Lower cognitive performance in healthy G2019S *LRRK2* mutation carriers

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ABSTRACT

Objective: To assess cognitive abilities of healthy first-degree relatives of Ashkenazi patients with Parkinson disease (PD), carriers of the G2019S mutation in the *LRRK2* gene.

Methods: In this observational study, 60 consecutive healthy first-degree relatives (aged 50.9 ± 6.2 years; 48% male; 30 G2019S carriers) were assessed using a computerized cognitive program, the Montreal Cognitive Assessment questionnaire, the Unified Parkinson's Disease Rating Scale Part III, and the Geriatric Depression Scale.

Results: G2019S carriers scored significantly lower on the computerized executive function index ($p = 0.04$) and on specific executive function tasks (Stroop test, $p = 0.007$).

Conclusion: Carrying the *LRRK2* G2019S mutation was associated with lower executive performance in a population at risk for PD. ***Neurology*® 2012;79:1027–1032**

GLOSSARY

AJ = Ashkenazi Jewish; **EF** = executive function; **GDS** = Geriatric Depression Scale; **MoCA** = Montreal Cognitive Assessment test; **PD** = Parkinson disease; **RT** = reaction time; **UPDRS** = Unified Parkinson's Disease Rating Scale.

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The G2019S mutation in the *LRRK2* gene is one of the most common genetic causes of Parkinson disease (PD).[1] Although the clinical motor signs of PD in carriers of the G2019S mutation are largely typical, an earlier age at onset of motor symptoms has been reported in some studies.[2,3] The exact penetrance among carriers of the G2019S mutation is currently unknown, with rates ranging between 17% at age 50 and 85% at age 70.[4,5] Therefore, asymptomatic healthy carriers of the G2019S mutation in the *LRRK2* gene are an at-risk population for future development of PD.[6]

Cognitive impairment is a well-recognized nonmotor feature of PD, affecting most patients if tested with sensitive tools. One of the main features of cognitive decline associated with PD is represented by impairment of executive functions (EFs), which can already be demonstrated shortly after motor symptoms appear.[7,8] Computerized cognitive assessment tools have been used extensively over the past decade to assess different cognitive domains. They have been used and validated in PD[9,10] but never in asymptomatic mutation carriers. The purpose of this study was to assess the cognitive performance of healthy asymptomatic carriers and noncarriers of the G2019S mutation in the *LRRK2* gene. We hypothesized that the computerized assessment battery would identify subtle cognitive differences between nonmanifesting carriers of the G2019S *LRRK2* mutation and their first-degree noncarrier relatives.

Supplemental data at www.neurology.org

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LRRK2 Ashkenazi Jewish Consortium coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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Supplemental Data

METHODS

Subjects. A convenience sample of healthy, consecutive, asymptomatic, first-degree relatives of Ashkenazi Jewish (AJ) patients with PD who carry the G2019S mutation in the *LRRK2* gene were invited to participate in a comprehensive study that assessed cognitive capabilities. The study population of the AJ PD cohort included 920 patients treated in the Movement Disorders Unit at the Tel Aviv Sourasky Medical Center. All patients had a diagnosis of clinically definite PD made by a movement disorder specialist, according to the Parkinson's UK Brain Bank criteria.[11] All patients underwent a detailed interview to disclose family history of PD or other movement disorders, age at onset of motor symptoms and at diagnosis, and environmental and occupational risk factors. Ancestry and country of origin of both parents were reported by each participant, and only those with 2 AJ parents were included in the cohort. A total of 138 patients with PD were found to be carriers of the G2019S *LRRK2* mutation. These patients were approached, and, after receiving their consent to contact their first-degree relatives, recruitment for this study commenced.

Subjects were included in the study only if they reported no overt symptoms of PD, depression, or history of significant head trauma. Cognitive impairment was not an exclusion criterion in this study; however, none of the participants complained of functional significant cognitive decline. All first-degree relatives included in the study were assessed by a neurologist to guarantee that they did not fulfill the criteria for diagnosis of PD.

