Neurobiology of Aging 36 (2015) 1605.e1–1605.e6

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Brief communication

BDNF polymorphism associates with decline in set shifting in Parkinson's disease

Nicolien M. van der Kolk [a], Arlene D. Speelman [a,1], Marlies van Nimwegen [a,2], Roy P.C. Kessels [b], Joanna IntHout [c], Marina Hakobjan [d], Marten Munneke [a], Bastiaan R. Bloem [a], Bart P. van de Warrenburg [a,*]

[a] Department of Neurology, Donders Institute for Brain, Cognition, and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Department of Medical Psychology, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Department for Health Evidence, Radboud University Medical Center, Nijmegen, the Netherlands
[d] Department of Human Genetics, Research Lab for Multifactorial Diseases, Radboud University Medical Center, Nijmegen, the Netherlands

ARTICLE INFO

Article history:
Received 10 March 2014
Received in revised form 14 August 2014
Accepted 22 August 2014
Available online 27 August 2014

Keywords:
BDNF
Parkinson's disease
Executive function

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder caused by nigrostriatal dopaminergic degeneration. Brain-derived neurotrophic factor (BDNF) is a key protein in brain plasticity and is particularly important for survival of dopaminergic neurons. The Val66Met polymorphism of *BDNF* (rs6265) has been associated with functional differences (mainly cognitive) between healthy adults and also with differences in the clinical expression of several other neuropsychiatric illnesses including PD. However, these studies used different outcome measures, have not been replicated, and were cross sectional, making it difficult to establish the role of *BDNF* in the clinical variability of PD. Here, a large cohort of 384 PD patients were followed up for 2 years, and associations between *BDNF* genotype and various clinical characteristics were examined. The *BDNF* Met-allele carriers showed a significantly smaller decline in set shifting during follow-up compared with the homozygous *BDNF* Val-allele carriers. Contrary to previous assumptions, these results indicate that mental flexibility is one of the cognitive processes that may benefit from the *BDNF* Met allele in PD patients.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by disabling motor (tremor, bradykinesia, rigidity, and postural instability) and nonmotor (e.g., sleep, mood, and cognitive disturbances) symptoms. Degeneration of nigrostriatal dopaminergic neurons is the pathologic hallmark of the disease. Although the direct cause of this degeneration is unknown, it is believed that it results from the interaction between certain environmental and genetic factors. Such factors probably also contribute to the heterogeneity seen in the clinical presentation and progression of the disease. The gene encoding brain-derived neurotrophic factor (*BDNF*) is interesting in this respect, as its product is widely distributed throughout the brain and is especially important for survival and differentiation of dopaminergic neurons in the basal ganglia (Baydyuk et al., 2011b; Hyman et al., 1991). BDNF directs growth and differentiation of the developing nervous system, but it has also a modulating role in synaptic plasticity after the nervous system has matured (McAllister et al., 1999). Not only does it stimulate neuritic outgrowth and synaptic transmission after injury (McAllister et al., 1999; Rothman and Mattson, 2013) but it also prevents dopaminergic cell loss in an experimental animal model of PD (Levivier et al., 1995). Moreover, BDNF signaling, via its Tropomyosin related kinase B receptor tyrosine kinase, is important for the survival of nigrostriatal dopaminergic neurons in the aging brain (Baquet et al., 2004; Baydyuk et al., 2011a). In fact, postmortem studies revealed a reduced expression of BDNF messenger RNA in the surviving neurons of the substantia nigra pars compacta of PD patients compared with controls (Howells et al., 2000). Also, serum levels of BDNF are directly correlated with the amount of striatal dopamine transporter binding (Ziebell et al., 2012) and the severity of motor symptoms in PD (Scalzo et al., 2010).

Val66Met (rs6265) is a common single-nucleotide polymorphism causing a valine (Val) to methionine (Met) substitution

* Corresponding author at: Department of Neurology, Donders Institute for Brain, Cognition, and Behavior, Radboud University Medical Center, Reinier Postlaan 4, PO Box 9101, Nijmegen, the Netherlands. Tel.: +31 243616600; fax: +31 243542211.
E-mail address: Bart.vandewarrenburg@radboudumc.nl (B.P. van de Warrenburg).
[1] Present address: Comprehensive Cancer Centre Netherlands, PO Box 231, 5600AE Eindhoven, the Netherlands.
[2] Present address: Hogeschool Utrecht University of Applied Sciences, P.O. Box 13102, 3507 LC Utrecht, the Netherlands.

