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Research Report

Activation-Induced Rigidity in Neurologically and Cognitively Healthy Individuals Aged 18–90 Years: A Cross-Sectional Study

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Abstract.
Background: Rigidity is a key clinical feature of Parkinson's disease (PD), but in a very early phase of the disease it may be absent and can be enhanced through active movements of the arm contralateral to the one being tested.
Objective: To evaluate in a large cohort of neurologically and cognitively healthy (NCH) subjects aged 18–90 years if activation-induced rigidity (AR) is present in all age classes, and if there are biological differences between subjects showing AR (AR+) and not showing AR (AR−).
Methods: 2,228 NCH subjects categorized as young adult (18–44 years), adult (45–64 years), elderly (65–74 years), and old/oldest-old (75–90 years) were included in the analysis, and underwent brain MRI. White matter hyperintensities were assessed through two visual rating scales. Lacunes were also rated. Atrophy of the caudate nuclei and ventricular enlargement were assessed through the bicaudate ratio and the lateral ventricles to brain ratio. To elicit AR, the Froment's maneuver (FM) and the instructions of the UPDRS-ME were used.
Results: Among the sample, 1,689 (75.81%) subjects showed AR, of which 1,270 (57.00%) subjects showed AR by using FM, and 419 (18.81%) showed AR by using UPDRS-ME instructions. The latter subjects also showed AR by using FM. The number of AR+ subjects significantly increased with increasing age, regardless of the activation maneuver used. In each age class, the number of AR+ subjects was significantly higher by using the FM than the UPDRS-ME instructions.
Conclusion: Our findings suggest that AR is likely to be one of the signs of the prodromal phase of PD.

Keywords: Activation-induced rigidity, healthy aging subjects, white matter hyperintensities, lacunes, caudate atrophy, global cerebral atrophy

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INTRODUCTION

Together with bradykinesia, resting tremor, and asymmetric onset, rigidity is a key clinical feature of Parkinson's disease (PD) [1], and plays a significant role in the assessment of response to therapies. Rigidity is defined as a continuous and constant resistance on repetitive, passive stretching and shortening the muscles. However, rigidity may be absent particularly in the early phase of PD, and it may diminish or reinforce depending upon the static posture of the body. These former characteristics lead Froment and Gardére [2] to describe activation procedures in order to detect latent rigidity in very early PD. These authors assessed activation-induced rigidity (AR) by performing passive and repetitive extensor/flexion movements at the wrist or elbow joints when the patient executed on command contralateral shoulder movements as "swing the arm around like a windmill" (*faire la moulinette du bras*) (Froment maneuver) (FM) [2]. Procedures of activation-induced rigidity have been described in both the two versions of the Unified Parkinson's Disease Rating Scale (UPDRS) [3, 4]. In the 1987 version [3], rigidity is scored 1 if it is "slight or detectable only when activated by mirror or other movement". In the 2008 version [4], rigidity is scored 1 if it is detected only with activation maneuvers. In both versions, the instructions suggest using the active movement of contralateral distal muscles as an activation maneuver. Resting and activated rigidity has been studied with objective measurements [5–10] in PD patients in on- and off-state, and in normal subjects. The results achieved suggest that AR is specific to PD and may help to identify PD subjects with very mild or latent rigidity. Conflicting findings, instead, have been reported about whether activation maneuvers enhance normal muscle tone in neurologically healthy subjects. It has been reported that the activation maneuvers do not enhance muscle tone in young and elderly subjects [5, 7, 9], while other researchers have found that AR is presented by elderly [6] and by 20% of old subjects [8]. According to Powel et al. [10], AR is presented by PD patients as well as by healthy adult subjects. Much of these conflicting results is likely to be explained by the very small sizes of the cohorts examined, and the different modalities of activation maneuvers used. The existing uncertainty in the frequency of AR on healthy aging people prompted us to conduct a study of AR in a large cohort of neurologically and cognitively healthy (NCH) subjects aged 18–90 years. The 3 following questions were to be answered: (1) Is AR present in all ages? (2) Are the Froment and UPDRS-ME maneuvers equally effective in eliciting AR? (3) Are there biological differences between subjects presenting and not presenting AR? In this paper, the terms "young-adult", "adult", "elderly", "old", and "oldest-old", will refers to those individuals aged 18–44, 45–64, 65–74, 75–84, and >85, respectively.

METHODS

Participants

This study is embedded in the Cognitive Impairment through Aging (CogItA) study, a large hospital-based prospective study focused on normal and pathological aging in middle-aged and older individuals launched in January 2000. Subjects participating to the study were inpatients and outpatients self-referred or referred by general practitioners for neurological and/or cognitive screening to the clinics of the Department of Neurology and Cognitive Disorders of the teaching Hospital (AOUP "P. Giaccone") of the School of Medicine of the University of Palermo, Italy. Details of the inclusion and exclusion criteria of the CogItA study have been reported elsewhere [11, 12]. A complete explanation of the study protocol was provided to all participants before their inclusion in the study. Written informed consent was obtained from all participants. All the CogItA's procedures complied with the ethical rules of the Hospital and were performed in line with the Declaration of Helsinki and its later amendments. For the present study, data of CogItA's participants neurologically and cognitively healthy (NCH) recruited from 2006 onward were used. NCH subjects had no lifetime history of neurological disturbances, nor any clinically overt neurological and/or psychiatric disease, or history of orthopedic surgery, pain in joints of spine and limbs, and shoulders complaints. NCH subjects underwent a detailed neuropsychological testing, and an extensive assessment of other variables such as medical history, laboratory tests, behavioral assessments, and brain magnetic resonance imaging (MRI). Vascular risk factors (VRF) and vascular diseases (VD) were considered and assessed as reported elsewhere [11, 12]. The NCH participants aged 18–44 years were part of the CogItA-Headache study aimed to select subjects with episodic tension type headache.

