J Neurol (2008) 255:1372–1377
DOI 10.1007/s00415-008-0923-6

ORIGINAL COMMUNICATION

Subclinical sensory abnormalities in unaffected PINK1 heterozygotes

Mirta Fiorio
Enza Maria Valente
Mattia Gambarin
Anna Rita Bentivoglio
Tamara Ialongo
Alberto Albanese
Paolo Barone
Maria Teresa Pellecchia
Francesco Brancati
Giuseppe Moretto
Antonio Fiaschi
Michele Tinazzi

Received: 3 October 2007
Received in revised form: 23 January 2008
Accepted: 15 February 2008
Published online: 3 July 2008

M. Fiorio, PhD (✉) · M. Gambarin, MD · A. Fiaschi, MD · M. Tinazzi, MD
Dept. of Neurological and Vision Sciences
Section of Rehabilitative Neurology
University of Verona
Via Casorati 43
37131 Verona, Italy
Tel.: +39-045/8425124
Fax: +39-045/8425131
E-Mail: mirta.fiorio@medicina.univr.it

E. M. Valente, MD · F. Brancati, MD
IRCCS CSS, Mendel Institute
Viale Regina Margherita 26
00198 Rome, Italy

E. M. Valente, MD
Operative Unit of Pediatric Genetics and Immunology
Dept. of Medical and Surgical Pediatric Sciences
University of Messina
Viale Gazzi
98100 Messina, Italy

A. R. Bentivoglio, MD · T. Ialongo, MD
Institute of Neurology
Catholic University
Largo Gemelli 8
00168 Rome, Italy

A. Albanese, MD
IRCCS National Neurological Institute
Carlo Besta
Via Celoria 11
20133 Milan, Italy

P. Barone, MD · M. T. Pellecchia, MD
Dept. of Neurological Sciences
University Federico II
Corso Umberto I
80138 Naples, Italy

F. Brancati, MD
CeSI, Aging Research Centre and Dept. of Biomedical Sciences
G. d'Annunzio University Foundation
Via dei Vestini 31
66013 Chieti, Italy

G. Moretto, MD · M. Tinazzi, MD
Neurology Unit
Borgo Trento Hospital
Piazzale Stefani 1
37100 Verona, Italy

Abstract *Background* Mutations in the PINK1 gene, encoding a mitochondrial protein kinase, represent the second cause of autosomal recessive parkinsonism (ARP) after Parkin. While homozygous or compound heterozygous mutations in these genes are unequivocally causative of ARP, the role of single heterozygous mutations is still largely debated. An intriguing hypothesis suggests that these mutations could represent a risk factor to develop parkinsonism, by contributing to nigral cell degeneration. Since the substantia nigra plays an important role in temporal processing of sensory stimuli, as revealed from studies in idiopathic PD, we sought to investigate whether any subclinical sensory abnormalities could be detected in patients with PINK1-related parkinsonism and in unaffected PINK1 heterozygous carriers. *Methods* We adopted a psychophysical method, the temporal discrimination paradigm, to assess PINK1 homozygous patients, unaffected relatives who were heterozygous carriers of the same mutations and healthy control subjects. Temporal discrimination threshold (TDT) and temporal order judgement (TOJ) for pairs of tactile, visual or visuo-tactile stimuli were measured according to a standardized protocol. *Findings* Higher mean tactile and visuo-tactile TDTs and TOJs were detected in PINK1 mutation carriers, including not only homozygous patients but also healthy heterozygotes, compared to control subjects (for all comparisons, $p < 0.001$). *Interpretation* In clinically unaffected subjects, the mere presence of a heterozygous PINK1 mutation is sufficient to determine sensory alterations which can be disclosed by a psychophysical task. Deficits in temporal processing might be considered as subclinical signs of alteration at least in PINK1-related parkinsonism.