Subjects were recruited on a rolling basis and were only subsequently genotyped. After 45 recruits, a study coordinator examined the groups to assess matching. There were more mutation carriers than nonmutation carriers; therefore, a paired sampling was performed to ensure equality in group numbers. Subjects and researchers were blinded to mutation status throughout the study until the time of data analysis.

This study was performed in the Tel Aviv Sourasky Medical Center as part of a larger effort to understand the significance of the G2019S mutation in the *LRRK2* gene among AJ individuals by a consortium created and supported by the Michael J. Fox Foundation, which also includes Beth Israel Medical Center and Columbia Presbyterian Medical Center in New York, New York.

Standard protocol approvals, registrations, and patient consents. Before the beginning of the study, all subjects signed an informed consent form approved by Tel Aviv Sourasky Medical Center institutional review board. Basic demographic data, medical history, and medications were collected for all participants. Motor signs were quantified using the motor portion (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS).[12] Cognitive screening was performed using the Montreal Cognitive Assessment test (MoCA).[13] Depression was assessed using the Geriatric Depression Scale (GDS).[14] All participants were Hebrew speakers. Subjects completed a computerized cognitive test battery (MindStreams; NeuroTrax Corp., NY)[15] designed to evaluate multiple cognitive domains including attention, memory, EF, visuospatial, and motor skills. The tests did not require prior knowledge and included subset scores of different tasks including Go-No-Go, verbal memory, Stroop, nonverbal memory, finger tapping, catch game, visuospatial processing, and verbal function. All tests were run in the same fixed order on a desktop computer using a mouse and a keyboard.

Subjects were familiarized with the test procedure before the beginning of the test. The program provides both raw scores such as accuracy rates, reaction times (RTs), response selection, response inhibition, and speed of processing on each domain, as well as an index score relating to the domain tested. Indices were normalized to age and years of education and are presented similarly to an IQ-like scale (mean ± SD 100 ± 15).[15]

Genetic testing was performed subsequently to the clinical and cognitive assessment. Genomic DNA was isolated from peripheral blood using standard protocols or from saliva according to the manufacturer's instructions (Oragene, Ottawa, Canada). To detect the 6055G_A (G2019S) mutation (rs34637584) in *LRRK2* exon 41, we amplified a 171-bp fragment with the following primers: forward 5′ CCTGTGCATTTTCTGGCAGATA 3′ and reverse 5′ CCTCTGATGTTTTTATCCCCATTC 3′.[2] PCR fragments were sequenced using the BigDye Terminator Chemistry (Applied Biosystems, Foster City, CA) and analyzed using an automated ABI Prism 3130xl Genetic Analyzer (Applied Biosystems). In addition, G2019S *LRRK2* mutation was also detected using TaqMan assay C_63498123_10 in the StepOnePlus Real-Time PCR System (Applied Biosystems).

Statistical analysis. Means and SDs were calculated for all dependent variables. Histograms and frequency distributions were constructed to evaluate the normality and homogeneity of the dependent variables. The relationship between the presence of the G2019S mutation and different cognitive indices was examined using the Student's t test or χ^2 for continuous and dichotomous variables, respectively.

The subtests of each of the cognitive domains that were significantly different between the groups were further examined. Four subjects, not otherwise atypical in any of the cognitive or clinical tests (1 noncarrier and 3 carriers with MoCA scores between 23 and 27), had extreme poorer scores on the Stroop test (>3 SD above the mean). Their data were removed from the analysis to avoid disproportionate leverage on the statistical models. Generalized estimating equations were used to assess any cluster effect based on familial data. Analysis was adjusted for multiple comparisons. p values reported are based on two-tailed comparisons, with significance levels set at 0.05. Statistical analysis was performed with SPSS version 17 (SPSS Inc., Chicago, IL).