0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.08.023

at amino acid position 66 in the prodomain of the BDNF protein. Approximately 20%–30% of the human population is heterozygous for the Met allele. The presence of the minor allele (Met) of this polymorphism causes an altered intracellular distribution and a reduced activity-induced secretion of the BDNF protein in neurons (Chen et al., 2004). Compared with Val homozygotes, subjects with the Met allele show a worse performance in motor-based learning tasks, compatible with a diminished capacity for motor cortex plasticity (Kleim et al., 2006; McHughen et al., 2010). In addition, BDNF genes have been shown to modulate dopamine-dependent executive functions, specifically set shifting and spatial working memory (SWM), effects that may even be enhanced in older adults (Nagel et al., 2008). Furthermore, hippocampal-dependent episodic memory function is affected by the *BDNF* Val66met polymorphism (Egan et al., 2003).

Given the role as a trophic factor for dopaminergic neurons and the diminished plasticity capacity of Met-allele carriers, a possible role for this *BDNF* polymorphism in the pathogenesis of PD has been previously examined. The prevalence of this polymorphism in PD, however, appears to be similar to that of the healthy population (Zintzaras and Hadjigeorgiou, 2005). In recent years, attention therefore, shifted toward the possibility of a modifiable role of the *BDNF* polymorphism on the clinical expression of PD. However, these studies are sparse and have provided conflicting results. The *BDNF* Met/Met genotype was, for instance, associated with a higher risk of developing dyskinesias earlier in the course of treatment with dopaminergic agents (Foltynie et al., 2009) and an older age of onset (Karamohamed et al., 2005), whereas other studies were unable to find any association with clinical characteristics, including dyskinesias or age at onset (Gao et al., 2010; Karakasis et al., 2011). As these studies used different outcome measures, have individually not been replicated, and were all cross sectional, it is difficult to establish the exact role, if any, of *BDNF* in explaining the clinical variability of PD.

We performed a study to explore the associations between *BDNF* genotype and various clinical parameters in a large cohort of PD patients who have participated in a 2-year follow-up study (the ParkFit study) (van Nimwegen et al., 2010, 2012) allowing both cross-sectional and longitudinal analyses.

2. Participants and methods

Of the 586 patients who participated in the ParkFit study (van Nimwegen et al., 2010, 2012), 392 consented to blood sampling. The following clinical variables, gathered in the original ParkFit study, were included in the present study: IQ (Dutch version of the National Adult Reading Test), gender, age at PD onset, age at baseline, disease duration, Unified Parkinson's Disease Rating Scale (UPDRS) motor score, Hoehn and Yahr stage, Levodopa Equivalent Dose (LED, Tomlinson et al., 2010) at baseline, 6-Minute Walking Test, Nine-Hole Peg Test (NHPT), the Hospital Anxiety and Depression Scale (HADS), the time spent on outdoor and sport activities (measured with the Longitudinal Aging Study Amsterdam Physical Activity Questionnaire [LAPAQ], Stel et al., 2004), and a neuropsychological test battery. The neuropsychological test battery consisted of 3 computerized tests of the Cambridge Neuropsychological Automated Testing Battery (CANTAB), Rey Complex Figure Test (copy trial), and semantic and phonemic verbal fluency (number of words within 1 minute). The following cognitive domains were tested using the CANTAB—(1) executive function (Intra-Extra Dimensional Set Shifting [IED]: total errors adjusted for stages not completed and number of patients passing the Extra-dimensional Set Shifting [EDS] stage); (2) learning and episodic memory (Paired Associate Learning [PAL] Test: total errors adjusted for stages not completed); and (3) working memory (SWM Test: within- and between-search errors). The cognitive tests were selected based on the involvement of their cognitive domains in PD (Aarsland et al., 2011). Specifically, SWM, IED, and PAL can be hypothesized to be sensitive to *BDNF* genotype, although the selection of tests for the original trial was not guided by such an a priori hypothesis. All patients were tested in their "on" phase of dopaminergic medication. Full ethical approval has been granted for the study (CMO Regio Arnhem, Nijmegen). Written informed consent was given by all patients before enrollment in the trial.

2.1. Genotyping

Blood sampling was performed in 392 participants. For *BDNF* genotyping (Val66Met, G196A, and rs6265), peripheral venous blood was drawn from the study subjects. Genomic DNA was extracted using standard protocols. Genetic analyses were carried out at the Department of Human Genetics of the Radboud University Medical Center using Taqman genotyping as described previously (Gerritsen et al., 2012). Genotyping was performed blinded to the clinical status.