Assessment of activated rigidity (AR)

To standardize the procedure, muscle tone and AR were tested first in the dominant arm, and successively in the non-dominant arm. Subjects were seated comfortably in a chair, and the resting muscle tone was tested passively extending and flexing the arm at the elbow joint. Subjects having at rest muscle tone different from normal tone were excluded. The AR in the tested arm was assessed performing on command contralateral FM [2] and finger tapping [4, 5]. The assessment of the resting tone was repeated 10 times, then the command for executing the FM was given during which the examiner continues for other 10 times the flexion and extension of the tested arm. Successively, the AR was tested with the command being to tap the contralateral thumb with index finger 10 times as quickly and as big as possible. The same procedure was repeated with the non-dominant arm. The AR was considered present if the enhancement of muscle tone in the tested arm persisted during all the active movement of the contralateral shoulder or fingers. For both FM and UPDRS-ME maneuvers, the AR was dichotomized as "absent" (score = 0) and "present" (scores = 1), and the subjects were subdivided into two groups according to whether activated rigidity was present (AR+) or absent (AR−). For each subject, all procedures were repeated by a second neurologist. The raters were blinded to the patients' history and neuroimaging. The interrater reliability assessed over time in random samples was always excellent.

Neuropsychological and behavioral assessments

Subjects AR+ and AR– of the cohort underwent an extensive neuropsychological assessment including the Mini-Mental State Examination (MMSE) [13] as a test of global cognition (MMSE $\geq$ 23.83), and a battery of 12 tests covering 6 cognitive domain as following: verbal memory (Story Recall Test and the immediate and delayed recall of Rey's Auditory Verbal Learning Test) [14, 15], attention (Visual Search Test and Trail Making Test (TMT) part A) [14, 16], executive function (TMT parts B and B-A, Raven's Colored Progressive Matrices, and the Frontal Assessment Battery) [16–18], language (Token Test for verbal comprehension and the naming subtest of the Aachener Aphasie Battery) [14, 19], constructional abilities (Clock Drawing Test) [14], and visuospatial skill (position discrimination subtest of the Visual Object and Space Perception Battery) [20]. The raw scores of each test were converted to z-scores based on the mean and standard deviation of the same tests. The *z*-scores of the neuropsychological test for which higher scores represent poorer performances were log-transformed and multiplied by -1, so that the lowest scores indicated the worst performance. For the domains evaluated with more than one test, composite *z*-scores were obtained by averaging the z-scores of individual tests. Neuropsychological performance scored 1.5 standard deviation (SD) below our age-adjusted norms on memory and non-memory tests were considered as impaired. Functional status of the participants was evaluated through the basic Activities of Daily Living (ADL) [21] and the Instrumental Activities of Daily Living (IADL) [22] scales. All participants scored a 0 on the Clinical Dementia Rating (CDR) scale [23]. Depressive symptoms were evaluated through the Beck depression inventory [24], while the Hamilton Anxiety Rating Scale (HAM-A) [25] was used to evaluate anxiety symptoms.

Imaging assessment

Participants had brain MRI on a 1.5T scanner (Signa HDxt; General Electric, Milwaukee, WI, USA) by using the previously detailed image acquisition protocol [11]. WMH and lacunes were evaluated according to the published criteria [26]. WMH were identified on FLAIR images and were assessed according to the ARWMC scale (range 0–3) [27]. To measure WMH severity, the scores of frontal, parieto-occipital, temporal, infratentorial, and basal ganglia regions of both hemispheres were summed in order to obtain the partial scores of deep/subcortical WMH (WMH-SC) (range 0 to 18), infratentorial WMH (WMH-INF) (range 0 to 6), and basal ganglia WMH (WMH-BG) (range 0 to 6), and the total WMH score (WMH-T) (range 0 to 30). To define the WMH status, a cut-off score $\geq$ 2 in at least one of the above regions was used. Since the ARWMC scale does not evaluate periventricular WMH (WMH-PV), we also used the scale of Fazekas et al. (range 0–3) [28], and a cut-off score $\geq$ 2 was used. Lacunes were identified on T2-w and FLAIR images, were assessed topographically according to the ARWMC regions used to score WMH, and were categorized as lacunes-SC, lacunes-INF, and lacunes-BG. A cut-off score $\geq$ 2 in at least one of the regions evaluated with the ARWMC scale was used to define the status of lacunes. Interrater reliability for the presence/absence of WMH and lacunes in random samples of 10% showed excel-

Table 1
Distribution of unilateral and bilateral activated rigidity (AR) by using the Froment (A) and the UPDRS-ME (B) maneuvers in 2228 NCH subjects of different age classes

Age classes N° of subjects		18–44 ($n = 716$)	45–64 ($n = 1,057$)	65–74 ($n = 3,11$)	≥ 75 ($n = 144$)	p
A)						
AR by Froment maneuver	AR+	342 (47.77)	596 (56.39)	220 (70.74)	112 (77.78)	**< 0.001**
	AR−	374 (52.23)	461 (43.61)	91 (29.26)	32 (22.22)	
Unilateral AR	AR+	84 (11.73)	161 (15.23)	50 (16.08)	27 (18.75)	0.055
	AR−	632 (88.27)	896 (84.77)	261 (83.92)	117 (81.25)	
Bilateral AR	AR+	258 (36.03)	435 (41.15)	170 (54.66)	85 (59.03)	**< 0.001**
	AR−	458 (63.97)	622 (58.85)	141 (45.34)	59 (40.97)	
B)						
AR by UPDRS-ME maneuver	AR+	54 (7.54)	204 (19.30)	103 (33.12)	58 (40.28)	**< 0.001**
	AR−	662 (92.46)	853 (80.70)	208 (66.88)	86 (59.72)	
Unilateral AR	AR+	2 (0.28)	44 (4.16)	12 (3.86)	7 (4.86)	**< 0.001**
	AR−	714 (99.72)	1,013 (95.84)	299 (96.14)	137 (95.14)	
Bilateral AR	AR+	52 (7.26)	160 (15.14)	91 (29.26)	51 (35.42)	**< 0.001**
	AR−	664 (92.74)	897 (84.86)	220 (70.74)	93 (64.58)	