RESULTS

Sixty asymptomatic subjects (mean age 50.9 ± 6.2 years; 30 carriers of G2019S mutation) participated in this study. Of the subjects, 44 were children of patients, 15 were siblings, and 1 was a parent of a patient with PD. Subjects' characteristics are presented in the table. Groups were well-matched with regard to age, gender, and years of education. MoCA scores were similar between groups (noncarriers 26.4 ± 2.2 vs carriers 26 ± 2.4, $p = 0.54$). None of the subjects had motor signs suggesting PD based on the motor UPDRS (noncarriers 3.1 ± 2.4 vs carriers 2.7 ± 2.9, $p = 0.60$) or were deemed to be depressed based on the GDS (noncarriers 2.5 ± 3.2 vs carriers 1.8 ± 1.7, $p = 0.29$).

Average total scores on the MindStreams battery were within the normal range (figure 1) and did not reflect cognitive impairment. Significant between-group differences were observed in the EF index score ($p = 0.04$) with better performance by the noncarriers. In addition, noncarriers performed significantly better on the Stroop interference task ($p =$

Table Characteristics of the study population

	Noncarriers (n = 30)	Carriers (n = 30)	*p* Value (between groups)
Gender (M/F)	15/15	14/16	0.79
Parents (M/F)	0/1		
Siblings (M/F)	1/4	5/5	0.25
Children (M/F)	10/14	9/11	0.37
Age, y, mean ± SD (range)	50.3 ± 5.6 (41-62)	51 ± 6.9 (41-67)	0.61
p/s/c	62/50.8/49.6	—/58.6/47.3	—/0.49/0.12
MoCA score (maximum 30), mean ± SD (range)	26.4 ± 2.2 (23-30)	26 ± 2.4 (22-30)	0.54
p/s/c	24/26.0/26.6	—/25.9/26.1	—/0.94/0.48
UPDRS Part III	3.1 ± 2.4 (0-5)	2.7 ± 2.9 (0-8)	0.60
p/s/c	5 /5.4 /2.5	—/3.8/2.1	—/0.01/0.56
Education, y, mean ± SD (range)	16.4 ± 3.1 (12-21)	15.8 ± 2.1 (12-19)	0.1
p/s/c	15/17.7/16.6	—/15.3/16.08	—/0.25/0.58
Depression (GDS) score, mean ± SD (range)	2.5 ± 3.2 (0-6)	1.8 ± 1.7 (0-7)	0.29
p/s/c	10/5.4/1.58	—/1.70/1.85	—/0.06/0.62

Abbreviations: GDS = Geriatric Depression Scale; MOCA = Montreal Cognitive Assessment; p/s/c = parents/siblings/children; UPDRS = Unified Parkinson's Disease Rating Scale.

0.007), with a significant difference in RT of performance ($p = 0.05$) (figure 2).

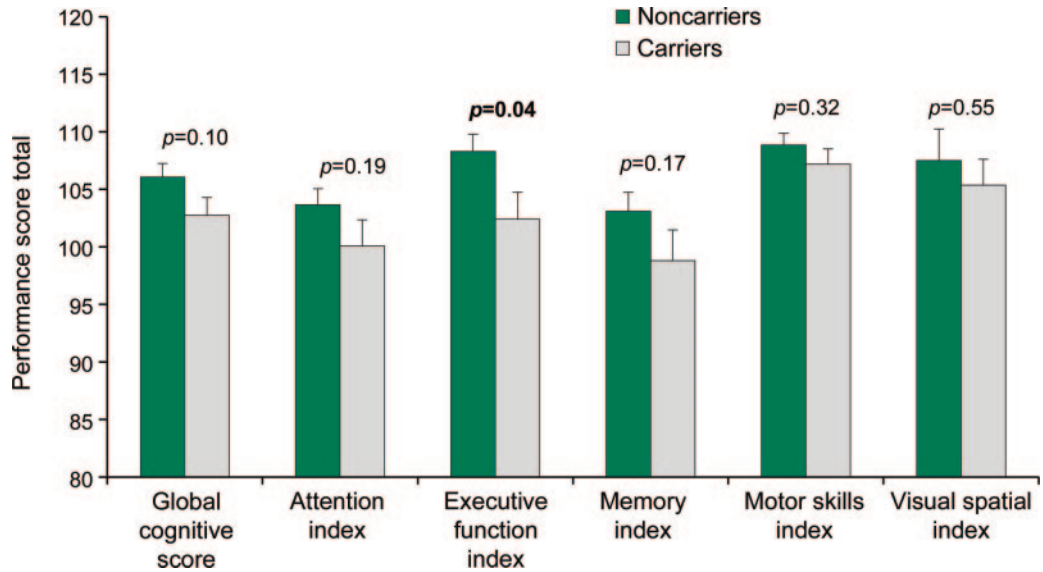
Of the subjects in this cohort, 38 were related to each other, which corresponded to 16 families. The other 22 individuals did not have a first-degree relative in this cohort; therefore, there were a total of 38 families of patients with PD represented in this study. No significant cluster effects were found between families based on cognitive scores ($p > 0.12$) or any of the factors assessed (GDS: $p > 0.64$, UPDRS: $p > 0.31$).