2.2. Statistics

Given the small number of patients in the Met/Met group, the Met allele–containing groups were combined, resulting in 2 groups: the homozygous valine (Val/Val) and the Met-containing (Val/Met and Met/Met) groups. Only when significant differences between the 2 groups were found, an additional analysis of covariance (ANCOVA) was performed separating the genotype into 3 groups (Val/Val, Val/Met, and Met/Met) to determine whether the effect size differed between the 3 genotypes. As the data of the LAPAQ outdoor, the CANTAB Tests, Rey Complex Figure Test, HADS, LED, and NHPT were positively skewed, logarithmic transformations were performed for these variables. Baseline characteristics were compared between the homozygote *BDNF* Val allele carriers versus the Met-allele carriers: continuous variables by means of *t* tests (if necessary after log transformation) and dichotomous variables with chi-square tests.

Changes between baseline and the mean score during the follow-up period were calculated. For UPDRS, 6-Minute Walking Test, NHPT, LAPAQ, IED, PAL, SWM, Rey Complex Figure drawing, semantic and phonemic fluency, and HADS (if necessary after log transformation), the relation between these changes and the genotype was evaluated by means of ANCOVA, with adjustment for the corresponding baseline value and the preselected variables age at baseline, IQ at baseline, disease duration, gender, and treatment arm. In addition, clinical variables that showed an uncorrected statistically significant difference ($p < 0.05$) between the genotype groups at baseline were used as a covariate. Results of log-transformed variables were back transformed. For the IED stages, the number of patients who reached the EDS at baseline and during either one of the follow-up assessments were calculated, resulting in a new variable (EDS change) showing whether a patient was improved, equal, or worse with respect to EDS stage compared with baseline. The association between the EDS change and the genotype was evaluated by ordinal logistic regression analysis, with adjustment for the same variables as used in the ANCOVA analysis.

To correct for inflated type I errors because of multiple testing, a Bonferroni adjustment was applied, resulting in a significance level of 0.0033. All *p* values are 2 sided.

3. Results

Genotyping was successfully performed in 384 participants. As expected, the Val/Val genotype was more prevalent (59.1%) than the

Val/Met (38.3%) and Met/Met (2.6%) variants. The LED at baseline was significantly lower in the Met allele–containing group compared with the Val/Val group. None of the variables including demographic characteristics and motor and nonmotor symptoms showed a significant difference between *BDNF* genotypes at baseline (Table 1).

Changes from baseline to follow-up are displayed in Table 2. Increases in the total number of errors made on the IED task were significantly different between the genotypes. Those carrying at least 1 Met allele showed a better preserved performance on this test compared with those with the homozygous Val genotype. When analyzing the 3 genotype groups separately, the number of errors on the IED task showed significantly less increase over time in the groups with Met alleles (Val/Val 47%, Val/Met 12%, and Met/Met 3% increases in errors during the IED at follow-up, p value = 0.003). Correcting for the UPDRS motor score at baseline did not alter the results.

4. Discussion

The present study is the first to show a significant association between the Val66Met *BDNF* polymorphism and the course of several cognitive functions in PD patients over time. Specifically, the *BDNF* Met allele appeared to be associated with less decline in executive functioning.

At first glance, our results might seem contradictory to the overall believe that the Met allele is associated with a decreased neuroplastic capacity and therefore decreased cerebral functioning. However, the effects of the polymorphism appear to be highly complex. For instance, it is suggested that at younger age, the Val/Val genotype provides some neuronal and cognitive benefits (better episodic memory and task switching) (Egan et al., 2003; Erickson et al., 2008). With increasing age, those with this genotype, however, show a faster decay in task-switching performance (Erickson et al., 2008). Several studies in the elderly indicate that at an older age the Val/Met genotype provides some protection against cognitive decline (Erickson et al., 2008; Gajewski et al., 2011; Harris et al., 2006), whereas others observed an association with an increased incidence of dementia for this genotype, especially in patients with a sedentary lifestyle (Kim et al., 2011). The latter indicates that even more factors play a role in the downstream "phenotypic" effects of this polymorphism. The different tests used in these studies also suggest that the effect might be highly specific to certain cognitive processes; this could explain why conflicting results are found when a more global cognitive function test like the Mini-Mental State Examination (Kim et al., 2011) is used. Relevant to the results of our study is, for example, the fact that the Met allele has been shown to be associated with superior memory-based task switching, interference control, and response inhibition in healthy elderly (Beste et al., 2010a; Gajewski et al., 2011, 2012). Moreover, a lower age-related increase in switching costs in healthy older adults was found over a 10-year follow-up period (Erickson et al., 2008), and a specific advantage for the tower of London task was observed in

