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Eye movement abnormalities in essential tremor versus tremor dominant Parkinson's disease

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HIGHLIGHTS

- Saccade features differ between essential tremor (ET) and tremor dominant Parkinson's disease (PD-T).
- Both patient groups have a reduced sustained smooth pursuit eye movements gain.
- Eye movement abnormalities reflect cerebellar dysfunction in ET and basal ganglia pathology in PD-T.

ABSTRACT

Objective: To show that eye movement abnormalities differ between essential tremor (ET) and tremor dominant Parkinson's disease (PD-T), and that these abnormalities reflect cerebellar dysfunction in ET and basal ganglia pathology in PD-T.
Methods: In this exploratory study, in 23 patients with ET, 21 age-matched patients with PD-T, and 19 age-matched healthy controls (HCs), we investigated visually guided saccades, antisaccades, and smooth pursuit eye movements (SPEM).
Results: While the ET group had a normal gain (saccade amplitude/target amplitude) and latency of saccades, the PD-T group had hypometric visually guided saccades, and a prolonged latency of visually guided saccades and antisaccades. The SPEM gain was similarly low in both ET and PD-T and was significantly lower in both patient groups than in the HC group.
Conclusions: In ET, SPEM gain was reduced in the presence of normal saccades, whereas in PD-T, the reduced SPEM gain was accompanied by delayed saccade initiation and hypometric saccades, in line with cerebellar dysfunction in ET and basal ganglia dysfunction in PD-T.
Significance: These findings support the presumed cerebellar pathology in ET. In addition, the difference in saccade features may contribute to the groundwork for a quantitative diagnostic test to differentiate between these disorders.

1. Introduction

Although essential tremor (ET) presumably affects the cerebellum and tremor dominant Parkinson's disease (PD-T) is associated with basal ganglia pathology, ET can be difficult to differentiate from PD-T due to overlapping symptoms (Tolosa et al., 2006; Louis, 2018; Lees et al., 2009). As the cerebellum and basal ganglia play a different role in the generation of eye movements, ocular motor symptoms may differ between these disease entities (Yerram et al., 2013).

The cerebellum is crucial for smooth pursuit eye movements (SPEM) and also mediates the accuracy of saccades (see Beh et al. for review) (Beh et al., 2017; Leigh and Zee, 2015). For this study relevant afferent projections of the cerebellum arise from the cortical eye fields and the superior colliculus, while relevant efferent projections are through the vestibular nuclei to the paramedian

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pontine reticular formation (PPRF) (Beh et al., 2017). The basal ganglia, on the other hand, mediate the amplitude and latency of saccades and SPEM, and their influence is largest on volitional saccades, i.e. saccades following an internal cue, as opposed to visually guided saccades, i.e. saccades following a visual cue (see Terao et al. for review) (Terao et al., 2013). The basal ganglia also receive input from the cortical eye fields, and project through the superior colliculus on the PPRF (Terao et al., 2013; Leigh and Zee, 2015). Identification of eye movement differences between ET and PD-T would both enlighten on the pathophysiology of these disorders, and potentially contribute to the development of a quantitative diagnostic test to differentiate ET from PD-T (Yerram et al., 2013).

Previous studies investigating eye movements in ET are sparse. Two pioneering studies in patients with ET showed normal saccade gain and low smooth pursuit eye movements (SPEM) gain, consistent with cerebellar dysfunction (Helmchen et al., 2003; Trillenberg et al., 2006). Previous investigations of eye movements in Parkinson's disease, although without subdivision of tremor-dominant versus non-tremor patients, showed a prolonged latency of especially volitional saccades, e.g. antisaccades, reflecting dysfunction of fronto-striatal circuits (Terao et al., 2011; Amador et al., 2006).

