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Pupillary response to light and tasks in early and late onset essential tremor patients

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ABSTRACT

Introduction: Late-onset essential tremor is characterised by shorter life expectancy and more advanced aging parameters and may therefore be an 'aging-related' tremor. Brainstem functions involved in pupillary responses are hypothesized to reflect such earlier aging. The pupillary light response (PLR) and a task evoked pupillary response (TEPR) were used to test this hypothesis in same-aged patients with early onset (EOET) and late onset (LOET) essential tremor and healthy controls.

Subjects and methods: Age related changes of the PLR and TEPR during the paced auditory serial addition test (PASAT) were tested in 57 normal subjects. Subsequently, 13 patients with LOET and 16 patients with EOET were compared with 15 age matched healthy controls. Standard parameters of PLR were recorded, amongst others the time to maximum acceleration of the PLR (T1) and the time to maximum velocity (T2). The TEPR was determined during the PASAT as the percentage change in pupil size (PCPS). Data were analysed with ANOVA and post-hoc testing.

Results: In normal subjects the pupil diameter, latency, maximum acceleration/velocity and percentage amplitude were correlated with age. Latency of the pupillary light response was significantly longer in LOET compared to controls and EOET while no differences were found between EOET and controls. The TEPR showed no significant differences between the three groups.

Conclusion: LOET showed a prolonged latency of the PLR compared to EOET possibly indicating premature aging or rather pathophysiological differences on brainstem level. This study further supports the hypothesis of abnormal aging in LOET.

1. Introduction

According to the current consensus statement on the classification of tremors essential tremor (ET) is defined as a syndrome with bilateral upper limb action tremor with a duration of at least three years in the absence of other neurological signs [1]. The new classification emphasizes that ET is rather a syndrome than a unique disease, thus recognizing multiple etiologies. The prevalence of ET is steeply increasing in the elderly and the age distribution is bimodal [2–4]. Patients with tremor onset after the age of 60 show a faster disease progression, worse aging parameters such as grip strength and cognitive performance and most importantly they have a shorter life expectancy [3,5,6]. These findings might indicate an underlying neurodegenerative or abnormal aging process and led to the term "aging-related tremor" to subclassify these patients, although there is no common definition for the age limit yet [6].

Pathological studies could not find consistent hallmarks in ET patients. While some studies detected abnormalities mainly affecting the cerebellum [7,8], others could not replicate these findings [9,10]. A possible affection of the locus coeruleus (LC) in ET was suggested by a biochemical assessment of parvalbumin, a marker of GABAergic neurons. Interestingly, reduction of parvalbumin was mainly found in a subgroup of patients with a late age at tremor onset, whereas in most patients with younger onset age parvalbumin was normal [11,12]. These results support considerations that late onset ET differs in brain stem affection from ET syndromes with younger onset age [6].

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Pupillometry is a tool to assess the related brainstem- and midbrain located autonomous nervous system pathways. The pupil diameter is controlled by the constricting iris sphincter muscle, which is under parasympathetic control and the dilatory pupil muscle, which is controlled by the sympathetic nervous system. Disturbed functional integrity of either branch of the autonomic nervous system affects the pupil reaction differently: lesions of the parasympathetic pathways impede the pupillary light response, while lesions of the sympathetic pathways result in an attenuated dilation to changes in arousal [13,14].

While the PLR is driven by a well-known polysynaptic reflex pathway, the supranuclear control of pupil dilation is less understood [14]. The pupil size coincides with cognitive arousal and the task evoked pupillary response (TEPR) is considered a function of the mental effort required to perform a cognitive task [15]. The pupil dilates in response to increasing demands, with an inverse relation to the cognitive ability. From animal studies there is evidence for a causal relationship between LC activation and pupil dilation [16]. However, it is still not entirely clear if the LC directly influences the Edinger-Westphal nucleus and possibly other circuits such as cholinergic pathways and structures such as the colliculus superior or the nucleus paragigantocellularis might be involved too [17,18]. The paced auditory serial addition test (PASAT) was applied to evoke cognitive arousal [19] and was shown sensitive to impairments of cognitive processing in a wide variety of neurological disease conditions [20]. Thus, testing pupillary functions during the PASAT may possibly serve as a measure of LC function.