Table 1
Baseline characteristics according to the genotype

	Val/Val (n = 227)	Val/Met and Met/Met (n = 157)	p Value
Demographics			
Age at baseline (y)[a]	65.2 (7.8)	65.9 (7.6)	0.367
Gender (no. of men)[b]	147 (64.3%)	104 (66.2%)	0.663
Intervention (no. of ParkFit program)[b]	110 (48.5%)	85 (54.1%)	0.300
IQ at baseline[a]	102.5 (19.4)	102.7 (17.6)	0.916
MMSE at baseline[a]	28 (1.6)	28 (1.6)	0.356
Disease characteristics			
Disease duration (y)[a]	5.4 (4.2)	5.1 (5.0)	0.629
Age at onset (y)[a]	59.8 (8.7)	60.8 (9.1)	0.300
LED at baseline[a]	480 (300–670)	363.9 (160–608.9)	**0.004**
Motor symptoms			
UPDRS III motor part[a]	31.7 (9.7)	32.1 (11.0)	0.687
Modified H&Y stage[b]			0.325
1	4 (1.8%)	4 (2.5%)	
1.5	6 (2.6%)	5 (3.2%)	
2	171 (75.3%)	124 (79%)	
2.5	36 (15.9%)	14 (8.9%)	
3	10 (4.4%)	10 (6.4%)	
6MWT (m)[a]	390.8 (87.5)	397.7 (82.4)	0.435
NHPT (s)[a]	30.0 (26.3–36)	30.2 (26.3–36.5)	0.937
LAPAQ outdoor (min)[a]	330 (177–555)	340 (192–560)	0.578
Nonmotor symptoms			
HADS total[a]	9 (5–14)	9 (5–13)	0.693
HADS, depression[a]	4 (2–7)	4 (2–7)	0.725
HADS, anxiety[a]	5 (3–7)	5 (3–7)	0.710
IED (total errors, adjusted)[a]	38 (18–60)	47.5 (19–61)	0.320
IED (no. of patients who reached the EDS stage)[b]	129 (57.8%)	84 (53.8%)	0.463
PAL Test (total errors, 6 shapes, adjusted)[a]	8 (4–24)	10 (4–24.8)	0.312
SWM (between errors)[a]	40 (25–60.3)	41 (27–55)	0.889
SWM (within errors)[a]	2 (0–4)	2 (0–4)	0.889
Complex figure drawing (total errors)[a]	29 (24–32)	28 (24.5–33)	0.602
Semantic fluency (no. of words)[a]	18.8 (5.6)	18.6 (5.5)	0.659
Phonemic fluency (no. of words)[a]	11.1 (4.7)	11.7 (4.1)	0.193

Data reflect mean (standard deviation), median (interquartile range), or n (%).
p-values stated in bold are considered significant with a cut-off value of $p < 0.05$.
Key: EDS, Extradimensional Set Shifting; HADS, Hospital Anxiety and Depression Scale; H&Y, Hoehn and Yahr stages; IED, Intra-Extra Dimensional Set Shifting; LAPAQ, LASA Physical Activity Questionnaire; LED, Levodopa Equivalent Dose; Met, methionine; MMSE, Mini-Mental State Examination; NHPT, Nine-Hole Peg Test; PAL, Paired Associate Learning; SWM, Spatial Working Memory; UPDRS, Unified Parkinson's Disease Rating Scale; Val, valine; 6MWT, 6-Minute Walking Test.
[a] Analyses were performed (if necessary after logarithmic transformation) using a t test.
[b] Analyses were performed (if necessary after logarithmic transformation) using a chi-square test.