It is still not clear whether ocular motor symptoms truly differ between ET and PD-T. The differences between these separately studied patient groups could for instance have been caused by age, since patients with ET were of a relatively younger age than patients with Parkinson's disease and saccadic eye movements are adversely influenced by age (Irving et al., 2006; Helmchen et al., 2003; Amador et al., 2006; Terao et al., 2011). Here, we aim to show that eye movement abnormalities differ between ET and PD-T, and that these abnormalities reflect cerebellar dysfunction in ET and basal ganglia pathology in PD-T.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

This study employed an observational cross-sectional design and followed the Declaration of Helsinki Principles. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Written informed consent was obtained from all participants. The study took place in the Amsterdam UMC (AMC) between February 2014 and May 2017.

2.2. Participants

This exploratory study included 23 patients with ET, 21 age- and sex-matched patients with PD-T and 19 age- and sex-matched healthy controls (HCs). Patients were recruited from two primary care hospitals (Onze Lieve Vrouwe Gasthuis West in Amsterdam and Zaans Medical Center in Zaandam) and from one teaching hospital (Amsterdam UMC, AMC) in the Netherlands.

Patients with ET were included if they met the following conditions: definite diagnosis according to the criteria defined by the Tremor Investigation Group (Deuschl et al., 1998), moderate to severe tremor of upper extremities (defined as a tremor score > 2 on the Essential Tremor Rating Assessment Scale (TETRAS)) (Elble et al., 2012), positive effect of propranolol on tremor, and positive family history of ET. Inclusion of patients with PD-T required diagnosis of Parkinson's disease fulfilling the UK Parkinson's disease society (PDS) Brain Bank criteria (Hughes et al., 1992), tremor dominance (defined as a ratio of at least 1.5 of the mean MDS-UPDRS (Unified Parkinson's Disease Rating Scale, version 3.0) tremor score to the mean MDS-UPDRS postural instability/gait difficulty score (Goetz et al., 2007), as described in detail in the study of Stebbins et al. (2013), no major fluctuations in symptoms due to medication, absence of severe dyskinesia (subjects had to sit still to enable accurate recording of eye movements).

Exclusion criteria for all participants were age < 40 years, MMSE < 26, suspicion of a neurodegenerative disorder (other than ET in patients with ET and PD-T in patients with PD-T), a history of deep brain stimulation and use of antipsychotic, anti-epileptic or antidepressant medication (as these drugs may influence eye movement parameters) (Reilly et al., 2008), a visual acuity < 0.4, blurry vision, diplopia, and visual field disturbances. An additional exclusion criterion for HCs was a first degree relative with ET or Parkinson's disease.

To prevent the influence of anti-tremor medication on eye movement parameters, patients with ET were requested to temporarily discontinue their anti-tremor medication 12 h before the investigation or, in case of slow release tablets, 24 h before the investigation, until the study protocol was completed. Likewise, patients with PD-T were asked to taper their levodopa treatment. However, if tapering led to compromised mobility in patients, or had done so in the past, levodopa treatment was continued. All patients were recorded on video for assessment of TETRAS, MDS-UPDRS motor score and MDS-UPDRS tremor score by a trained movement disorder specialist, who was blinded to the study results (Elble et al., 2012; Goetz et al., 2007). Also documented were disease duration, level of education, medication use, and patients' subjective tremor score on a scale from zero to ten, in which zero meant no noticeable tremor and ten meant "worst tremor ever".

2.3. Eye movement recordings

We investigated visually guided saccades, antisaccades and SPEM using the double magnetic induction method. With this method, eye position is detected indirectly: in a primary magnetic field, a short-circuited coil on the subject's eye induces a secondary magnetic field of which the strength reflects the movement of the eye. The position of the eye is determined by means of a detection coil placed in front of the eye. To only measure eye movements, as opposed to head movements, the head is fixated with a chinrest and a head band, completely restricting head movements. The double magnetic induction method has a high accuracy and resolution. The accuracy during a recording of 20 minutes is ±15 minarcs; the resolution is 5 minarcrs for the range of ±20 degrees in both horizontal and vertical direction. This has been described more fully in previous articles (Bour et al., 1984; Nieman et al., 2000). If patients had a refractive error, this was corrected with spectacles compatible with this method. To reduce influences on the level of attention, the eye movement tasks were consistently explained and performed in the same sequence. In addition, the recordings took place in a dimmed and soundproof room. The total duration of the eye movement tasks was 20 min.

