417]
34. Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011; 146:37–52. [PubMed: 21700325]
35. Nalls MA, Duran R, Lopez G, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013; 70:727–735. [PubMed: 23588557]
36. Tsuang D, Leverenz JB, Lopez OL, et al. APOE ε4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013; 70:223–228. [PubMed: 23407718]
37. Siderowf A, Xie SX, Hurtig H, et al. CSF amyloid {beta} 1–42 predicts cognitive decline in Parkinson disease. Neurology. 2010; 75:1055–1061. [PubMed: 20720189]
38. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebrospinal fluid β-amyloid 1–42, T-tau, P-tau181, and α-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol. 2013; 70:1277–1287. [PubMed: 23979011]
39. Donaghy P, Thomas AJ, O'Brien JT. Amyloid PET imaging in Lewy body disorders. Am J Geriatr Psychiatry. 2013 Jul 3. pii: S1064-7481(13)00168-1.
40. Gomperts SN, Locascio JJ, Rentz D, et al. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. Neurology. 2013; 80:85–91. [PubMed: 23243071]
41. Defina LF, Willis BL, Radford NB, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. Ann Intern Med. 2013; 158:162–168. [PubMed: 23381040]
42. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol. 2010; 68:311–318. [PubMed: 20818789]
43. Gons RA, Tuladhar AM, de Laat KF, et al. Physical activity is related to the structural integrity of cerebral white matter. Neurology. 2013; 81:971–976. [PubMed: 23921884]
44. Head D, Bugg JM, Goate AM, et al. Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. Arch Neurol. 2012; 69:636–643. [PubMed: 22232206]
45. Hindle JV, Petrelli A, Clare L, Kalbe E. Nonpharmacological enhancement of cognitive function in Parkinson's disease: a systematic review. Mov Disord. 2013; 28:1034–1049. [PubMed: 23426759]
46. Tanaka K, Quadros ACJ, Santos RF, Stella F, Gobbi LT, Gobbi S. Benefits of physical exercise on executive functions in older people with Parkinson's disease. Brain Cogn. 2009; 69:435–441. [PubMed: 19006643]

47. Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson's: benefits for cognition and quality of life. Acta Neurol Scand. 2011; 123:13–19. [PubMed: 20199518]

48. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol. 2013; 12:716–726. [PubMed: 23769598]

49. Edwards JD, Hauser RA, O'Connor ML, Valdés EG, Zesiewicz TA, Uc EY. Randomized trial of cognitive speed of processing training in Parkinson disease. Neurology. 2013; 81:1284–1290. [PubMed: 24014503]

50. Freund HJ, Kuhn J, Lenartz D, et al. Cognitive functions in a patient with Parkinson-dementia syndrome undergoing deep brain stimulation. Arch Neurol. 2009; 66:781–785. [PubMed: 19506141]

51. Hescham S, Lim LW, Jahanshahi A, Blokland A, Temel Y. Deep brain stimulation in dementia-related disorders. Neurosci Biobehav Rev. 2013; 37:2666–2675. [PubMed: 24060532]

52. Laxton AW, Tang-Wai DF, McAndrews MP, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol. 2010; 68:521–534. [PubMed: 20687206]

53. Gratwicke J, Kahan J, Zrinzo L, et al. The nucleus basalis of Meynert: a new target for deep brain stimulation in dementia? Neurosci Biobehav Rev. 2013; 37:2676–2688. [PubMed: 24035740]

54. Boggio PS, Ferrucci R, Rigonatti SP, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci. 2006; 249:31–38. [PubMed: 16843494]