Table 2
Course of clinical parameters during follow-up

	Within-group comparison	Between-group comparison	
	Mean estimated change from baseline (95% CI)	Mean estimated difference between genotypes during follow-up (95% CI)	*p* Value
Nonmotor symptoms			
IED (total errors, adjusted)[a]			
Val/Val	47.0% (33, 6%)	32.1% (12.9, 54.7%)	**0.001**
Val/Met and Met/Met	11.0% (−2, 3%)		
EDS change (increase in the number of patients who reached the EDS stage of the IED)[b,c]			
Val/Val	17.9%	OR 0.6 (0.4–0.9)	0.026
Val/Met	29.5%	OR 1 (reference)	
PAL Test (total errors, adjusted)[a]			
Val/Val	−4.0% (−15.0, 8.0%)	−11.4% (−26.2, 6.4%)	0.194
Val/Met and Met/Met	8.0% (−6.0, 25.0%)		
SWM (within errors)[a]			
Val/Val	−3.0% (−15%, 11%)	−14.5% (−30.3, 4.9%)	0.132
Val/Met and Met/Met	14.0% (−3%, 34%)		
SWM (between errors)[a]			
Val/Val	6.0% (−0.4, 13%)	−2.3% (−11.5, 118.2%)	0.656
Val/Met and Met/Met	9.0% (0.4, 18%)		
Phonemic Fluency (no. of words)[d]			
Val/Val	−0.2 (−0.3, 0.3)	0.1 (−0.6, 0.9)	0.718
Val/Met and Met/Met	−0.3 (−0.3, 0.4)		
Semantic fluency (no. of words)[d]			
Val/Val	−6.9 (−7.3, −6,4)	−1.0 (−1.8, −0.3)	0.006
Val/Met and Met/Met	−5.8 (−6.4, −5.3)		
Complex Figure Rey (total errors)[a]			
Val/Val	2.0% (−0.2, 5.0%)	−0.7% (−4.5, 3.3%)	0.744
Val/Met and Met/Met	3.0% (−0.01, 6.0%)		
HADS total score[a]			
Val/Val	12.0% (5.0, 21.0%)	3.3% (−7.5, 15.3%)	0.573
Val/Met and Met/Met	9.0% (−0.4, 19.0%)		
HADS, anxiety[a]			
Val/Val	10.0% (3.0, 18.0%)	0% (−10.7, 12.0%)	0.997
Val/Met and Met/Met	8.0% (−0.2, 17.0%)		
HADS, depression[a]			
Val/Val	15.0% (6, 25.0%)	1.4% (−10.6, 14.9%)	0.831
Val/Met and Met/Met	14.0% (3, 26.0%)		
Motor functions			
6MWT (m)[d]			
Val/Val	0.4 (−7.8, 8.6)	4.2 (−8.4, 16.8)	0.511
Val/Met and Met/Met	−3.8 (−13.8, 6.2)		
NHPT (s)[a]			
Val/Val	−2.0% (−4.0%, 0.8)	−1.0% (−3.1, 5.1%)	0.637
Val/Met and Met/Met	−3.0% (−5.0, 0.5%)		
UPDRS[d]			
Val/Val	5.1 (3.9, 6.2)	0.4 (−1.3, 2.2)	0.637
Val/Met and Met/Met	4.7 (3.3, 6.0)		
LAPAQ outdoor (min)[a]			
Val/Val	−2% (−13.0, 11%)	13.0% (−6.5, 36.3%)	0.206
Val/Met and Met/Met	−13% (−25.0, 1%)		

Values are corrected for the corresponding baseline value, age at baseline, IQ at baseline, disease duration, gender, treatment arm, and LED at baseline. Analyses were performed using an analysis of covariance or ordinal regression analysis (EDS change).
p-values stated in bold are considered significant with a cut-off value of $p < 0.0033$.
Key: CI, confidence interval; EDS, Extradimensional Set Shifting; HADS, Hospital Anxiety and Depression Scale; H&Y, Hoehn and Yahr stages; IED, Intra-Extra Dimensional Set Shifting; LAPAQ, LASA Physical Activity Questionnaire; LED, Levodopa Equivalent Dose; Met, methionine; MMSE, Mini-Mental State Examination; NHPT, Nine-Hole Peg Test; OR, odds ratio; PAL, Paired Associate Learning; SWM, Spatial Working Memory; UPDRS, Unified Parkinson's Disease Rating Scale; Val, valine; 6MWT, 6-Minute Walking Test.
[a] Mean estimated change and difference data reflect percentages.
[b] Mean estimated change and difference data reflect OR.
[c] The EDS occurs at IED stage 8. For the within-group comparison, the percentage of patients who were able to reach this stage at follow-up, but not at baseline (i.e., they improved), is shown. The between-group comparison depicts the likelihood that patients reached the EDS stage during follow-up if they did not reach the EDS stage at baseline ("improved") compared with the likelihood that patients performed similar to baseline or decreased in performance during follow-up.
[d] Mean estimated change and difference data reflect absolute numbers.

PD patients carrying the Met allele (Foltynie et al., 2005). Therefore, these previous data, together with the present study, suggest that some executive functions that are disrupted in normal aging (Wecker et al., 2000, 2005) and early-stage PD (Cools et al., 2001) seem to benefit from the Met allele at an older age in both healthy adults and early-stage PD patients.