DISCUSSION Asymptomatic carriers of the G2019S mutation demonstrated poorer performance on one computerized measure of executive functioning compared with that of noncarriers. Differences were not observed in any other cognitive domain, suggesting subtle specific differences in performance of EF.

The cognitive decline in PD is characterized by executive dysfunction and visuospatial, memory, language, planning, and attentional set shifting impairments.[16] However, the executive domain, a theorized cognitive system that controls and manages other cognitive processes, is affected in early stages of PD[7,8]

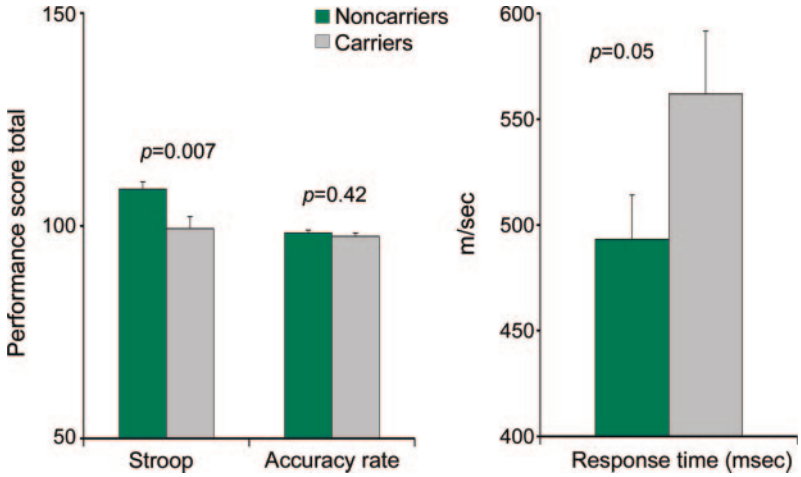
In the Stroop task, the strong interference of word reading on color naming is quantified in terms of increased RT and decreased accuracy rate to color naming when noun and presentation color are incongruent compared with when they are congruent. Greater Stroop interference and slower RT on the Stroop task in patients with PD compared with healthy control subjects has been previously demonstrated.[17] This slowness is mainly due to deficits in response inhibition. Several studies have found the Stroop task to be one of the best predictors of cognitive deterioration in patients with both early- and late-stage PD.[18–20] Our present report extends these findings to the premotor stage of the disease and

Figure 1 Comparison between carriers and noncarriers of the G2019S mutation in the *LRRK2* gene in cognitive indices on the computerized cognitive battery



Both groups demonstrated normal cognitive function but noncarriers (n = 30) performed better on all tests examined than the noncarriers (n = 30) with significant between groups differences in the executive function index.

Figure 2 Differences between groups in the performance on the Stroop test



Total performance score on the interference level of the test and response time were significantly different between the groups. Means and SEs are presented; noncarriers n = 29; carriers n = 27.

raises the possibility that cognitive changes can also be demonstrated at least in some populations at risk.

No significant differences in other domains of cognitive capabilities known to be impaired in PD could be demonstrated between carriers and noncarriers of the mutation. This finding could indicate either that these cognitive domains are relatively preserved or that the tools used were not sensitive enough to detect subtle changes in mutation carriers.