NCH, neurologically and cognitively healthy; UPDRS-ME, Unified Parkinson's Disease Rating Scale motor examination. Data presented are number (%); p values are based on chi-square test.

lent agreement. Subjects having WMH-SC and/or lacunes-SC both with a score ≥ 2 in at least one of the ARWMC scale topographical regions, and/or WMH-BG, WMH-INF, lacunes-BG, lacunes-INF, and/or WMH-PV with a score ≥ 2 were categorized SVD positive (SVD+). In contrast, those having a score ≤ 1 in the regions listed above were categorized as SVD negative (SVD-). Bicaudate ratio (BCr) and lateral ventricles to brain ratio (LVBr) as proxies of subcortical and global brain atrophy respectively, were calculated as reported elsewhere [11].

Statistical analysis

Descriptive statistics were used to summarize data. Continuous variables were compared between AR+ and AR− subjects using one-way analysis of variance (ANOVA). Differences in categorical variables between AR+ and AR− subjects were analyzed by using χ^2 test. Results were summarized as absolute numbers with percentages, mean, and standard deviation (SD). The association between presence/absence of AR and putative risk factors/diseases was assessed by using multiple logistic ridge regression models [29]. The analyses were stratified according to the age classes and were adjusted for sex and education and for the variables which resulted significant from the descriptive analyses. All tests were two-tailed, and statistical significance was set at $p \leq 0.05$. Results are presented as odd ratios (ORs) with 95% confidence intervals (95% CI). All analyses were performed using R (3.6.1 version) statistical software.

RESULTS

Muscle tone and AR were assessed in a sample of 2,228 NCH subjects whose age-distribution was as following: young adult ($n = 716$; 32.14%; mean age = 31.94 ± 7.38), adult ($n = 1,057$; 47.44%; mean age = 53.12 ± 6.09), elderly ($n = 311$; 13.96%; mean age = 69.16 ± 3.02), old ($n = 134$; 6.01%; mean age = 78.18 ± 2.49), and oldest-old ($n = 10$; 0.45%; mean age = 87.10 ± 1.91). Because the oldest-old subjects were very few, the old and oldest-old subjects were grouped in a unique class of subjects aged ≥ 75 years (subjects old/oldest-old) ($n = 144$; 6.46%; mean age = 78.80 ± 3.35). Among the sample, 1,689 (75.81%) subjects showed AR (Table 1), of which 1,270 (57.00%) subjects showed AR by using FM, and 419 (18.81%) showed AR by using UPDRS-ME maneuver. The latter subjects showed also AR by using FM. The number of AR+ subjects significantly increase with increased age whatever the activation maneuver used was. In each age class, the number of AR+ subjects was higher by using the FM than the UPDRS-ME maneuver. Further, in each age class, bilateral AR was more common than unilateral AR. In fact, by using FM, AR was presented unilaterally by 25.35% ($n = 322$) of subjects and bilaterally by 74.65% of subjects ($n = 948$), while by using the UPDRS-ME maneuver 19.57% ($n = 82$) of subjects presented AR unilaterally and 80.43% ($n = 337$) presented AR bilaterally. In all age classes, AR either unilateral or bilateral was stronger in the dominant arm whatever the activation maneuver used was.

Baseline characteristics of AR+ and AR− subjects of the four age classes are reported in Table 2. In each age class, female outnumbered males. In each age class, the mean age of females and males did not vary significantly among AR+ and AR− subjects except in the adult group where both female and male AR+ were significantly older than female and male AR−. In each age class, constipation was more common among AR+ than AR− subjects although statistical significance was present in the adult group only. With the exception of arterial hypertension and obesity that were higher in AR+ than AR− subjects, VRF and VD did not differ significantly between subjects of the two groups. However, VRF and VD summary scores were significantly higher in AR+ subjects of the young-adult and adult age classes suggesting a higher vascular burden in these age classes than in the other classes.

Concerning neuroimaging, no significant difference was found in all age classes in the distribution of WMH-SC, WMH-BG, and WMH-PV between AR+ and AR− subjects with the exception of parieto-occipital WMH that among the elderly were significantly higher in AR+ than AR− subjects. Concerning lacunes, significant difference between AR+ and AR– subjects was found in the distribution of frontal lacunes in the adult age classes only. However, the Hachinski ischemic score was higher in AR+ subjects of the young-adult and adult classes, and AR+ subjects of the adult class were more SVD + than AR− subjects. Subcortical brain atrophy was higher in AR+ than in AR− subjects in all age groups.

The cognitive performances of AR+ and AR− subjects were above age- and education-corrected cut-offs for cognitive normality (Table 3). However, AR+ subjects of the young-adult and adult age classes showed significant lower performance than AR− subjects in test evaluating general cognition (MMSE) ($p < 0.05$). Concerning cognitive domains, no significant difference was found between AR+ and AR– subjects of the various age classes although in some of them a trend of worse performances in AR+ subjects was present. Regarding behavioral performances, AR+ subjects of the adult and elderly age classes were significantly more depressed and more anxious than AR− subjects.