The explanation for the better preservation of this part of executive functioning in the Met-allele carriers is merely speculative. A change in the balance between the direct and indirect nigrostriatal pathways seems to be involved, as decreases in nigrostriatal activity are related to increases in response inhibitory performance, which might result in better set shifting (Beste et al., 2010a, 2010b). Correspondingly, high midbrain D3 receptor availability (the expression of which is controlled by BDNF, Guillin et al., 2001) is associated with reduced functional connectivity between the orbitofrontal cortex and frontoparietal networks (Cole et al., 2012), which are implicated in executive function. Inhibition control plays a part in the CANTAB IED, but not in the CANTAB SWM,

offering a possible explanation for the lack of effect on the SWM Test. Interestingly, the dopamine D1, but not the D3 receptor, was found to play a role in SWM in mice (Xing et al., 2012). Consistent with our observation, previous studies in healthy adults did not find a difference on working memory between the *BDNF* genotypes either (Hansell et al., 2007). Although there is evidence that hippocampal-dependent episodic memory function (as measured with the PAL subtest) is also modulated by the *BDNF* genotype, episodic memory deficits are not the most prominent cognitive impairments in PD patients (Hildebrandt et al., 2013). This may explain why we did not observe a relation in our patient group. Possibly, long-term follow-up assessments are required to reveal such an association, as a significant proportion of patients will develop episodic memory function or even dementia.

As activity-dependent secretion of BDNF is attenuated by both the *BDNF* Met allele and aging (Adlard et al., 2005; Hayashi et al., 2001), it is likely that a crucial threshold for BDNF secretion exists that allows the balance to shift. This could offer a possible explanation for why the observed difference in executive function is found in elderly and not in young adult Met-allele carriers. The fact that these results are found both in PD patients and the healthy elderly indicates that it is not disease specific but rather polymorphism and age specific. The balance between the amount of activity-dependent BDNF secretion in a specific area of the brain and performance on a specific cognitive function test apparently differs between the cognitive domains. Because of the ongoing dopamine depletion in PD, it is conceivable that the observed benefit might fade in more advanced stages.

Despite the large number of patients included in the present study, the Met/Met genotype group was small, which has hampered reliable explorations of dose-response relations. Moreover, the intervention that patients received could potentially have interfered with the BDNF effect as the goal of the intervention was to increase physical activity. However, the result for the primary outcome for physical activity of the ParkFit trail was negative, and we also corrected for the intervention in the analyses.

Our results need to be confirmed in other PD cohorts, and similar studies that explore the effect of other genetic variants on the phenotypic variability of PD would be of high interest.

Disclosure statement

All authors state that they received no support from any organization for the submitted work (other than those listed under funding).

Acknowledgements

We would like to thank all the patients who participated in this study and Ms Y. Cornelissen for her assistance in collecting the blood samples. Funding: The ParkFit study was primarily funded by the Netherlands Organization for Health Research and Development (75020012) and the Michael J. Fox Foundation for Parkinson's Research. Additional financial support was provided by VGZ (Health Insurance Company), GlaxoSmithKline, and the National Parkinson Foundation. The study sponsors played no role in study design; data collection, analysis, and interpretation; or writing of the article and the decision to submit it for publication. All researchers' activities were independent of the funding source, and the research team had full and unrestricted access to all the data. Ethical approval: full ethical approval has been granted for this study (CMO Regio Arnhem, Nijmegen). Written informed consent was given by all patients before enrollment in the trial.