Several studies in normal controls have shown that different PLR parameters (reflex latencies, pupil diameter, constriction velocity) are changing with increasing age [21]. Interestingly, patients suffering from degenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) have several abnormal pupillometric parameters compared with healthy controls [22]. Accordingly, we tested the PLR and the TEPR during the PASAT in patients suffering from LOET or EOET and age-matched healthy controls to investigate whether diagnostically meaningful differences exist. Based on the above mentioned potential pathophysiological differences in LOET and EOET we hypothesized that LOET will demonstrate significant alterations regarding the measured pupillometric parameters compared with EOET. This might indicate potential differences in biological aging between the two groups or rather pathophysiological differences on brainstem level.

2. Participants and methods

2.1. Study design

In the first instance age-related changes of the PLR and TEPR were assessed in a sample of 57 healthy controls of different age groups. Afterwards 16 EOET and 13 LOET patients were recruited consecutively from our outpatient clinic database. EOET and LOET patients were compared with those healthy subjects that were older than 60 years (n = 15). All patients were neurologically examined by a movement disorder specialist and tremor was rated according to the Fahn-Tolosa-Marin Tremor-Rating-Scale (FTM-TRS). ET was diagnosed according to the current diagnostic IPMDS criteria [1]. Muscle strength was measured for each arm with a dynamometer (Smedley digital hand dynamometer). Cognitive functioning was assessed by using an established four-component cognitive composite score [23].

Exclusion criteria were competing neurologic diseases apart from ET, systemic diseases possibly influencing the pupillary light reflex (e.g. diabetes mellitus, peripheral neuropathy) and ocular diseases (cataract, glaucoma, history of eye surgery). Medication possibly affecting the pupillary motion (i.e. cholinesterase inhibitors, betablockers, benzodiazepines, caffeine) had to be paused for at least 24 h.

2.2. Pupillometry

Pupillometry was performed with an iView X Hi-Speed stationary eye-tracker. The tracking column consists of a built-in infrared camera and a fixture that keeps the test-person's head still in front of the camera. Pupil diameter was recorded monocularly from the left eye with an infrared video-based eye tracker (iView-X Hi-Speed 1250, SMI GmbH, Munich, Germany) at a sampling rate of 500 Hz, a spatial resolution of 0.01° and a system latency of less than 2 ms. Stimuli for the PLR paradigm were presented in the centre of a screen (Advantech, IDS-3115N-K2XGA1E, 15″ XGA 1200 cd/m^2 LED, viewing angle 80°/80°) using the E-Prime Software (Psychology Software Tools, Pittsburgh, PA), which syncs the timing of stimulus presentation with the computer that records the pupil data.

2.3. Pupillary light reflex

The PLR paradigm was examined in darkness. The participants viewed a red cross on black background in the centre of the stimulus screen for 2 min. The PLR was evoked by rectangularly appearing bright white circles of 7 different diameters, projected consecutively to the centre of the screen. The stimulus duration was 200 ms each. The luminous intensity emitted was: 1.5, 6.0, 18.5, 37.7, 84.8, 182.5, 317.0 cd, depending on the diameter of the circles. The inter stimulus interval was 12 s, to allow a complete re-dilatation of the pupil between the stimuli.

The participants' eye position was controlled by the examiner on the control monitor. If the patient lost fixation the trial was dismissed. The paradigm was repeated five times, resulting in a total of 35 measurements of the PLR for each patient.

2.4. Task evoked pupillary response

The TEPR was assessed during the PASAT [19] in darkness. Participants viewed the screen with a dark red cross. A series of single digit numbers was presented auditory at four different inter stimulus intervals (5.0s, 4.0s, 3.0s, 2.0s) from a recording tape, thus resulting in a specific number of digits presented within each 1-min lasting trial (12, 15, 20, 30). The different rates were presented in a randomized order. The participants were instructed to sum the two preceding digits after a new digit was presented. The response had to be given before the presentation of the next digit to be scored as correct. A series of practice trials was performed prior to the beginning of the first trial.