As opposed to a previous study,[21] we could not detect any motor differences within our study population even when breaking the UPDRS into its different motor components or stratifying our population according to age. This could be due to the different sizes of our cohorts, the fact that our groups were evenly distributed between carriers and noncarriers, the younger age of our cohort (by 2–4 years), or the fact that we only tested carriers of the G2019S mutation and did not include carriers of the N1437H mutation.

The latency period between the beginning of the pathologic changes and motor manifestations of PD is currently unknown and so is the timeline of the premotor symptoms, which include constipation, olfactory impairment, REM sleep behavior disorder, and anxiety disorders.[22,23] Although many patients with PD show cognitive decline over time, the possibility of cognitive changes at the prediagnosis stage has not been demonstrated before.

It is currently accepted that dopamine depletion in early PD is restricted to the putamen and the dorsal caudate nucleus, which are connected to the dorsolateral regions of the frontal lobe, areas that have been implicated in EF.[24] However, nondopaminergic pathology including cholinergic, noradrenergic, and serotoninergic deficiencies may also play a role in some of the cognitive deficits observed in PD[25,26] possibly even before motor symptoms appear.

Nonmanifesting Parkin carriers did not demonstrate any differences on 5 cognitive domains (psychomotor speed, attention, memory, visuospatial function, and EF) compared with noncarriers.[27] However, the use of pen and paper tests as opposed to the computerized assessment performed by our group might be responsible for the lack of findings in this group. In a population-based study assessing risk of cognitive impairment in relatives of patients with PD, the risk of cognitive impairment was modestly increased in first-degree relatives of patients with PD and was sizably increased for relatives of patients with younger age at onset of disease.[28] A study assessing first-degree relatives of patients with PD with the G2019S *LRRK2* mutation found that regardless of genetic status, first-degree relatives demonstrated higher rates of constipation and worse color discrimination than first-degree relatives of patients with PD who were noncarriers of *LRRK2* but could not demonstrate cognitive impairments.[29]

Although our sample is the largest cohort of healthy nonmanifesting carriers of the G2019S mutation in the *LRRK2* gene to be published to date, it is still rather small. Therefore, findings need to be considered with caution and confirmed by additional longitudinal studies and in other populations. Our consortium is currently assessing the cognitive capabilities of a large cohort of healthy first-degree relatives of patients with PD with the G2019S *LRRK2* mutation, using a standard battery of neuropsychological tests.

In addition, subjects in different age range strata should be evaluated to understand whether our findings represent degenerative cognitive capabilities or congenital differences that are related to the mutation but not necessarily to the risk of future development of PD. Our cohort was constructed by family members of patients who were aware of their mutation status; this may have created bias toward participating in this study.

Another limitation of the study is that the results of the MindStreams tests were not adjusted for multiple comparisons. However, because they were all adjusted to age and years of education and compared as index scores, this would have had negligible impact on the outcomes.

The findings of this study together with previous work done by our group[30] indicate that healthy nonmanifesting carriers of the G2019S mutation per-

form differently on motor as well as cognitive tasks when tested with sensitive tools. The significance of our present observation is not clear in terms of early markers for the presymptomatic state of PD. It is to be determined whether the differences between groups represent a disease state with a progressive course or a congenital state due to genotype. Only a prospective follow-up of a cohort of *LRRK2* carriers, which is currently in progress by our consortium, will provide the necessary information to resolve this fundamental question.

AUTHOR CONTRIBUTIONS

Avner Thaler: conception, study design, data collection, statistical analysis, and manuscript composition. Anat Mirelman: conception, study design, data collection, manuscript composition, and statistical analysis. Tanya Gurevich: review of manuscript. Ely Simon: review of manuscript. Avi Orr-Urtreger: review of manuscript and obtaining funding. Karen Marder: conception, review of manuscript, and obtaining funding. Susan Bressman: conception, review of manuscript, and obtaining funding. Nir Giladi: conception, review of manuscript, and obtaining funding.

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DISCLOSURE

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