To evaluate the association of vascular risk factors/diseases and imaging findings to the risk of AR+, multiple logistic regression analyses were carried out separately in the classes of young-adult, adult, elderly, and old/oldest-old subjects (Table 4). In the former class, VRF summary score (OR = 1.177; 95% CI, 1.056 –1.311) was significantly associated to an increased risk of AR, i.e., a unit increase in VRF score provide an increased risk of about 18% to be AR+. In the class of adult, constipation (OR = 1.484; 95% CI, 1.209 –1.821), VRF summary score (OR = 1.073; 95% CI, 1.000 –1.151), VD summary score (OR = 1.276; 95% CI, 1.033–1.576), SVD (OR = 1.318; 95% CI, 1.017–1.710), LVBr (OR = 1.479; 95% CI, 1.174–1.864), and anxiety (OR = 1.539; 95% CI, 1.183–2.003) were significantly associated to an increased risk of AR. In the class of elderly, gender, i.e., to be male (OR = 1.683; 95% CI,1.196 –2.369), was significantly associated to an increased risk ($\sim$ 68%) of showing AR. In the old/oldest-old class, gender (OR = 0.529; 95% CI, 0.344–0.812), and constipation (OR = 1.677; 95% CI, 1.049 –2.679) were significantly associated to AR. Males have a decreased risk of about 47% to be AR+, and constipated old subject have an increased risk of about 68% to present AR. When analyzing all samples, and adjusting also for age, all variables except gender, education, and BCr resulted significantly associated with an increased risk of showing AR.

DISCUSSION

We found that in NCH subjects, AR is induced in the tested arm by the simultaneous execution of proximal or distal movements of the contralateral arm. The AR is present in all age bands and increases with age by using either the FM or the UPDRS-ME instructions. However, the former was better than the latter in eliciting AR. In fact, by using FM, AR was presented by 49% of young-adult subjects, 56% of adult, 70% of elderly, and 78% of old/oldest-old subjects. In contrast, by using the UPDRS instructions, AR was presented by 7.5% of young-adult subjects, 19% of adult, 33% of elderly, and 41% of old/oldest-old subjects.

The findings of the present study do not address the level at which rigidity is mediated, nor the elucidation of the mechanism(s) of AR which are both beyond the scope of the present study. However, some considerations should be made to explain our results since AR could reflect possible change from health to disease.

The nature and origin of rigidity in PD are not fully explained by the classical model of basal ganglia pathophysiology [30]. Still, disinhibition of brainstem structures mediating muscle tone and posture

Table 2
Baseline clinical characteristics of 2228 NCH subjects of different age classes with activated rigidity (AR+) and without activated rigidity (AR−) by using the Froment maneuver

Age classes	18–44 ($n=716$)			45–64 ($n=1057$)			65–74 ($n=311$)			≥ 75 ($n=144$)		
Activated rigidity (AR)	AR+	AR−	*p*	AR+	AR−	*p*	AR+	AR−	*p*	AR+	AR−	*p*
N° of subjects	342 (47.77)	374 (52.23)		596 (56.39)	461 (43.61)		220 (70.74)	91 (29.26)		112 (77.78)	32 (22.22)	
Mean age (SD), (y)	32.40 ± 7.31	31.51 ± 7.43	0.107	53.70 ± 6.23	52.37 ± 5.84	**< 0.001**	69.30 ± 3.03	68.81 ± 2.98	0.197	78.58 ± 3.32	79.56 ± 3.38	0.144
Female	261 (76.32)	289 (77.27)		413 (69.30)	320 (69.41)		128 (58.18)	65 (71.43)		75 (66.96)	13 (40.62)	
Mean age (SD), (y)	32.28 ± 7.35	31.91 ± 7.31	0.552	53.34 ± 6.21	52.20 ± 5.80	**0.011**	69.41 ± 3.06	68.77 ± 3.01	0.166	78.84 ± 3.68	80.38 ± 3.86	0.169
Years in education	11.51 ± 3.87	10.44 ± 3.82	**0.001**	8.90 ± 4.19	8.97 ± 4.43	0.816	7.36 ± 4.75	8.03 ± 5.01	0.363	6.32 ± 4.02	6.15 ± 3.44	0.889
Male	81 (23.68)	85 (22.73)		183 (30.70)	141 (30.59)		92 (41.82)	26 (28.57)		37 (33.04)	19 (59.38)	
Mean age (SD), (y)	32.80 ± 7.21	30.18 ± 7.71	**0.025**	54.49 ± 6.19	52.75 ± 5.91	**0.011**	69.14 ± 3.01	68.92 ± 2.98	0.744	78.05 ± 2.39	79.00 ± 2.98	0.203
Years in education	11.59 ± 3.28	11.04 ± 3.34	0.280	10.34 ± 4.14	10.16 ± 4.09	0.683	9.45 ± 6.64	9.50 ± 5.29	0.969	6.95 ± 4.28	8.37 ± 5.04	0.273
Diarrhea	1 (0.29)	3 (0.80)	0.680	6 (1.01)	5 (1.08)	1.000	3 (1.36)	1 (1.10)	1.000	3 (2.68)	0 (0.00)	0.815
Constipation	62 (18.13)	54 (14.44)	0.216	136 (22.82)	69 (14.97)	**0.002**	47 (21.36)	14 (15.38)	0.293	33 (29.46)	4 (12.50)	0.088
Vascular Risk Factors												
Former smoking	23 (6.73)	23 (6.15)	0.872	31 (5.20)	20 (4.34)	0.614	26 (11.82)	9 (9.89)	0.770	11 (9.82)	1 (3.12)	0.397
Current smoking	71 (20.76)	91 (24.33)	0.293	96 (16.11)	84 (18.22)	0.410	20 (9.09)	9 (9.89)	0.995	4 (3.57)	5 (15.62)	**0.038**
Arterial hypertension	31 (9.06)	10 (2.67)	**< 0.001**	266 (44.63)	174 (37.74)	**0.029**	165 (75.00)	64 (70.33)	0.478	94 (83.93)	26 (81.25)	0.929
Diabetes mellitus	9 (2.63)	9 (2.41)	1.000	84 (14.09)	58 (12.58)	0.533	56 (25.45)	15 (16.48)	0.117	29 (25.89)	11 (34.38)	0.471
Hypercholesterolemia	44 (20.66)	47 (18.73)	0.685	224 (42.50)	161 (41.18)	0.737	92 (45.54)	39 (46.43)	0.995	59 (54.13)	14 (46.67)	0.604
Hypertriglyceridemia	20 (9.39)	20 (7.91)	0.686	102 (19.35)	67 (17.22)	0.462	46 (22.77)	21 (25.00)	0.801	26 (23.85)	4 (13.33)	0.322
Obesity	65 (19.17)	36 (10.98)	**0.004**	200 (34.48)	109 (29.70)	0.145	83 (38.60)	32 (37.65)	0.982	48 (43.24)	10 (31.25)	0.311
VRF summary score	2.70 ± 0.97	2.32 ± 1.08	**< 0.001**	1.65 ± 1.30	1.43 ± 1.29	**0.004**	2.17 ± 1.25	2.03 ± 1.20	0.364	2.46 ± 1.21	2.31 ± 1.06	0.546
Vascular Diseases												
Ischemic heart diseases	0 (0.00)	0 (0.00)	–	24 (4.03)	13 (2.82)	0.373	31 (14.09)	9 (9.89)	0.412	20 (17.86)	5 (15.62)	0.977
Cardiac valvulopathies	6 (1.75)	8 (2.14)	0.919	13 (2.18)	10 (2.17)	1.000	10 (4.55)	8 (8.79)	0.233	4 (3.57)	2 (6.25)	0.867
Cardiac arrythmias	3 (0.88)	0 (0.00)	0.216	17 (2.85)	7 (1.52)	0.217	25 (11.36)	5 (5.49)	0.166	18 (16.07)	3 (9.38)	0.508
Atrial fibrillation	0 (0.00)	1 (0.27)	1.000	6 (1.01)	1 (0.22)	0.235	17 (7.73)	5 (5.49)	0.649	12 (10.71)	2 (6.25)	0.679
Lower limb arteriopathy	0 (0.00)	0 (0.00)	–	4 (0.67)	0 (0.00)	0.209	3 (1.36)	1 (1.10)	1.000	2 (1.79)	2 (6.25)	0.456
History of TIA	6 (1.75)	1 (0.27)	0.101	24 (4.03)	12 (2.60)	0.274	11 (5.00)	6 (6.59)	0.773	9 (8.04)	4 (12.50)	0.669
VD summary score	0.04 ± 0.23	0.03 ± 0.18	0.265	0.17 ± 0.45	0.10 ± 0.32	**0.004**	0.49 ± 0.79	0.42 ± 0.70	0.472	0.67 ± 0.92	0.59 ± 0.91	0.682