2.5. Processing of the pupillometric data

MATLAB and Psychtoolbox-3 (Release 2017b, The MathWorks, Inc., Natick, Massachusetts, United States), were used for data processing. The track of the horizontal pupil diameter was smoothed and artefacts (e.g. eye blinks) were removed by linear interpolation.

Standard parameters of the PLR were measured (Fig. 1): baseline pupil diameter (D1), minimum pupil diameter after constriction (D2), constriction amplitude (D1–D2; AMP), maximum velocity (VCmax), maximum acceleration (ACmax), latency from the onset of the light stimulus to the maximum acceleration (T1), time for maximum velocity (T2), time for maximum constriction (T3), relative constriction amplitude (%AMP, ratio of AMP divided by D1). The mean values of at least 3 artefact-free pupil diameter tracks of the left eye of each subject were taken for further analyses.

The TEPR was defined as the percentage change in pupil size (PCPS) during each 1-min task minus the baseline pupil size, divided by the baseline.

2.6. Statistical analysis

IBM SPSS Statistics (Version 24.0. Armonk, NY: IBM Corp) was used

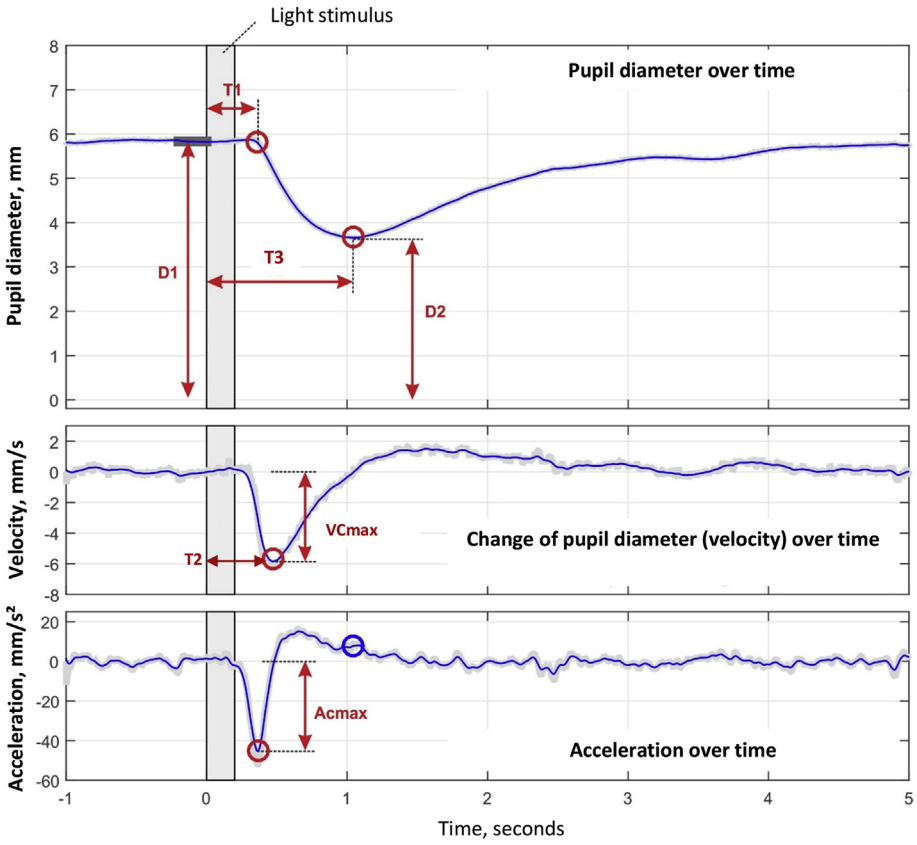

Fig. 1. Pupil diameter over time and change of the diameter (velocity and acceleration) over time. D1: baseline pupil diameter; D2: minimum pupil diameter; VCmax: maximum velocity; ACmax: maximum acceleration; T1: latency from the onset of the light stimulus to the maximum acceleration; T2: time for maximum velocity; T3: time for maximum constriction.