Visually guided saccades were investigated using the 'main sequence task' (Leigh and Kennard, 2004). Subjects were instructed to continuously fixate on a 'jumping target' as accurately as possible. The target started in a central position. Thereafter, the target switched off and immediately reappeared at a random location in a horizontal plane, with a variable interval (800–1500 ms) and a variable distance from the previous location (2–20°). The paradigm was repeated in the vertical plane, resulting in a total number of 76 trials, i.e. 38 horizontal trials and 38 vertical trials.

In the antisaccade task, subjects were required to fixate on a central target, present for 2000 to 3200 ms, which would disappear and immediately reappear at 6° in a horizontal plane for 1500 ms. On reappearance of the target, subjects had to inhibit a

reflexive prosaccade towards the target and look in the opposite direction (i.e. produce an antisaccade). The antisaccade task included 36 trials.

For the recording of SPEM, subjects were instructed to follow a moving target with their eyes as accurately as possible. The target moved back and forth in a horizontal plane (between −10° and +10°), with a constant velocity (10 °/s), for 31 trials. Details of the procedure have been described elsewhere (van Tricht et al., 2010), including the division of segments of recorded eye movements into SPEM and saccades. The 150 ms before and after each turning point were excluded from analysis due to the sudden alteration of eye velocity at the turning point (van Tricht et al., 2010).

2.4. Eye movement analysis (off line)

Processing of eye movement data was performed with a custom-made program developed by T. Boeree of the department of Clinical Neurophysiology, AMC in Amsterdam (de Wilde et al., 2008). Eye velocity was used to determine the onset and ending of a saccade, and the relevant eye movement parameters were automatically detected (de Wilde et al., 2008). In visually guided saccades, relevant eye movement parameters comprised the mean saccade gain (defined as primary saccade amplitude divided by target amplitude) and the mean saccade latency (defined as the time interval between target appearance and the start of a saccade). Post-hoc, we also analyzed accuracy of saccades, focusing on the percentage of inaccurate saccades, which comprised hypometria (gain < 0.08) and hypermetria (gain > 1.1). In addition, we analyzed velocity profiles: peak velocity, acceleration time (duration of start saccade to peak velocity), deceleration time (duration of peak velocity to end saccade) and duration of the saccade. Peak velocity for five, ten and twenty degree saccades was derived from an exponential fit (peak velocity = Vmax*$(1 - e^{-\text{amplitude}/c})$ of a scatterplot of peak velocity and amplitude of saccades (Leigh and Kennard, 2004). Furthermore, we evaluated the gain and latency of visually guided saccades for five, ten- and twenty-degree saccades by extracting these values from a linear fit of the gain and latency versus the amplitude of the target, in each subject group. Relevant eye movement parameters in the antisaccade task were the mean antisaccade latency, the error rate (the number of times a subject failed to inhibit a prosaccade towards the target divided by the total number of trials in the antisaccade task) and, post-hoc, the velocity profiles. In the SPEM task, the relevant parameter was the mean horizontal sustained SPEM gain (defined as eye velocity divided by target velocity) (van Tricht et al., 2010).

All recorded eye movement data were evaluated independently by two researchers (F.V. and Y.X.L), who excluded trials from analysis if a saccade was absent (e.g. if the program accidently included a blink due to absence of a saccade), or if the subject looked away from the target during the main sequence task or the SPEM task. For inclusion in the analysis, we required a minimum of 25 recorded trials in each eye movement task. As an exception to this rule, no minimum of antisaccades was required for the analysis of latency of antisaccades. This exception was made to prevent a selection bias by excluding patients with a high error rate and therefore a low number of antisaccades.