Table 2
Continued

Age classes	18–44 ($n=716$)			45–64 ($n=1057$)			65–74 ($n=311$)			≥ 75 ($n=144$)		
Activated rigidity (AR)	AR+	AR−	p	AR+	AR−	p	AR+	AR−	p	AR+	AR−	p
Imaging findings												
WMH												
WMH-PV	8 (2.34)	3 (0.80)	0.172	38 (6.38)	17 (3.69)	0.070	50 (22.73)	14 (15.38)	0.193	42 (37.50)	9 (28.12)	0.442
Frontal WMH	6 (1.75)	2 (0.53)	0.232	36 (6.04)	18 (3.90)	0.155	35 (15.91)	13 (14.29)	0.851	24 (21.43)	7 (21.88)	1.000
Parieto-occipital WMH	3 (0.88)	0 (0.00)	0.216	8 (1.34)	7 (1.52)	1.000	27 (12.27)	3 (3.30)	**0.026**	16 (14.29)	3 (9.38)	0.669
Temporal WMH	1 (0.29)	0 (0.00)	0.964	1 (0.17)	3 (0.65)	0.445	6 (2.73)	0 (0.00)	0.255	6 (5.36)	0 (0.00)	0.403
WMH-SC	6 (1.75)	2 (0.53)	0.232	38 (6.38)	19 (4.12)	0.141	38 (17.27)	15 (16.48)	0.998	25 (22.32)	7 (21.88)	1.000
WMH-INF	0 (0.00)	0 (0.00)	–	7 (1.17)	2 (0.43)	0.336	10 (4.55)	0 (0.00)	0.087	6 (5.36)	0 (0.00)	0.403
WMH-BG	0 (0.00)	0 (0.00)	–	1 (0.17)	0 (0.00)	1.000	0 (0.00)	2 (2.20)	0.154	3 (2.68)	0 (0.00)	0.815
Lacunes												
Frontal lacunes	4 (1.17)	4 (1.07)	1.000	41 (6.88)	15 (3.25)	**0.013**	24 (10.91)	5 (5.49)	0.201	24 (21.43)	4 (12.50)	0.383
Parieto-occipital lacunes	2 (0.58)	1 (0.27)	0.938	12 (2.01)	3 (0.65)	0.111	5 (2.27)	0 (0.00)	0.340	2 (1.79)	2 (6.25)	0.456
Temporal lacunes	0 (0.00)	1 (0.27)	1.000	5 (0.84)	2 (0.43)	0.672	0 (0.00)	0 (0.00)	–	0 (0.00)	0 (0.00)	–
Lacunes SC	5 (1.46)	4 (1.07)	0.893	47 (7.89)	19 (4.12)	**0.017**	25 (11.36)	6 (6.59)	0.285	24 (21.43)	6 (18.75)	0.934
Lacunes-INF	1 (0.29)	0 (0.00)	0.964	10 (1.68)	2 (0.43)	0.110	13 (5.91)	5 (5.49)	1.000	17 (15.18)	5 (15.62)	1.000
Lacunes-BG	0 (0.00)	1 (0.27)	1.000	3 (0.50)	2 (0.43)	1.000	4 (1.82)	2 (2.20)	1.000	5 (4.46)	2 (6.25)	1.000
Hachinski ischemic score	0.76 ± 0.93	0.50 ± 0.75	**< 0.001**	1.51 ± 1.40	1.04 ± 1.23	**< 0.001**	2.14 ± 1.49	1.81 ± 1.26	0.067	2.46 ± 1.58	2.22 ± 1.56	0.439
SVD+	15 (4.39)	7 (1.87)	0.084	104 (17.45)	46 (9.98)	**< 0.001**	84 (38.18)	29 (31.87)	0.356	70 (62.50)	16 (50.00)	0.286
SVD -	327 (95.61)	367 (98.13)		492 (82.55)	415 (90.02)		136 (61.82)	62 (68.13)		42 (37.50)	16 (50.00)	
Measures of brain atrophy												
BCr	0.081 ± 0.007	0.080 ± 0.009	0.086	0.102 ± 0.015	0.099 ± 0.013	**< 0.001**	0.140 ± 0.015	0.138 ± 0.014	0.181	0.173 ± 0.011	0.173 ± 0.009	0.059
LVBr	1.344 ± 0.069	1.337 ± 0.065	0.133	1.560 ± 0.182	1.526 ± 0.177	**0.003**	2.231 ± 0.466	2.160 ± 0.423	0.210	3.429 ± 0.442	3.245 ± 0.3990	0.965