for statistical analyses. A Pearson correlation analysis was applied to correlate PLR parameters with age in healthy controls. Nonparametric Kruskal-Wallis test with post-hoc Dunn-Bonferroni correction was applied for group comparisons of baseline patient characteristics and Pearson's chi-squared test was applied to test categorical variables (gender, family history). Pupillometric data were tested for normality (Kolmogorov-Smirnov) and parametric tests were applied. Mixed model ANOVA were applied with stimulus intensities (for the PLR paradigm) or stimulus presentation rates (for the TEPR paradigm) as within subject factor and group (EOET, LOET or healthy control) as between subject factor. Bonferroni's correction was used for post-hoc analysis.

The study was approved by the local research ethics committee and adhered to the ethical standards of the Declaration of Helsinki.

3. Results

3.1. Subject characteristics

Fifty-seven healthy individuals (female n = 34) between 20 and 80 years old underwent the pupillometry paradigm. 13 patients with late onset ET (mean onset age 60.8 years), 16 patients with early onset ET (mean onset age 17.6y, $p < 0.001$) and 15 age matched healthy controls were included (Table 1). Both patient groups did not differ significantly in tremor severity and all three groups did not differ in age. Within the group of EOET patients, 2 had additional tremor of the head and lower limbs, 1 of the head and 1 of the lower limbs. Within the LOET group, 1 patient had additional head tremor and 1 patient had tremor of the lower limbs. Cognitive performance and grip force were non-significantly worse for LOET patients compared to EOET patients and controls.

3.2. Age related changes of the PLR in 57 healthy controls

Baseline pupil diameter (Pearson's $r = -0.42$; $p < 0.01$) and minimum pupil diameter (range of Pearson's r across all stimulus intensities: $r = -0.40/-0.54$; $p < 0.01$) showed a negative correlation with age for all stimulus intensities. T1 was significantly correlated with age for all stimulus intensities ($r = 0.35/0.48$; $p < 0.01$). ACmax and VCmax were correlated negatively with age in those trials with higher stimulus intensities (37.7, 84.8, 182.5, 317.0 cd; ACmax: $r = -0.31/-0.45$; $p < 0.05$, VCmax: r = -0,31/−0.41; $p < 0,05$), while there was no significant correlation in those trials with weaker stimulus intensities. %AMP was correlated negatively with age in trials with weaker stimulus intensities (1.5, 6.0, 18.5, 37.7 cd; $r = -0.29/-0.41$; $p < 0.05$).

3.3. TEPR in healthy controls

Healthy controls were divided into three age groups (20-40y, 41-60y and 61-80y). The percentage error rates were calculated for each trial ((errors/count of numbers presented) *100). A mixed model ANOVA with presentation rate as within subject factor and group as between subject factor showed a significant effect of the presentation rate ($F(2.4, 129.5) = 85.1$, $p < 0.001$), with higher error rates during faster number presentation. Additionally, there was a significant group effect ($F(2, 53) = 3.476$, $p < 0.05$, partial eta squared = 0.12), with post-hoc testing showing significantly higher error rates in the old aged (61-80y) group compared to the young group (20-30y, $p < 0.05$) and no significant differences between the old aged and middle aged (41-60y) group or the young and middle aged groups.

The percentage change in pupil size for each PASAT condition was tested with a mixed model ANOVA with 4 different presentation rates (5.0, 4.0, 3.0, 2.0 s) as within subject factor and group as between subject factor, showing a significant main effect of the presentation rate on pupil dilation ($F(1.93, 96.93) = 6.24$, $p < 0.01$), but there was no significant group effect.

Table 1
Baseline characteristics of subjects. EOET: early-onset essential tremor; LOET: late-onset essential tremor; FTM: Fahn-Tolosa-Marin Tremor-Rating-Scale.