Key words PINK1 · Parkinson's disease · sensory systems · temporal discrimination · endophenotype

JON 2923

Introduction

Parkinson's disease (PD) is clinically characterized by resting tremor, bradykinesia, rigidity and good response to levodopa. The most significant alteration in PD is the loss of dopaminergic neurons in the substantia nigra pars compacta, an inherent constituent of the basal ganglia, which control movements through the cortical-striato-cortical loop [1]. However, the pathogenetic mechanisms leading to neurodegeneration in PD are only partially understood.

Although the majority of cases are sporadic, mutations in autosomal dominant (SNCA, LRRK2) and recessive (Parkin, PINK1, DJ-1) genes have been identified in a small subset of patients [2]. Autosomal recessive parkinsonism (ARP) differs from idiopathic PD for the earlier age at onset, slower progression and more sustained response to levodopa, yet there is wide phenotypic overlap and no specific clinical clues clearly allow differentiating between genetic and non-genetic PD [3]. While two pathogenic mutations in a recessive gene unequivocally cause ARP, in a large subset of patients only one heterozygous mutation can be detected despite extensive screening. Such heterozygous mutations are also detected in some healthy controls, and their significance is still debated. While these mutations are clearly not sufficient per se to cause the disease, it has been suggested that they could act as susceptibility factors that interplay with other genetic and/or environmental factors in a multifactorial setting [4, 5]. In line with this hypothesis, functional neuroimaging studies have demonstrated subclinical signs of dopaminergic dysfunction in clinically unaffected Parkin or PINK1 heterozygous carriers [6–9], but these results warrant confirmation through alternative approaches.

It has been long believed that the basal ganglia were merely involved in controlling and programming movements. In the last two decades, owing to newly available techniques, the role of these subcortical structures in sensory and perceptual functions has been more precisely defined. Neuroimaging studies (PET and fMRI) demonstrated that basal ganglia play a role in temporal discrimination of sensory stimuli [10, 11] and in the reproduction of short and long time intervals [12]. Moreover, studies in patients with basal ganglia dysfunctions, such as PD and dystonia, revealed that the ability of these patients to process stimuli in time, such as to discriminate the interval between two stimuli [13–17], to estimate and reproduce the duration of a time interval [18, 19], and to tap finger according to precise time interval [19] is highly compromised. Worth noting, a recent study showed that a specific role in temporal processing has to be attributed to the substantia nigra pars compacta [12], the more impaired structure in PD.

The main aims of the present study were 1) to reveal whether PINK1 mutated patients had any dysfunctions in temporal processing of sensory stimuli and 2) to evaluate whether such dysfunctions were present also in healthy carriers of heterozygous mutations, thus representing a possible preclinical sign of disease related to the underlying abnormal genetic substrate. To this purpose, we applied to affected homozygous and non-affected heterozygous mutation carriers, as well as to external control subjects, a paradigm previously developed to investigate temporal discrimination [16, 20], a function already proven to be altered in idiopathic PD [13].

Methods

Participants

We recruited a total of 35 subjects who were part of the following three groups: I) patients with homozygous PINK1 mutations (n = 7); II) unaffected relatives of these patients, who were heterozygous carriers of the same mutations (n = 14); III) external control subjects, in whom PINK1 mutations had been excluded (n = 14). PINK1 exon deletions or multiplications, as well as point mutations and exon rearrangements in the other two ARP genes Parkin and DJ-1, had been also excluded in all cases. Inclusion criteria for all groups were the absence of any neurological diseases (apart from PD in the patients' groups) and normal sight, or corrected to normal.

I) PINK1 homozygous patients

This group was made up of seven patients (4 males and 3 females) with clinical diagnosis of definite PD. Six patients (n. 2, 3, 4, 5, 6 and 7 in Table 1) belonged to the two original PARK6-linked families (families 1 and 2 in Bentivoglio et al., 2001 [21]) and were homozygous for the W437X mutation [22], while one patient (n. 1 in Table 1) was an isolated case from Abruzzi carrying the homozygous A168P mutation [23]. Age ranged from 44 to 73 years (mean 56.6 ± 12.0 years), education level from 5 to 16 years (mean 10.1 ± 3.9 years) and duration of disease from 7 to 27 years (mean 16.4 ± 8.1 years). Patients were examined after overnight withdrawal of their medications including levodopa or dopaminergic drugs; the washout period lasted at least 12 hours. Severity scores were obtained by applying the Unified Parkinson's Disease Rating Scale (UPDRS III) in the off state. Demographic, clinical information of all patients are provided in Table 1.