NCH, neurologically and cognitively healthy; (y), years; ADL (f.l.), activities of daily living (functions lost); IADL (f.l.), instrumental activities of daily living (functions lost); TIA, transient ischemic attack; WMH, white matter hyperintensities; SVD, small vessel disease; BCr, bicaudate ratio; LVBr, lateral ventricles to brain ratio. Data presented are number (%) for categorical and mean (SD) for continuous data. p values are based on chi-square for categorical variables and on ANOVA for continuous variables. Bold values indicate significance at $p \leq 0.05$.

Table 3
Neuropsychological and behavioral performances of 2228 NCH subjects of different age classes with (AR+) and without (AR−) activated rigidity (AR) by Froment maneuver

Age classes	18–44 (n = 716)			45–64 (n = 1057)			65–74 (n = 311)			≥ 75 (n = 144)		
Activated rigidity (AR)	AR+	AR−	p	AR+	AR−	p	AR+	AR−	p	AR+	AR−	p
N° of subjects	346 (48.94)	361 (51.06)		599 (55.77)	475 (44.23)		214 (70.39)	90 (29.61)		112 (78.32)	32 (22.22)	
Neuropsychological performances												
MMSE, mean (SD)	28.69 (1.55)	29.21 (1.22)	**< 0.001**	28.77 (1.39)	28.97 (1.36)	**0.016**	28.49 (1.51)	28.21 (3.00)	0.139	28.12 (1.66)	27.81 (1.67)	0.364
Cognitive domains z scores, mean (SD)												
Memory	–0.09 (0.77)	–0.01 (0.60)	0.126	0.02 (0.97)	0.00 (0.75)	0.678	0.09 (0.91)	0.03 (0.93)	0.613	0.17 (0.94)	0.06 (0.95)	0.573
Attention	–0.14 (0.74)	–0.10 (0.69)	0.437	0.10 (0.78)	0.05 (0.72)	0.289	0.14 (0.84)	0.19 (0.85)	0.631	–0.04 (0.83)	–0.09 (0.78)	0.765
Executive	–0.22 (0.58)	–0.27 (0.55)	0.248	0.22 (0.57)	0.17 (0.58)	0.143	0.24 (0.58)	0.25 (0.61)	0.933	0.10 (0.59)	–0.02 (0.48)	0.304
Language	0.47 (0.76)	0.37 (0.72)	0.092	–0.20 (0.80)	–0.14 (0.66)	0.222	–0.68 (1.00)	–0.50 (0.98)	0.137	–0.99 (1.22)	–0.87 (0.92)	0.604
Constructional	0.08 (0.74)	0.16 (0.75)	0.197	–0.04 (1.16)	–0.13 (1.14)	0.215	–0.10 (0.97)	–0.06 (1.08)	0.745	0.17 (0.93)	0.16 (1.01)	0.952
Visuospatial	0.03 (0.87)	–0.02 (0.66)	0.395	0.11 (1.12)	0.04 (1.09)	0.337	–0.05 (1.55)	–0.06 (1.54)	0.976	–0.28 (1.68)	–0.24 (1.01)	0.890
Behavioral performances												
Depression	102 (29.82)	100 (26.74)	0.405	267 (44.80)	149 (32.32)	**< 0.001**	131 (59.55)	41 (45.05)	**0.027**	86 (76.79)	22 (68.75)	0.487
Anxiety	53 (15.50)	54 (14.44)	0.770	282 (47.32)	151 (32.75)	**< 0.001**	134 (60.91)	42 (46.15)	**0.024**	86 (76.79)	21 (65.62)	0.296

NCH, neurologically and cognitively healthy; MMSE, Mini-Mental State Examination. Data presented are mean, standard deviation (SD), for continuous data, and number (%) for categorical data. p values are based on chi-square for categorical variables, and on ANOVA for continuous variables. Bold values indicate significance at $p \leq 0.05$.

by the overactive globus pallidus pars interna and substantia nigra pars reticulata has been suggested [31]. It is reasonable to hypothesize that brainstem mechanisms are also likely to be engaged in the activation-induced rigidity. We could also speculate that the better performances in AR by using the Froment maneuver compared to the UPDRS maneuver is likely due to the fact that the voluntary movement of proximal muscles recruits an amount of motoneurons greater than that recruited by the voluntary movement of the fingers, since behind the primary motor cortex it involves motor cortical areas in which proximal movements are mostly represented [32, 33].