	EOET		LOET		Controls		P1	P2	P3
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation			
n	16		13		15				
Male, n	9		9		7		n.s.	n.s.	n.s.
Family history of ET, n	13,0		6,0		1,0		< 0.001	< 0.001	< 0.001
Age	70,3	3,3	72,3	4,2	69,6	4,9	n.s.	n.s.	n.s.
Dioptre right eye	1,3	1,6	0,9	1,1	0,8	1,3	n.s.	n.s.	n.s.
Dioptre left eye	2,3	1,4	0,9	1,1	0,8	1,4	n.s.	n.s.	n.s.
Age at tremor onset, y	17,6	7,1	60,8	7,4			< 0.001		
Disease duration, y	52,7	8,1	11,8	5,7			< 0.001		
Cognitive composite test	53,4	7,8	44,5	12,0	50,9	8,8	n.s.	n.s.	n.s.
Becks Depression Inventory	7,0	6,3	5,4	3,2	5,2	4,6	n.s.	n.s.	n.s.
Quality of Life	71,9	19,0	75,4	11,1	78,6	17,8	n.s.	n.s.	< 0,05
FTM total score	33,5	10,7	30,4	9,7			n.s.		
FTM-A (tremor score)	10,1	3,9	10,2	4,9			n.s.		
Grip force dominant hand, kg	37,1	12,6	34,8	8,3	36,5	11,0	n.s.	n.s.	n.s.
Grip force non-dominant hand, kg	33,2	11,2	30,8	8,5	33,6	11,6	n.s.	n.s.	n.s.

P1: Level of significance for nonparametric group comparisons (EOET vs LOET; post-hoc Dunn-Bonferroni test).
P2: Level of significance for non-parametric group comparisons (Controls vs LOET; post-hoc Dunn-Bonferroni test).
P3: Level of significance for non-parametric group comparisons (EOET vs Controls; post-hoc Dunn-Bonferroni test).

3.4. Pupillary light response in ET patients

For each target parameter (T1, T2, T3, D2, VCmax, ACmax, AMP, %AMP) separate mixed model ANOVAs with the 7 different stimulus intensities as within subject factors and group (EOET, LOET, Control) as between subject factors were performed. For all parameters a significant main effect of the light intensity ($p < 0.001$ for each parameter) and no significant interaction of the light intensity with the group effect were shown. A significant group effect was found for T1 ($F(2, 37) = 7.747$, $p < 0.01$, partial eta squared = 0.296) and T2 ($F(2, 36) = 7.430$, $p < 0.01$, partial eta squared = 0.292). Post-hoc analysis demonstrated that T1 and T2 values were significantly longer in LOET patients compared to healthy controls (for T1: $p < 0.001$, T2: $p < 0.01$) and EOET patients ($p < 0.05$ each), while EOET patients did not differ significantly from healthy controls (Fig. 2). For the other PLR parameters, the LOET group showed similar but non-significant changes (Table 2,supplementary figures 1-6).

A multiple linear regression was calculated to predict T1 for all ET patients based on the onset age, age, tremor severity (Fahn A) and cognitive composite score. The R^2 for the overall model was 0.282 (adjusted $R^2 = 0.145$), and the whole model showed no statistical significance ($F(2, 21) = 2.058$, $p > 0.05$). Only the onset age significantly predicted T1 ($\beta = 0.516$, $p < 0.05$), while the other parameters showed no significant predictive values.