II) PINK1 asymptomatic heterozygous carriers

Fourteen healthy individuals (3 women and 11 men) heterozygous for either the W437X or the A168P mutation were recruited among rela-

Table 1 Demographic and clinical information about the patients' group

Patient	Age (yrs)	Gender	Duration of disease (yrs)	UPDRS III
1	53	m	16	7
2	44	m	7	6
3	46	f	16	15
4	73	f	8	28
5	57	m	27	12
6	73	m	27	27
7	50	f	14	6

tives of PINK1 homozygous patients (group I). A detailed clinical examination by at least two neurologists with expertise in movement disorders did not disclose any manifestation of clinical parkinsonism. Age ranged from 24 to 79 years (mean 45.8 ± 19.8 years) and education level ranged from 5 to 18 years (mean 10.6 ± 4.5 years).

III) External control subjects

Fourteen unrelated healthy subjects (10 women and 4 men) were also recruited. Age ranged from 32 to 80 years (mean 46.0 ± 15.1 years) and education level ranged from 5 to 18 years (mean 12.1 ± 5.3 years).

Mean age and education levels of the three groups were not significantly different (ANOVA, age: $p = 0.330$; education: $p = 0.595$). All subjects gave their written informed consent prior to participation in the study. The procedure was approved by the institutional ethics committee and the study was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Stimuli and procedure

We applied the temporal discrimination paradigm described in previous studies [16, 20] and briefly summarized here. Pairs of tactile, visual or visuo-tactile stimuli were delivered in blocked, counterbalanced order to the left or right hemispace. Tactile stimuli (electrical shocks) were applied to the left or right index and middle fingers, while visual stimuli (green light emitting diodes) were positioned in front of the subjects and aside from a central fixation point. Intervals between stimuli (ISI) increased from 0 to 400 ms (in 10 ms steps). On each trial, subjects had to report whether stimuli occurred simultaneously or asynchronously. We measured temporal discrimination threshold (TDT), as the first out of three consecutive ISIs at which subjects recognized the stimuli as asynchronous and temporal order judgement (TOJ), as to the first of three consecutive ISIs at which subjects not only recognized the stimuli as separated in time, but also reported correctly which stimulus in the pair preceded (or followed) the other.

Results

Mean intensity of stimulation used in homozygous PINK1 patients (15.9 mA, SD 11.9), asymptomatic PINK1 heterozygotes (15.7 mA, SD 12.2) and external control subjects (14.6 mA, SD 14.5) was comparable (ANOVA, $p = 0.970$).

Since the PINK1 heterozygous carriers group and the control subjects group were unbalanced for gender distribution (3 women/11 men and 10 women/4 men, respectively), we preliminarily ran separate t-tests for independent samples in each group, in order to test whether performance could be influenced by gender. The t-tests had "gender" (male vs. female) as a between-subjects factor and "Combination of stimuli" (visual, tactile and visuo-tactile) and "Side of stimulation" (right and left) as within-subjects factors. Analyses were performed for TDT and TOJ values separately. We found no significant effect of gender on TDT/TOJ neither in the control group (for all comparisons: TDT: $t(12) < 0.098$, $P > 0.114$; TOJ: $t(12) < 0.438$, $P > 0.155$) nor in the heterozygous group (for all comparisons: TDT: $t(12) < 0.984$, $P > 0.232$; TOJ: $t(12) < 0.343$, $P > 0.373$). This suggests that female and male participants perform comparably the TDT task.

TDT and TOJ values were then analyzed through two ANOVAs for repeated measures, in which the between-subjects factor was the "Group" (PINK1 homozygous patients; PINK1 asymptomatic heterozygous carriers; external control subjects), and the within-subjects factors were the "Combination of stimuli" (visual, tactile and visuo-tactile) and the "Side of stimulation" (right and left). Post hoc comparisons were carried out by using t-tests with Bonferroni correction.