The clinical diagnosis of PD is currently based on the presence of motor disturbances [1] whose assessment is largely qualitative, whereby a clinician rates these disturbances according to an ordinal rating scale as the UPDRS. It is estimated that the motor deficits of PD become clinically evident when approximatively 70% of dopaminergic neurons in the pars compacta of the substantia nigra (SNc) are lost [34] due to the presence of α-synuclein pathology (Lewy bodies and Lewy neurites). The motor deficits of PD are, however, predated by a wide range of nonmotor symptoms (NMS) which involve several domains such as behavior, cognition, sleep, as well as cardiac, gastrointestinal, and sexual functions [35]. NMS are quite common also among normal aging subjects [35], and the corresponding α–synuclein pathology usually first develops in the peripheral autonomous nervous system, to spread to the lower brainstem, and to progress towards the SNc, the allocortex, and the neocortex [36]. The NMS are now recognized as additional clinical criteria within the prodromal phase of PD whose duration can be reasonably hypothesized in about 20 years with estimated ranges from 2 to 50 years [37]. The AR exhibited by the NCH subjects of our sample could be consequence of the initial lower brainstem dysfunction, and to be considered one of the neurological dysfunctions presented by individuals in the early stages [36] of the prodromal phase of PD. The high co-occurrence of some NMS such as constipation, depressive, and anxious symptoms in the NCH subjects showing AR supports our hypothesis. Finally, it is worth noting that the prevalence of clinical PD is between 45–74 years, and that ∼60% of NCH subjects of our sample included in this age range exhibit AR by Froment maneuver. Further, among the elderly and old/oldest-old subjects, to be male was significantly associated to an increased risk, (68%) and (53%) respectively, of showing AR.

Table 4
Association of constipation, VRF and VD summary scores, SVD, BCr, LVBr, and behavioral performances with the risk of having activated rigidity (AR) by Froment maneuver in young adult, adult, elderly, and old/oldest-old NCH subjects

	Age classes (y)				All classes (y)
	18–44 ($n = 716$) OR (95% CI)	45–64 ($n = 1057$) OR (95% CI)	65–74 ($n = 311$) OR (95% CI)	≥ 75 ($n = 144$) OR (95% CI)	18–91 ($n = 2228$) OR (95% CI)
Age, (y)	–	–	–	–	**1.019 (1.014–1.023)**
Gender, (ref. female)	1.010 (0.866–1.178)	1.041 (0.866–1.252)	**1.683 (1.196–2.369)**	**0.529 (0.344–0.812)**	1.007 (0.957–1.061)
Years in education	1.016 (0.989–1.045)	1.009 (0.988–1.030)	0.991 (0.960–1.022)	0.961 (0.905–1.021)	1.005 (0.991–1.019)
Constipation	1.110 (0.949–1.299)	**1.484 (1.209–1.821)**	1.373 (0.930–2.026)	**1.677 (1.049–2.679)**	**1.080 (1.027–1.135)**
VRF summary score	**1.177 (1.056–1.311)**	**1.073 (1.000–1.151)**	1.046 (0.909–1.203)	1.060 (0.850–1.321)	**1.071 (1.026–1.118)**
VD summary score	1.057 (0.918–1.219)	**1.276 (1.033–1.576)**	1.031 (0.849–1.283)	1.086 (0.827–1.426)	**1.055 (1.001–1.111)**
SVD, (ref. SVD-)	1.028 (0.956–1.104)	**1.318 (1.017–1.710)**	1.150 (0.821–1.609)	1.007 (0.710–1.428)	**1.022 (1.002–1.042)**
BCr	1.035 (0.973–1.101)	1.135 (0.853–1.509)	1.116 (0.790–1.577)	0.970 (0.613–1.536)	1.044 (0.997–1.092)
LVBr	1.104 (0.969–1.257)	**1.479 (1.174–1.864)**	1.068 (0.756–1.507)	1.170 (0.760–1.799)	**1.072 (1.023–1.123)**
Depression	1.082 (0.932–1.256)	1.060 (0.813–1.383)	1.312 (0.808–2.132)	1.028 (0.684–1.547)	**1.092 (1.043–1.143)**
Anxiety	1.013 (0.868–1.182)	**1.539 (1.183–2.003)**	1.305 (0.800–2.130)	1.217 (0.809–1.830)	**1.090 (1.042–1.140)**

(y), years; VRF, vascular risk factors; VD, vascular diseases; SVD, small vessel disease; BCr, bicaudate ratio; LVBr, lateral ventricles to brain ratio; NCH, neurologically and cognitively healthy.

CONCLUSION

Our results answered to all the three arguments we questioned in the introduction and suggest that activation-induced rigidity by using the Froment maneuver could be an early sign of the prodromal phase of PD. However, huge data sets of NCH subjects spanning all ages and with long-term follow-ups are needed to clearly document if AR has prospective ability to predict clinical PD and, hence, to be considered a marker of prodromal PD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson's disease. *Arch Neurol* **56**, 33-39.

[2] Broussolle E, Krack P, Thobois S, Xie-Brustolin J, Pollak P, Goetz CG (2007) Contribution of Jules Froment to the study of Parkinsonian Rigidity. *Mov Disord* **22**, 909-914.

[3] Fahn S, Elton RL, UPDRS Program Members (1987) Unified Parkinson's disease rating scale. In *Recent developments in Parkinson's disease* (Vol 2), Fahn S, Marsden CD, Goldstein M, Calne DB, eds. Macmillan Healthcare Information, London, pp. 153-163.

[4] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, C. Sampaio C, Stern MB, Dode R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord* **23**, 2129-2170.

[5] Meara RJ, Cody FWJ (1992) Relationship between electromyographic activity and clinically assessed rigidity studied at the wrist joint in Parkinson's disease. *Brain* **115**, 1167-1180.

[6] Kirollos C, Charlett A, O'Neill CJ, Kosik R, Mozol K, Purkiss AG, Bowes SG, Nicholson PW, Hunt WB, Weller C, Dobbs SM, Dobbs RJ (1996) Objective measurement of activation of rigidity: Diagnostic, pathogenetic, and therapeutic implications in parkinsonism. *Br J Clin Pharmacol* **41**, 557-564.