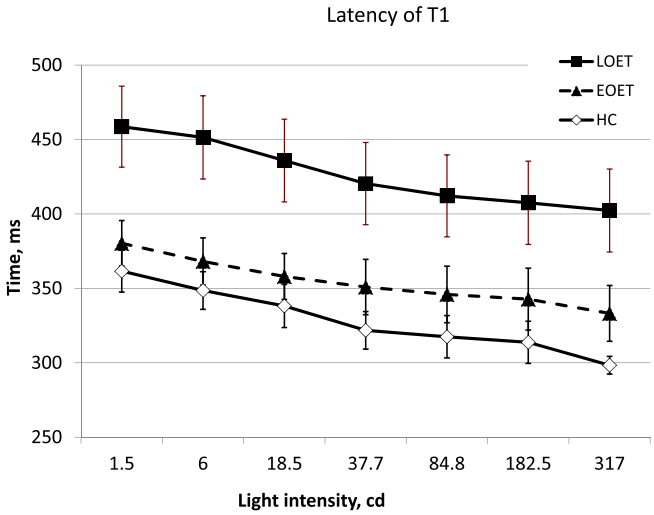

Fig. 2. T1 values (and standard error mean bars) for different stimulus intensities in patient groups and controls, EOET: early-onset essential tremor; LOET: late-onset essential tremor; HC: healthy controls.

Table 2
Standard PLR parameters for a stimulus intensity of 37.7cd. EOET: early-onset essential tremor; LOET: late-onset essential tremor.

	EOET n = 16		LOET n = 13		Control n = 15		
	mean	std	mean	std	mean	std	ANOVA
Vcmax, mm/s	5,37	0,78	4,89	0,96	5,12	0,84	0,350
Acmax, mm/s²	40,69	7,00	35,50	7,10	37,24	7,25	0,154
T1, ms	350,91	74,42	420,40	99,62	321,84	48,79	0,005*
T2, ms	444,32	64,09	526,32	101,76	435,72	63,25	0,006*
T3, ms	951,16	72,63	1023,60	129,98	978,07	104,91	0,192
D1, mm	5,39	0,68	5,30	1,20	5,50	0,94	0,858
D2, mm	3,51	0,51	3,56	0,82	3,60	0,68	0,938
AMP, mm	1,88	0,34	1,73	0,43	1,90	0,32	0,455
%AMP	65,25	4,59	67,32	3,05	65,38	2,81	0,253

3.5. Task evoked pupillary response in ET patients

Percentage error rates during the PASAT were analysed with a mixed model ANOVA with 4 presentation rates as within subject factor and group as between subject factor. A significant effect of the presentation rate ($F(2.47, 96.61) = 109.37$, $p < 0.001$, partial eta squared = 0.737), with higher error rates during faster number presentation was shown, but there were no significant group differences (Table 3) and no significant interaction.

A mixed model ANOVA including the PCPS at 4 different presentation rates (5.0, 4.0, 3.0, 2.0 s,supplementary figure 7) as within subject factor and group as between subject factor, showed a significant main effect of the presentation rate on pupil dilation ($F(2.73, 98.42) = 9.426$, $p < 0.001$, partial eta squared = 0.207) but no significant group effect and no significant interaction.

4. Discussion

In this study the PLR and TEPR were examined to indicate aging effects of the autonomic nervous system function in EOET and LOET patients (with a cut-off onset age of 50 years). We found that the

Table 3
Mean numbers and rates of errors during the paced auditory serial addition task (PASAT) according the presentation rate. EOET: early-onset essential tremor; LOET: late-onset essential tremor; HC: healthy controls.

		Presentation rate			
		5 s	4 s	3 s	2 s
EOET	**mean (%)**	0.9 (7.5)	2.6 (17.3)	4.7 (23.5)	15.3 (51.0)
	std	1,0	2,2	2,1	6,2
LOET	**mean (%)**	1 (8.3)	2.5 (16.7)	5.6 (28.0%)	14.8 (49.3)
	std	1,1	2,0	3,4	5,4
HC	**mean (%)**	1.3 (10.8)	2.3 (15.3)	4.7 (23.5)	13.3 (44.3)
	std	1,8	2,1	3,4	6,2
all	**mean (%)**	1.0 (8.3)	2.5 (16.7)	5.0 (25.0)	14.4 (48.0)
	N	44,0	44,0	44,0	44,0
	std	1,3	2,1	3,0	5,9

latency of the PLR was significantly increased in LOET patients. Moreover, a multiple regression analysis showed that only the onset age significantly predicted the PLR latency in the whole group of ET patients. The age, tremor severity and the cognitive score had no significant effect. The TEPR showed no differences between the tremor groups.