The main effect of "Group" was significant (TDT: $F(2,32) = 16.1$, $p < 0.001$; TOJ: $F(2,32) = 24.1$, $p < 0.001$), in that control subjects had lower thresholds (mean ± standard deviation: TDT: 62.2 ± 30.0 ms; TOJ: 66.4 ± 32.4 ms) compared to PINK1 homozygous patients (TDT: 120.4 ± 64.4 ms; TOJ: 155.5 ± 81.3 ms) and to PINK1 unaffected heterozygotes (TDT: 110.7 ± 59.7 ms; TOJ: 129.3 ± 73.5 ms). No difference was observed within the last two groups.

The factor "Combination of stimuli" was also significant (TDT: $F(2,64) = 67.4$, $p < 0.001$; TOJ: $F(2,64) = 68.1$, $p < 0.001$), insofar as visuo-tactile combinations (TDT: 132.0 ± 62.1 ms; TOJ: 148.8 ± 70.1 ms) required longer inter-stimulus intervals than tactile (TDT: 89.8 ± 42.0 ms; TOJ: 115.4 ± 64.1 ms) and visual (TDT: 58.0 ± 20.4 ms; TOJ: 64.1 ± 28.4 ms) combinations. Moreover, temporal thresholds in the tactile combinations were significantly higher than in visual combinations. The interaction "Group" X "Combination of stimuli" (TDT: $F(4,64) = 7.0$, $p < 0.001$; TOJ: $F(4,64) = 9.4$, $p < 0.001$) was also significant. Post hoc comparisons showed that PINK1 patients and PINK1 unaffected heterozygotes were significantly more impaired than control subjects in tactile and visuo-tactile tasks (for all comparisons, TDT: $p < 0.003$; TOJ: $p < 0.001$). Conversely, in the visual combination, only PINK1 homozygous patients had abnormal performance when compared to control subjects (TDT: $p = 0.022$; TOJ: $p = 0.010$). Mean values and standard deviations of the three groups in the three experimental conditions are shown in Fig. 1. Ranges of TDT and TOJ values in the three groups are shown in Table 2.

The Spearman correlation coefficient was used for assessing the possible relationships between the UPDRS severity score and TDT and TOJ. Severity of disease in PINK1 homozygous patients correlated with performance only in the visual condition ($p = 0.006$).

In order to define a threshold value discriminating between PINK1 heterozygous carriers and control subjects, we calculated the upper limit of normal TDT and TOJ. The normal upper limits of TDT and TOJ values were determined as the mean TDT (or TOJ) of the external control group plus 2 standard deviations. These values were calculated for the tactile and visuo-tactile combinations of stimuli, since only these two conditions were significantly different between PINK1 unaffected heterozygotes and controls. Normal upper limits were