2.5. Outcome measures and statistical analysis

Primary outcome measures were mean gain and mean latency of visually guided saccades, mean latency of antisaccades and mean SPEM gain. A secondary outcome measure was the error rate in the antisaccade task. Post-hoc, we additionally analyzed saccade accuracy and saccade velocity profiles (i.e. peak velocity, acceleration time, deceleration time and total duration of a saccade) in visually guided saccades and antisaccades. Furthermore, we analyzed gain and latency for different target amplitudes (i.e. five, ten and twenty degrees). Statistical analysis was performed using IBM SPSS Statistics (version 23). Normal distribution was evaluated on visual inspection and verified using the Shapiro-Wilk test.

The associations between primary and secondary outcome measures and subject groups were investigated with a one-way ANOVA. To further determine the association of primary and secondary outcome measures and different subject groups, i.e. patients with ET, patients with PD-T and the HC group, we used a Gabriel post-hoc test (applicable in case of slightly different sample sizes and in case of equal variances assumed) (Field, 2013). Post-hoc evaluations were not statistically tested, considering the small sample size of this study.

Significant associations between outcome measures and ET or PD-T were corrected for age by means of multiple regression analysis. The Pearson product moment correlation coefficient was used to assess the correlation of eye movement abnormalities with disease duration and disease severity in both patient groups.

A p-value $p < 0.05$ was considered statistically significant. In view of the exploratory nature of this study, we decided not to correct for multiple testing (Rothman, 1990).

3. Results

3.1. Participants

Table 1 presents the participant characteristics. None of the participants had an ocular disorder other than a refractive error, which was corrected during the recordings. The three groups were well balanced in age, sex and level of education. The mean MMSE score was one point lower in the ET group and the PD-T group than in the

Table 1
Demographic and clinical characteristics of patient groups and the healthy control group.

	ET n = 23	PD-T n = 21	HC n = 19	*p Value*
Age (years), mean (SD)	63 (12)	65 (11)	64 (7)	*0.7*
Male, n	14	13	11	*1.0*
High level of education, n	11	12	15	*0.2*
MMSE, mean (SD)	29 (1)	29 (1)	30 (0)	*<0.01**
TETRAS, mean (SD)	16 (7)	7 (5)	NA	*<0.01**
MDS-UPDRS motor section, mean (SD)	8 (5)	17 (11)	NA	*<0.01**
MDS-UPDRS tremor score, mean (SD)	5 (3)	5 (4)	NA	*0.7*
Subjective tremor scale (0 – 10), mean (SD)	4 (3)	4 (3)	NA	*0.5*
Disease duration (years), mean (SD)	31 (18)	6 (4)	NA	*<0.01**
On levodopa treatment, n	NA	18	NA	*NA*
On propranolol treatment, n	12	0	NA	*NA*

ET = essential tremor, PD-T = tremor dominant Parkinson's disease, HC = healthy controls, SD = standard deviation, MMSE = minimal mental state examination, TETRAS = the Essential Tremor Rating Assessment Scale, MDS-UPDRS = Movement Disorder Society - unified Parkinson's disease rating scale (version 3.0), NA = not applicable.
* a p-value $p < 0.05$ was considered statistically significant.