In healthy aging characteristic changes of the PLR have been described. Most consistently an aging-related prolongation of light reflex latencies due to brainstem or peripheral nervous system changes and a decline of the pupil diameter in darkness, possibly caused by an unequal atrophy of the dilator relative to the sphincter muscle of the iris, iridal rigidity or a peripheral sympathetic deficit were shown [21,24]. Additionally, several studies demonstrated a decrease of the maximum constriction acceleration and -velocity [21,25]. We replicated these findings of age-related changes of the PLR in a large sample of 57 healthy controls to validate our examination paradigm. The latency was strongly correlated with age and additionally the baseline pupil diameter, VCmax and ACmax decreased with advancing age.

Since EOET and LOET patient groups did not differ in their ages at the time point of testing, our findings cannot be explained by normal age-related changes of the PLR. Furthermore, there were no associations of the PLR parameters with tremor severity, suggesting that these findings are not a side effect of the tremor but point towards underlying differences in the pathogenesis of EOET and LOET. In line with this, multichannel-EEG recordings have shown a brainstem source being present in EOET but absent in LOET [26].

For degenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) significantly lower levels of VCmax, ACmax, AMP and %AMP and significantly longer latencies compared to normal controls were found [22]. For both patient groups these findings are considered as evidence for a disintegrity of central cholinergic pathways. The cholinergic system has never been suggested to be causally involved into the pathophysiology of ET but this system like all other parts of the nervous system undergoes aging processes and this may be the underlying cause of the present finding. The current data show significant changes for the latencies only. However, the findings for VCmax, ACmax and AMP show similar although non-significant changes which may be since the study was underpowered for these parameters. Similarly, typical stigmata of LOET versus EOET like a lower grip force and worse cognitive performance [3,6] were not significant, possibly due to the relatively small sample size.

In contrast to the PLR, we found no differences regarding the TEPR in the examined ET subtypes. The TEPR is considered to mirror an activation of the noradrenergic system and has been shown abnormal in preclinical stages of AD, which is characterised by pathological changes of the LC in early disease course [27]. In this study, the PASAT was used to induce cognitive effort and a clear increase of PCPS was found in all groups depending on the presentation rate. This suggests reliable activation of the noradrenergic system during the paradigm. Therefore, our findings do not support the hypothesis of an impairment of the noradrenergic system in ET subgroups. However, the groups did also not differ in their PASAT performance, possibly indicating a floor effect: a more difficult task might have had more discriminatory power to reveal cognitive impairments and group differences in the TEPR, but this remains speculative.

Our study has several limitations. The small sample size limits the generalizability of the results and prevents a further statistical assessment of the diagnostic ability of the PLR parameters in differentiating groups on an individual basis. Clinical criteria to exclude ocular diseases have been strictly followed but as an ophthalmologic assessment was not done, we cannot finally rule out that ophthalmological factors have influenced the results [28].

We conclude, that our results demonstrate differences of the PLR in EOET versus LOET in patients with the same numerical age. While other explanations cannot be finally excluded, our findings are interpreted as reflecting age-related biological differences between these two ET-subgroups, supporting the concept of LOET representing a special form of aging. The results of the TEPR do not support the hypothesis of LC dysfunction in LOET but certainly cannot exclude this either. Further hypothesis-driven studies are needed to confirm our results and to further underline the hypothesis of a brainstem dysfunction in LOET.

Contributorship

(1.Research project: (A) Conception; (B) Organization; (C) Execution. 2. Manuscript Preparation: (A) Writing of the first draft; (B) Review and Critique).

JB, FG: 1 A, B, C; 2 A
LK, MY: 1 B, C, 2 B
KW: 1 A, 2 B
GD: 1 A, B, C, 2 B

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Dr. Gövert reports no disclosures
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.004.

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Glossary

ET: essential tremor
EOET: Early onset essential tremor
LC: locus coeruleus
LOET: late onset essential tremor
PASAT: paced auditory serial addition test
PLR: Pupillary light response
TEPR: Task evoked pupillary response