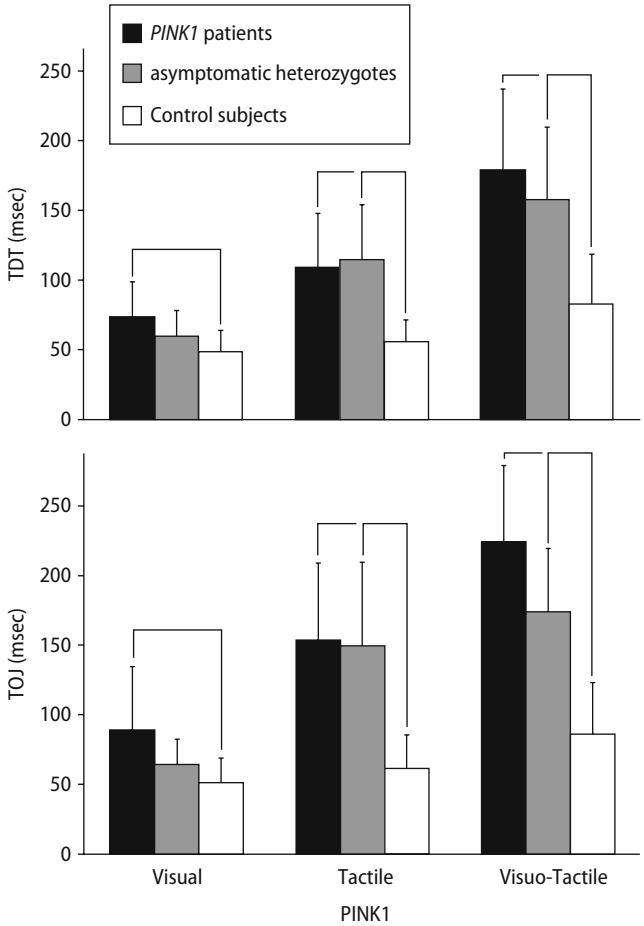

Fig. 1 Mean values and standard deviations of TDT and TOJ of PINK1 homozygous patients, PINK1 unaffected heterozygotes and control subjects in the three combinations of stimuli separately. Lines indicate significant comparisons. Ranges of TDT and TOJ values of the three groups are shown in Table 2

87.4 ms and 154.6 ms for the tactile and visuo-tactile TDT, and 109.3 ms and 160.3 ms for the tactile and visuo-tactile TOJ. Any TDT/TOJ greater than this value could be considered abnormal. Out of 14 PINK1 unaffected heterozygotes, 11 (78.6 %) and 9 (64.3 %) presented abnormal TDTs in the tactile and visuo-tactile condition, respectively. Similarly, abnormal tactile and visuo-tactile TOJs were detected in 10 (71.4 %) and 9 (64.3 %) healthy heterozygotes. Overall, 12 out of 14 heterozygous carriers had at least one abnormal value (85.7 %). Regarding the homozygous patients group, abnormal tactile and visuo-tactile TDT values were detected in 5 (71.4 %) and in 4 (57.1 %) out of 7 patients, respectively. Abnormal tactile and visuo-tactile TOJs were found in 5 (71.4 %) and in 6 (85.7 %) out of 7 patients. Overall, all homozygous patients had at least one abnormal value. Single values of each subject are illustrated in Fig. 2.

Discussion

Our study highlights, for the first time, a link between the presence of PINK1 mutations and the ability to perceive visual, tactile or visuo-tactile stimuli as temporally separated. More specifically, higher temporal discrimination thresholds of tactile and visuo-tactile stimuli have been found in PINK1 mutation carriers, including not only affected individuals, but also unaffected heterozygous carriers, when compared to control subjects. Additional visual impairment was found only in PINK1 affected PD patients, but not in PINK1 non-affected carriers, suggesting that sensory deficits are more extended in the former that in the latter group. This might due to a more general deficit in basal ganglia-related timing function in those who have developed a parkinsonian phenotype. Discrimination thresholds of our PINK1 homozygous patients were closely similar to those described in idiopathic PD patients [13, 18]. These deficits may be related to the primary disorder underlying PD, which can be explained by dysfunctions of a neural network involving basal ganglia. As now largely known, this set of structures is implicated not only in sensory-motor control but also in higher-order functions [24, 25], such as motor and perceptual timing operations [19, 26, 27], and integration of sensory signals from different modalities [28]. Moreover, the specific role of the substantia nigra, pars compacta, in processing time has been recently highlighted [12].

The detection of abnormal temporal discrimination thresholds in heterozygous PINK1 carriers without clinical signs of parkinsonism is of great interest and supports the hypothesis that heterozygous mutations in ARP genes might cause subclinical abnormalities in the basal ganglia circuitry, resulting in impairment to process stimuli in time. Interestingly, a PET study previously performed on three unaffected heterozygotes included in the present study had shown a significant

Table 2 Ranges of TDT and TOJ values (in ms), from minimum to maximum, in the three combinations of stimuli and in the three groups