References

Aarsland, D., Bronnick, K., Fladby, T., 2011. Mild cognitive impairment in Parkinson's disease. Curr. Neurol. Neurosci. Rep. 11, 371–378.
Adlard, P.A., Perreau, V.M., Cotman, C.W., 2005. The exercise-induced expression of BDNF within the hippocampus varies across life-span. Neurobiol. Aging 26, 511–520.
Baquet, Z.C., Gorski, J.A., Jones, K.R., 2004. Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. J. Neurosci. 24, 4250–4258.
Baydyuk, M., Nguyen, M.T., Xu, B., 2011a. Chronic deprivation of TrkB signaling leads to selective late-onset nigrostriatal dopaminergic degeneration. Exp. Neurol. 228, 118–125.
Baydyuk, M., Russell, T., Liao, G.Y., Zang, K., An, J.J., Reichardt, L.F., Xu, B., 2011b. TrkB receptor controls striatal formation by regulating the number of newborn striatal neurons. Proc. Natl. Acad. Sci. U. S. A. 108, 1669–1674.
Beste, C., Baune, B.T., Domschke, K., Falkenstein, M., Konrad, C., 2010a. Paradoxical association of the brain-derived-neurotrophic-factor val66met genotype with response inhibition. Neuroscience 166, 178–184.
Beste, C., Kolev, V., Yordanova, J., Domschke, K., Falkenstein, M., Baune, B.T., Konrad, C., 2010b. The role of the BDNF Val66Met polymorphism for the synchronization of error-specific neural networks. J. Neurosci. 30, 10727–10733.
Chen, Z.Y., Patel, P.D., Sant, G., Meng, C.X., Teng, K.K., Hempstead, B.L., Lee, F.S., 2004. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. J. Neurosci. 24, 4401–4411.
Cole, D.M., Beckmann, C.F., Searle, G.E., Plisson, C., Tziortzi, A.C., Nichols, T.E., Gunn, R.N., Matthews, P.M., Rabiner, E.A., Beaver, J.D., 2012. Orbitofrontal connectivity with resting-state networks is associated with midbrain dopamine D3 receptor availability. Cereb. Cortex 22, 2784–2793.
Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Mechanisms of cognitive set flexibility in Parkinson's disease. Brain 124 (Pt 12), 2503–2512.
Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269.
Erickson, K.I., Kim, J.S., Suever, B.L., Voss, M.W., Francis, B.M., Kramer, A.F., 2008. Genetic contributions to age-related decline in executive function: a 10-year longitudinal study of COMT and BDNF polymorphisms. Front. Hum. Neurosci. 2, 11.
Foltynie, T., Cheeran, B., Williams-Gray, C.H., Edwards, M.J., Schneider, S.A., Weinberger, D., Rothwell, J.C., Barker, R.A., Bhatia, K.P., 2009. BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 80, 141–144.
Foltynie, T., Lewis, S.G., Goldberg, T.E., Blackwell, A.D., Kolachana, B.S., Weinberger, D.R., Robbins, T.W., Barker, R.A., 2005. The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. J. Neurol. 252, 833–838.
Gajewski, P.D., Hengstler, J.G., Golka, K., Falkenstein, M., Beste, C., 2011. The Met-allele of the BDNF Val66Met polymorphism enhances task switching in elderly. Neurobiol. Aging 32, 2327.e7–2327.e19.
Gajewski, P.D., Hengstler, J.G., Golka, K., Falkenstein, M., Beste, C., 2012. The Met-genotype of the BDNF Val66Met polymorphism is associated with reduced Stroop interference in elderly. Neuropsychologia 50, 3554–3563.
Gao, L., Diaz-Corrales, F.J., Carrillo, F., Diaz-Martin, J., Caceres-Redondo, M.T., Carballo, M., Palomino, A., Lopez-Barneo, J., Mir, P., 2010. Brain-derived neurotrophic factor G196A polymorphism and clinical features in Parkinson's disease. Acta Neurol. Scand. 122, 41–45.
Gerritsen, L., Tendolkar, I., Franke, B., Vasquez, A.A., Kooijman, S., Buitelaar, J., Fernandez, G., Rijpkema, M., 2012. BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. Mol. Psychiatry 17, 597–603.
Guillin, O., Diaz, J., Carroll, P., Griffon, N., Schwartz, J.C., Sokoloff, P., 2001. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature 411, 86–89.
Hansell, N.K., James, M.R., Duffy, D.L., Birley, A.J., Luciano, M., Geffen, G.M., Wright, M.J., Montgomery, G.W., Martin, N.G., 2007. Effect of the BDNF V166M polymorphism on working memory in healthy adolescents. Genes Brain Behav. 6, 260–268.
Harris, S.E., Fox, H., Wright, A.F., Hayward, C., Starr, J.M., Whalley, L.J., Deary, I.J., 2006. The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol. Psychiatry 11, 505–513.
Hayashi, M., Mistunaga, F., Ohira, K., Shimizu, K., 2001. Changes in BDNF-immunoreactive structures in the hippocampal formation of the aged macaque monkey. Brain Res. 918, 191–196.
Hildebrandt, H., Fink, F., Kastrup, A., Haupts, M., Eling, P., 2013. Cognitive profiles of patients with mild cognitive impairment or dementia in Alzheimer's or Parkinson's disease. Dement. Geriatr. Cogn. Dis. Extra 3, 102–112.
Howells, D.W., Porritt, M.J., Wong, J.Y., Batchelor, P.E., Kalnins, R., Hughes, A.J., Donnan, G.A., 2000. Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp. Neurol. 166, 127–135.
Hyman, C., Hofer, M., Barde, Y.A., Juhasz, M., Yancopoulos, G.D., Squinto, S.P., Lindsay, R.M., 1991. BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350, 230–232.

Karakasis, C., Kalinderi, K., Katsarou, Z., Fidani, L., Bostantjopoulou, S., 2011. Association of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism with Parkinson's disease in a Greek population. J. Clin. Neurosci. 18, 1744–1745.