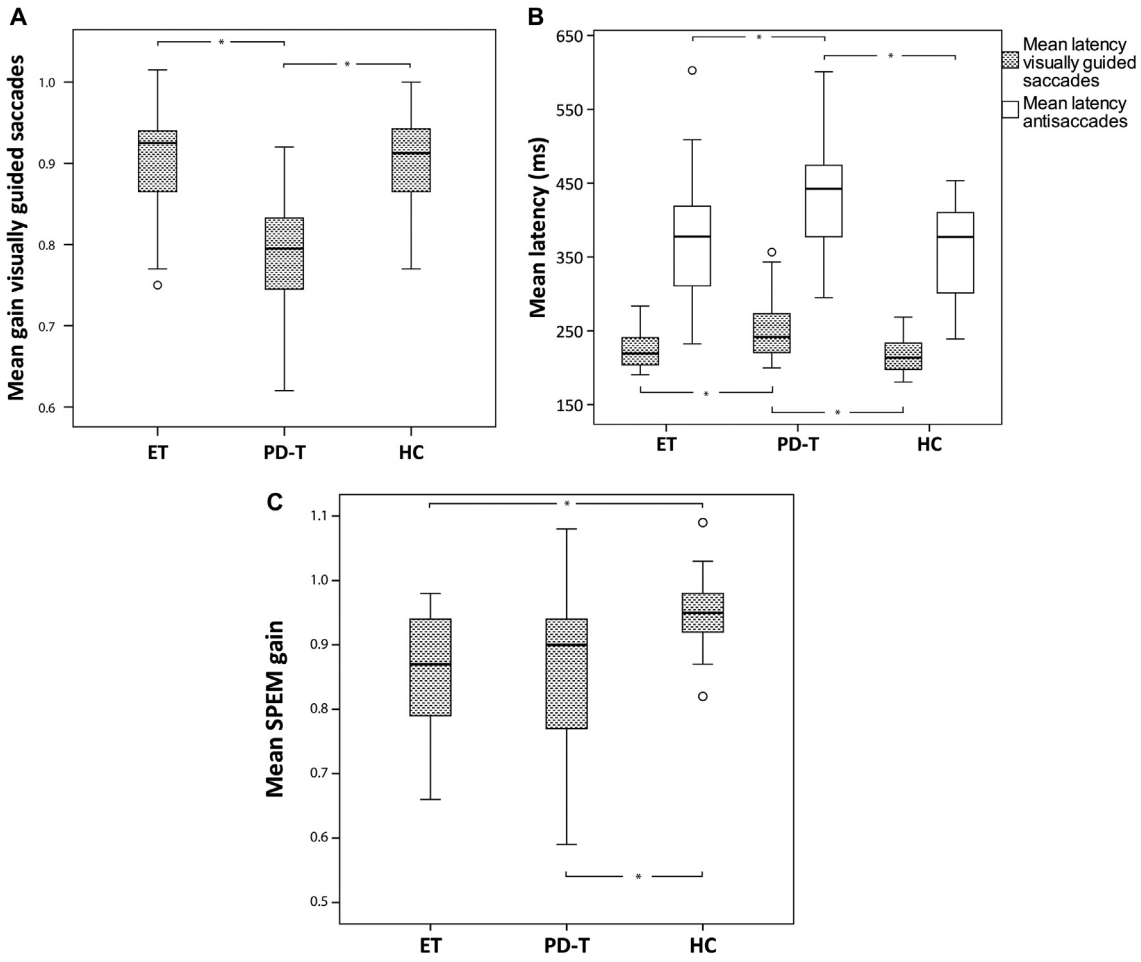

Fig. 1. Visually guided saccades, antisaccades and smooth pursuit eye movements (SPEM) in patient groups and the healthy control group. (A) Boxplots represent the mean gain of visually guided saccades. (B) Representation of the mean latency of visually guided saccades (grey boxplots) and mean latency of antisaccades (white boxplots). (C) Figure C shows the mean SPEM gain in the ET group, the PD-T group and the HC group. ET = essential tremor, PD-T = tremor dominant Parkinson's disease, HC = healthy controls. SPEM = smooth pursuit eye movements. The bars in the boxplots denote the median of the plots. 'o' denotes an outlier. *Statistically significant.

HC group, yet similar between the ET group and the PD-T group. No difference was seen in MDS-UPDRS tremor score and subjective tremor score between the ET group and the PD-T group. The mean TETRAS score was significantly higher in the ET group than in the PD-T group (ET: 16, PD-T: 7, $p < 0.01$), while compared to the ET group, the PD-T group had a higher mean MDS-UPDRS score (ET: 8, PD-T: 17, $p < 0.01$). Furthermore, the mean disease duration was significantly longer in the ET group than in the PD-T group (ET: 31 years, PD-T: 6 years, $p < 0.01$).