	TDT			TOJ		
	Visual	Tactile	Visuo-tactile	Visual	Tactile	Visuo-tactile
Homozygotes	32.5–111.3	55–170	115–275	37.5–183.8	76.3–220	148.8–286.5
Heterozygotes	32.5–91.3	61.3–181.3	70–255	32.5–98.8	67.5–268.8	96.3–257.5
Controls	33.8–94	33.8–80	37.5–162	33.8–105	33.8–114	37.5–171

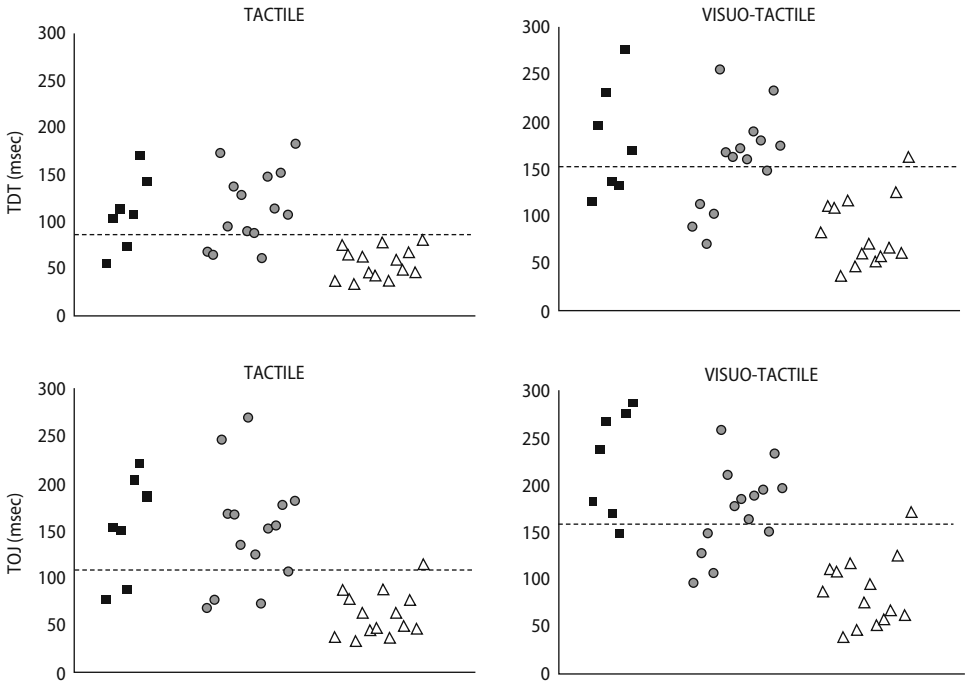

Fig. 2 Scatter plots of tactile and visuo-tactile values in PINK1 homozygous patients (black squares), PINK1 heterozygous carriers (grey circles) and control subjects (white triangles). The dashed line represents the normal upper limit (TDT/TOJ mean values of control subjects + 2SD)

reduction of 18F-dopa uptake in nigrostriatal neurons compared to healthy controls [7]. It is worth noting that, in these three subjects, individual TDT and TOJ values were all above the upper normal limits in both tactile and visuo-tactile tasks. The co-existence of metabolic and psychophysical deficits strengthens the hypothesis of a definite, albeit subclinical dopaminergic dysfunction in the striatum in healthy PINK1 heterozygous carriers. Similar PET results had been previously reported by independent groups showing significant dopaminergic terminal loss in unaffected Parkin carriers [6, 9]. Further supporting these findings, a recent functional MRI study in unaffected heterozygous Parkin carriers revealed a reorganization of the striatocortical motor loops in the context of internally selected movements, interpreted by the authors as a compensatory effort to overcome latent nigrostriatal dysfunction [8]. Interestingly, few Parkin and PINK1 heterozygotes have been reported who showed very mild signs of parkinsonism, not fulfilling the Brain Bank criteria for clinically definite PD but nevertheless suggestive of an underlying dopaminergic defect, as confirmed by PET studies [9, 29]. Taken together, these results imply that heterozygous mutations in ARP genes may act similarly to induce subclinical dopaminergic dysfunction. Whether this latent abnormality may represent a risk factor to develop parkinsonism, along with concurrent genetic and environmental factors, it remains to be established. If this were the case, it should be expected that the frequency of heterozygous mutations in ARP genes would be higher in patients than in healthy controls, but data from various mutation screenings are largely contradictory [30–33]. These discrepancies can depend on a number of variables, such as the pathogenic or benign nature of so called "mutations" or the age of control subjects (young ones are still liable to develop the disease in future years). A recent meta-analysis of the frequency of heterozygous mutations in Parkin and PINK1 genes in large case-control studies disclosed marginally significant odds ratios of 1.9 and 2.1, respectively, suggesting that ARP heterozygous mutations have only a slight effect on PD susceptibility [34]. Studies to explore the functional role of heterozygous mutations in experimental models, analyses of ARP genes in larger cohorts of healthy controls and clinical follow-up of unaffected and mildly affected heterozygous carriers are warranted to shed light on this pivotal issue.