Karamohamed, S., Latourelle, J.C., Racette, B.A., Perlmutter, J.S., Wooten, G.F., Lew, M., Klein, C., Shill, H., Golbe, L.I., Mark, M.H., Guttman, M., Nicholson, G., Wilk, J.B., Saint-Hilaire, M., DeStefano, A.L., Prakash, R., Tobin, S., Williamson, J., Suchowersky, O., Labell, N., Growdon, B.N., Singer, C., Watts, R., Goldwurm, S., Pezzoli, G., Baker, K.B., Giroux, M.L., Pramstaller, P.P., Burn, D.J., Chinnery, P., Sherman, S., Vieregge, P., Litvan, I., Gusella, J.F., Myers, R.H., Parsian, A., 2005. BDNF genetic variants are associated with onset age of familial Parkinson disease: GenePD Study. Neurology 65, 1823–1825.

Kim, J.M., Stewart, R., Bae, K.Y., Kim, S.W., Yang, S.J., Park, K.H., Shin, I.S., Yoon, J.S., 2011. Role of BDNF val66met polymorphism on the association between physical activity and incident dementia. Neurobiol. Aging 32, 551.e5–551.e12.

Kleim, J.A., Chan, S., Pringle, E., Schallert, K., Procaccio, V., Jimenez, R., Cramer, S.C., 2006. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat. Neurosci. 9, 735–737.

Levivier, M., Przedborski, S., Bencsics, C., Kang, U.J., 1995. Intrastriatal implantation of fibroblasts genetically engineered to produce brain-derived neurotrophic factor prevents degeneration of dopaminergic neurons in a rat model of Parkinson's disease. J. Neurosci. 15, 7810–7820.

McAllister, A.K., Katz, L.C., Lo, D.C., 1999. Neurotrophins and synaptic plasticity. Annu. Rev. Neurosci. 22, 295–318.

McHughen, S.A., Rodriguez, P.F., Kleim, J.A., Kleim, E.D., Marchal Crespo, L., Procaccio, V., Cramer, S.C., 2010. BDNF val66met polymorphism influences motor system function in the human brain. Cereb. Cortex 20, 1254–1262.

Nagel, I.E., Chicherio, C., Li, S.C., von Oertzen, T., Sander, T., Villringer, A., Heekeren, H.R., Backman, L., Lindenberger, U., 2008. Human aging magnifies genetic effects on executive functioning and working memory. Front. Hum. Neurosci. 2, 1.

Rothman, S.M., Mattson, M.P., 2013. Activity-dependent, stress-responsive BDNF signaling and the quest for optimal brain health and resilience throughout the lifespan. Neuroscience 239, 228–240.

Scalzo, P., Kummer, A., Bretas, T.L., Cardoso, F., Teixeira, A.L., 2010. Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J. Neurol. 257, 540–545.

Stel, V.S., Smit, J.H., Pluijm, S.M., Visser, M., Deeg, D.J., Lips, P., 2004. Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. J. Clin. Epidemiol. 57, 252–258.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25, 2649–2653.

van Nimwegen, M., Speelman, A.D., Overeem, S., van de Warrenburg, B.P., Smulders, K., Dontje, M.L., Borm, G.F., Backx, F.J., Bloem, B.R., Munneke, M., 2012. Promotion of physical activity and fitness in sedentary patients with Parkinson's disease, a randomized controlled trial. BMJ 346, f576.

van Nimwegen, M., Speelman, A.D., Smulders, K., Overeem, S., Borm, G.F., Backx, F.J., Bloem, B.R., Munneke, M., 2010. Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. BMC Neurol. 10, 70.

Wecker, N.S., Kramer, J.H., Hallam, B.J., Delis, D.C., 2005. Mental flexibility: age effects on switching. Neuropsychology 19, 345–352.

Wecker, N.S., Kramer, J.H., Wisniewski, A., Delis, D.C., Kaplan, E., 2000. Age effects on executive ability. Neuropsychology 14, 409–414.

Xing, B., Guo, J., Meng, X., Wei, S.G., Li, S.B., 2012. The dopamine D1 but not D3 receptor plays a fundamental role in spatial working memory and BDNF expression in prefrontal cortex of mice. Behav. Brain Res. 235, 36–41.

Ziebell, M., Khalid, U., Klein, A.B., Aznar, S., Thomsen, G., Jensen, P., Knudsen, G.M., 2012. Striatal dopamine transporter binding correlates with serum BDNF levels in patients with striatal dopaminergic neurodegeneration. Neurobiol. Aging 33, 428.e1–428.e5.

Zintzaras, E., Hadjigeorgiou, G.M., 2005. The role of G196A polymorphism in the brain-derived neurotrophic factor gene in the cause of Parkinson's disease: a meta-analysis. J. Hum. Genet. 50, 560–566.