Before the study protocol started, 12 of 23 patients with ET used propranolol (i.e. anti-tremor medication) and 18 of 21 patients with PD-T used levodopa treatment. Whereas all patients with ET on propranolol discontinued this without problems, only two of 18 patients with PD-T withdrew their medication, and 16 patients with PD-T continued the levodopa treatment because they had experienced comprised activities of daily living during tapering of levodopa treatment in the past. The three PD-T patients without medication had a relatively short mean disease duration of two years, and two of these patients had a positive DAT scan before this study, which confirmed diagnosis of PD.

3.2. Eye movement recordings

We excluded ten percent of the visually guided saccade trials due to the absence of a saccade or because the subject looked away from the target. In addition, we excluded three percent of the anti-saccade trials from analysis due to the absence of a saccade. All these excluded trials were equally distributed amongst the three subject groups. In all subjects, no SPEM trials were excluded. We obtained the minimally required trials in each eye movement task in all participants.

3.3. Visually guided saccades

Fig. 1A shows the mean gain of visually guided saccades in ET, PD-T and the HC group. One patient with ET with a low mean gain of saccades was an outlier. This patient had no remarkable clinical characteristics other than a rest tremor, and since data quality was good, he was included in the analysis. Fig. 1B presents the latency of visually guided saccades (and the latency of antisaccades). One patient with PD-T was an outlier because of a prolonged mean latency of visually guided saccades. This patient had no remarkable clinical characteristics or data recordings, and he was included in the analysis. Data-analysis was repeated without each outlier, which did not change the results.

Data analysis showed that compared to the ET group, the PD-T group had a significantly reduced mean gain (i.e. saccade amplitude/target amplitude, ET: 0.90, PD-T: 0.80, p-value < 0.01) and a significantly longer mean latency of visually guided saccades (ET: 222 ms, PD-T: 254 ms, $p < 0.05$). When comparing the PD-T group to the HC group, the PD-T group also had a lower mean gain (PD-T 0.80, HC: 0.90, $p < 0.01$) and a longer mean latency of saccades

(PD-T 254 ms, HC: 214 ms, $p < 0.01$). Mean gain and mean latency did not differ significantly between the ET group and the HC group ($p = 0.9$ and $p = 0.9$ respectively).

The significant difference between ET and PD-T in mean gain and mean latency of visually guided saccades persisted after correction for age ($p < 0.01$ for mean gain and $p < 0.05$ for mean latency). We found no significant correlation between visually guided saccade measures and disease duration or disease severity (see Table 2).

Post-hoc evaluation of accuracy of saccades showed that in ET, 40% of saccades were inaccurate, of which 76% were hypometric and 24% were hypermetric. In PD-T, 50% of saccades were inaccurate: 90% hypometric and 10% hypermetric. Thirty-five percent of saccades were inaccurate in HCs, 77% hypometric and 23% hypermetric. Analysis of velocity profiles showed no differences between subject groups (see Fig. S1, Supplementary Information). The differences between groups in gain, more than in latency, tended to increase with increasing amplitudes (see Fig. S2, Supplementary Information).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2019.01.026.

3.4. Antisaccades

Fig. 1B presents the latency of antisaccades. One outlier was noticed, a patient with ET with a high mean latency, and since this patient had no remarkable clinical characteristics or data recordings, he was included in the analysis. Subsequently, data-analysis was repeated without this outlier, which did not change the results. In the antisaccade task, the error rate was 48% in the ET group, 46% in the PD-T group and 45% in the HC group ($p = 0.9$).

In comparison to the ET group, the PD-T group had a significantly longer mean latency of antisaccades (ET: 373 ms, PD-T: 441 ms, $p < 0.05$), which was also the case in comparison to the HC-group (PD-T: 441 ms, HCs: 357 ms, $p < 0.01$). The mean latency of antisaccades did not differ significantly between the ET group and the HC-group ($p = 0.9$).

Between ET and PD-T, the difference in mean latency of antisaccades was larger than the difference in mean latency of visually guided saccades: 68 ms versus 32 ms, respectively.