In the present study, the overall proportion of false-negatives is quite low (14.3 %). Only two unaffected heterozygous carriers (male brothers of 25 and 27 years of age and of 13 years of education, heterozygotes for the A168P mutation) had, indeed, both tactile and visuo-tactile values in the normal range. This suggests that, despite the small sample of subjects, our paradigm has good sensitivity in excluding false-negative results. It should be noticed, however, that the normal threshold values given here can not be considered as absolute and generalized. Future studies on larger samples of control subjects and PINK1 heterozygotes are needed to better define precise TDT and TOJ values discriminating between groups.

The deficit of timing functions currently observed in unaffected carriers suggests that a single PINK1 heterozygous mutation may be sufficient to cause abnormality

in the temporal processing of sensory inputs, even in the absence of an overt clinical phenotype. Since the ability to process sensory stimuli is a pre-requisite to correctly plan and control movement execution, its impairment might prejudice an adequate control of motor functions and thus could represent a possible "endophenotypic" trait of basal ganglia dysfunction.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments This work was supported by grants from the Italian Ministry of Health (Ricerca Corrente 2007, Ricerca Finalizzata ex art. 56) and the Italian Telethon Foundation (grant n. GGP04291). We thank Mr. Marco Veronese for helping in figure preparation.

References

1. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9:357–381
2. Farrer MJ (2006) Genetics of Parkinson disease: paradigm shifts and future prospects. Nat Rev Genet 7:306–318
3. Kubo S, Hattori N, Mizuno Y (2006) Recessive Parkinson's disease. Mov Disord 21:885–893
4. Klein C, Lohmann-Hedrich K, Rogaeva E, Schlossmacher MG, Lang AE (2007) Deciphering the role of heterozygous mutations in genes associated with parkinsonism. Lancet Neurol 6:652–662
5. Valente EM, Ferraris A (2007) Heterozygous mutations in genes causing parkinsonism: monogenic disorders go complex. Lancet Neurol 6:576–578
6. Hilker R, Klein C, Ghaemi M, et al. (2001) Positron emission tomographic analysis of the nigrostriatal dopaminergic system in familial parkinsonism associated with mutations in the parkin gene. Ann Neurol 49:367–376
7. Khan NL, Valente EM, Bentivoglio AR, et al. (2002) Clinical and subclinical dopaminergic dysfunction in PARK6-linked parkinsonism: an 18F-dopa PET study. Ann Neurol 52:849–853
8. Buhmann C, Binkofski F, Klein C, et al. (2005) Motor reorganization in asymptomatic carriers of a single mutant Parkin allele: a human model for presymptomatic parkinsonism. Brain 128: 2281–2290
9. Khan NL, Scherfler C, Graham E, et al. (2005) Dopaminergic dysfunction in unrelated, asymptomatic carriers of a single parkin mutation. Neurology 64: 134–136
10. Pastor MA, Day BL, Macaluso E, Friston KJ, Frackowiak RSJ (2004) The functional neuroanatomy of temporal discrimination. J Neuroscience 24: 2585–2591
11. Pastor MA, Macaluso E, Day BL, Frackowiak RS (2006) The neural basis of temporal auditory discrimination. Neuroimage 30:512–520
12. Jahanshahi M, Jones CR, Dirnberger G, Frith CD (2006) The substantia nigra pars compacta and temporal processing. J Neurosci 26:12266–12273