[7] Prochazka A, Bennett DJ, Stephens MJ, Patrick SK, Sears-Duru R, Roberts T, Jhamandas JH (1997) Measurement of rigidity in Parkinson's disease. *Mov Disord* **12**, 24-32.

[8] Fung VS, Burne JA, Morris JG (2000) Objective quantification of resting and activated parkinsonian rigidity: A comparison of angular impulse and work scores. *Mov Disord* **15**, 48-55.

[9] Hong M, Perlmutter JS, Earhart GM (2007) Enhancement of rigidity in Parkinson's disease with activation. *Mov Disord* **22**, 1164-1168.

[10] Powell D, Hanson N, Threlkeld AJ, Fang X, Xia R (2011) Enhanced of parkinsonian rigidity with contralateral hand activation. *Clin Neurophysiol* **122**, 1595-1601.

[11] Camarda C, Torelli P, Camarda R, Battaglini I, Gagliardo C, Monastero R (2015) Isolated, subtle, neurological abnormalities in neurologically and cognitively healthy aging subjects. *J Neurol* **262**, 1328-1339.

[12] Camarda C, Torelli P, Pipia C, Battaglini I, Azzarello D, Rosano R, Ventimiglia GD, Sottile G, Cilluffo G, Camarda R (2018) Association between atrophy of the caudate nuclei, global brain atrophy, cerebral small vessel disease and mild parkinsonian signs in neurologically and cognitively healthy subjects aged 45-84 years: A cross-sectional study. *Curr Alzheimer Res* **15**, 1013-1026.

[13] Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental State: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
[14] Carlesimo GA, Caltagirone C, Gainotti G (1996) The Mental Deterioration Battery: Normative data, diagnostic reliability and quantitative analyses of cognitive impairment. The group for the standardization of the mental deterioration battery. *Eur Neurol* **36**, 378-384.
[15] Carlesimo GA, Buccione I, Fadda L, Graceffa A, Mauri M, Lorusso S (2002) Standardizzazione di due test di memoria per uso clinico: Breve Racconto e Figura di Rey. *Nuova Riv Neurol* **12**, 1-13.
[16] Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E (1996) Trail making test: Normative values from 287 normal adult controls. *Ital J Neurol Sci* **17**, 305-309.
[17] Basso A, Capitani E, Laiacona M (1987) Raven's coloured progressive matrices: Normative values on 305 adult normal controls. *Funct Neurol* **2**, 189-194.
[18] Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, Forapani E, Russo A, Nichelli P (2005) The Frontal Assessment Battery (FAB): Normative values in an Italian population sample. *Neurol Sci* **26**, 108-116.
[19] Luzzatti C, Willmes K, De Bleser R, Bianchi A, Chiesa G, De Tanti A, Gonella ML, Pozzoli C (1994) New normative data for the Italian version of the Aachen Aphasia Test (AAT). *Arch Psicol Neurol Psichiatria* **55**, 1086-1131.
[20] Warrington EK, James M (1991) *The Visual Object and Space Perception Battery*. Thames Valley Test Company, Bury St. Edmunds, Suffolk, UK.
[21] Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW (1963) Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA* **185**, 914-919.
[22] Lawton MP, Brody EM (1969) Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.
[23] Morris JC (1997) Clinical dementia rating: A reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* **9**, 173-176.
[24] Beck AT, Steer RA, Brown GK (1996) *Manual for Beck Depression Inventory-II*. Psychological Corporation, San Antonio.
[25] Hamilton M (1959) The assessment of anxiety states by rating. *Br J Med Psychol* **32**, 50-55.
[26] Wardlaw JM, Smith C, Biessels GJ, Cordonnier C, Fazekas F, Lindley RI, O'Brien JT, Benavente OR, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge RV, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M (2013) STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1), Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* **12**, 822-838.
[27] Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P (2001) A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* **32**, 1318-1322.
[28] Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* **149**, 351-356.
[29] Hoerl AE, Kennard RW (1970) Ridge regression: Biased estimation for nonorthogonal problems. *Technometrics* **12**, 55-67.
[30] Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E, Obeso JA (2009) Initial clinical manifestations of Parkinson's disease: Features and pathophysiological mechanisms. *Lancet Neurol* **8**, 1128-1139.
[31] Takakusaki K, Habaguchi T, Ohtinata-Sugimoto J, Saitoh K, Sakamoto T (2003) Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: A new concept for understanding motor disorders in basal ganglia dysfunction. *Neuroscience* **119**, 293-308.
[32] Matelli M, Camarda R, Glickstein M, Rizzolatti G (1986) Afferent and efferent projections of the inferior area 6 in the macaque monkey. *J Comp Neurol* **251**, 281-298.
[33] Luppino G, Matelli M, Camarda R, Rizzolatti G (1993) Corticospinal connections of area F3 (SMA-Proper) and area F6 (Pre-SMA) in the macaque monkey. *J Comp Neurol* **338**, 114-140.
[34] Gibb WR, Lees AJ (1991) Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **54**, 388-396.
[35] Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, Mas N, Hofeneder D, Brücke T, Bayes A, Wenzel K, Infante J, Zach H, Pirker W, Posada IJ, Alvarez R, Ispierto L, De Fabregues O, Callén A, Palasí A, Aguilar M, Martí MJ, Valldeoriola F, Salamero M, Poewe W, Tolosa E (2015) The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov Disord* **30**, 229-237.
[36] Braak H, Del Tredici K, Rueb U, de Vos RAI, Jansen Steur ENH, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* **24**, 197-211.
[37] Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow W, Poewe W, Stern M, Deuschl G (2015) MDS research criteria for prodromal Parkinson's disease. *Mov Disord* **30**, 1600-1611.