13. Artieda J, Pastor MA, Lacruz F, Obeso JA (1992) Temporal discrimination is abnormal in Parkinson's disease. Brain 115:199–210
14. Tinazzi M, Frasson E, Bertolasi L, Fiaschi A, Aglioti S (1999) Temporal discrimination of somesthetic stimuli is impaired in dystonic patients. Neuroreport 10:1547–1550
15. Tinazzi M, Fiorio M, Bertolasi L, Aglioti SM (2004) Timing of tactile and visuotactile events is impaired in patients with cervical dystonia. J Neurol 251: 85–90
16. Fiorio M, Tinazzi M, Bertolasi L, Aglioti SM (2003) Temporal processing of visuotactile and tactile stimuli in writer's cramp. Ann Neurol 53:630–635
17. Aglioti SM, Fiorio M, Forster B, Tinazzi M (2003) Temporal discrimination of cross-modal and unimodal stimuli in generalized dystonia. Neurology 60: 782–785
18. Pastor MA, Artieda J, Jahanshahi M, Obeso JA (1992) Time estimation and reproduction is abnormal in Parkinson's disease. Brain 115:211–225
19. Harrington DL, Haaland KY, Hermanowicz N (1998) Temporal processing in the basal ganglia. Neuropsychology 12:3–12
20. Fiorio M, Gambarin M, Valente EM, et al. (2007) Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia? Brain 130:134–142
21. Bentivoglio AR, Cortelli P, Valente EM, et al. (2001) Phenotypic characterisation of autosomal recessive PARK6-linked parkinsonism in three unrelated Italian families. Mov Disord 16:999–1006
22. Valente EM, Abou-Sleiman PM, Caputo V, et al. (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 304:1158–1160
23. Albanese A, Valente EM, Romito LM, Bellacchio E, Elia AE, Dallapiccola B (2005) The PINK1 phenotype can be indistinguishable from idiopathic Parkinson disease. Neurology 64:1958–1960
24. Bares M, Rektor I (2001) Basal ganglia involvement in sensory and cognitive processing. A depth electrode CNV study in human subjects. Clin Neurophysiol 112:2022–2030
25. Jahanshahi M, Rowe J, Saleem T, et al. (2002) Striatal contribution to cognition: working memory and executive function in Parkinson's disease before and after unilateral posteroventral pallidotomy. J Cogn Neurosci 14:298–310
26. Ivry RB (1996) The representation of temporal information in perception and motor control. Curr Opin Neurobiol 6:851–857
27. Rao SM, Mayer AR, Harrington DL (2001) The evolution of brain activation during temporal processing. Nat Neurosci 4:317–323
28. Graziano MS, Gross CG (1993) A bimodal map of space: somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. Exp Brain Res 97:96–109
29. Hedrich K, Hagenah J, Djarmati A, et al. (2006) Clinical spectrum of homozygous and heterozygous PINK1 mutations in a large German family with Parkinson disease: role of a single hit? Arch Neurol 63:833–838
30. Valente EM, Salvi S, Ialongo T, et al. (2004) PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol 56:336–341
31. Rogaeva E, Johnson J, Lang AE, et al. (2004) Analysis of the PINK1 gene in a large cohort of cases with Parkinson disease. Arch Neurol 61:1898–1904
32. Abou-Sleiman PM, Muqit MM, McDonald NQ, et al. (2006) A heterozygous effect for PINK1 mutations in Parkinson's disease? Ann Neurol 60: 414–419
33. Kay DM, Moran D, Moses L, et al. (2007) Heterozygous parkin point mutations are as common in control subjects as in Parkinson's patients. Ann Neurol 61: 47–54
34. Valente EM, Ferraris A (2007) Heterozygous mutations in genes causing parkinsonism: monogenic disorders go complex. Lancet Neurol 6:576–578