The difference in antisaccade latency between ET and PD-T remained significant after correction for age ($p < 0.05$). We found no significant correlation between antisaccade latency and disease duration or disease severity in PD-T (see Table 2). Post-hoc evaluation of velocity profiles showed no differences between the subject groups (see Fig. S1, Supplementary Information).

3.5. SPEM

The mean SPEM gain was 0.86 in the ET group, 0.87 in the PD-T group and 0.95 in the HC group, see Fig. 1C. Analysis of mean SPEM gain showed two outliers: one HC with a relatively high mean SPEM gain and one HC with a relatively low mean SPEM gain. No explanation was found in participant characteristics or data quality, and both outliers were included in the analysis. Subsequently, data-analysis was repeated without these outliers, which did not change the results.

The mean SPEM gain in the ET group did not differ significantly from the mean SPEM gain in the PD-T group ($p = 1.0$). However, both the ET group and the PD-T group had a significantly lower mean SPEM gain than the HC group ($p < 0.05$ and $p < 0.05$, respectively). Correction for age did not change these findings regarding SPEM gain in ET and PD-T ($p = 0.7$). Neither patient group showed a significant correlation between mean SPEM gain and disease duration or disease severity (see Table 2).

4. Discussion

Here, we show that eye movement abnormalities differ between ET and PD-T, indicating cerebellar dysfunction in ET and basal ganglia pathology in PD-T, see Fig. 2. We found a reduced SPEM gain in the ET group, accompanied by normal visually guided saccades and antisaccades, reflecting the prominent role of the cerebellum in SPEM (Beh et al., 2017). In contrast, the PD-T group had a reduced SPEM gain in combination with hypometric saccades, a prolonged latency of visually guided saccades, and an even more prolonged latency of antisaccades, which suggests basal ganglia dysfunction (Terao et al., 2013). The differences in saccade features between ET and PD-T remained significant after correction for age. Notably, a low SPEM gain was seen in both ET and PD-T and this can be added to the list of overlapping symptoms of ET and PD-T.

4.1. Essential tremor

The ET group had a normal gain of visually guided saccades and a slightly higher frequency of inaccurate saccades than the HC group, comprising hypometric saccades as well as hypermetric saccades, i.e. dysmetria. Previous studies in ET defined saccade accuracy as the saccade gain, which was normal (Gitchel et al., 2013; Trillenberg et al., 2006), as in our study, in which averaging of the hypometric and hypermetric saccades in ET resulted in a normal saccade gain.

We found no significant difference in latency of visually guided saccades between the ET group and the HC group. This is in line with previous studies (Helmchen et al., 2003; Trillenberg et al., 2006) with the exception of one study: Gitchel and colleagues found an increased latency of visually guided saccades in ET patients (Gitchel et al., 2013), possibly by including also saccades of 30° and larger (as opposed to saccades up to 20° in negative studies), and by having more power than the negative studies. This may also explain why Gitchel et al. found a reduced peak velocity and prolonged duration of saccades (Gitchel et al., 2013), while we found no differences between subject groups in the post-hoc anal-

Table 2
Correlations coefficients between eye movement abnormalities and disease duration or disease severity.

	Disease duration	*p Value*	Disease severity	*p Value*
Tremor dominant Parkinson's disease				
Mean gain visually guided saccades, rho	0.4	*0.1*	0.3	*0.3*
Mean latency visually guided saccades, rho	0.2	*0.3*	0.2	*0.6*
Mean latency antisaccades, rho	0.1	*0.6*	0.3	*0.2*
Mean gain smoot pursuit eye movements, rho	0.3	*0.2*	0.2	*0.5*
Essential tremor				
Mean gain smooth pursuit eye movements, rho	0.1	*0.05*	0.1	*1.0*

Disease severity was assessed using the Essential Tremor Rating Assessment Scale score in essential tremor and by the Movement Disorder Society - unified Parkinson's disease rating scale (version 3.0) motor score in tremor dominant Parkinson's disease.

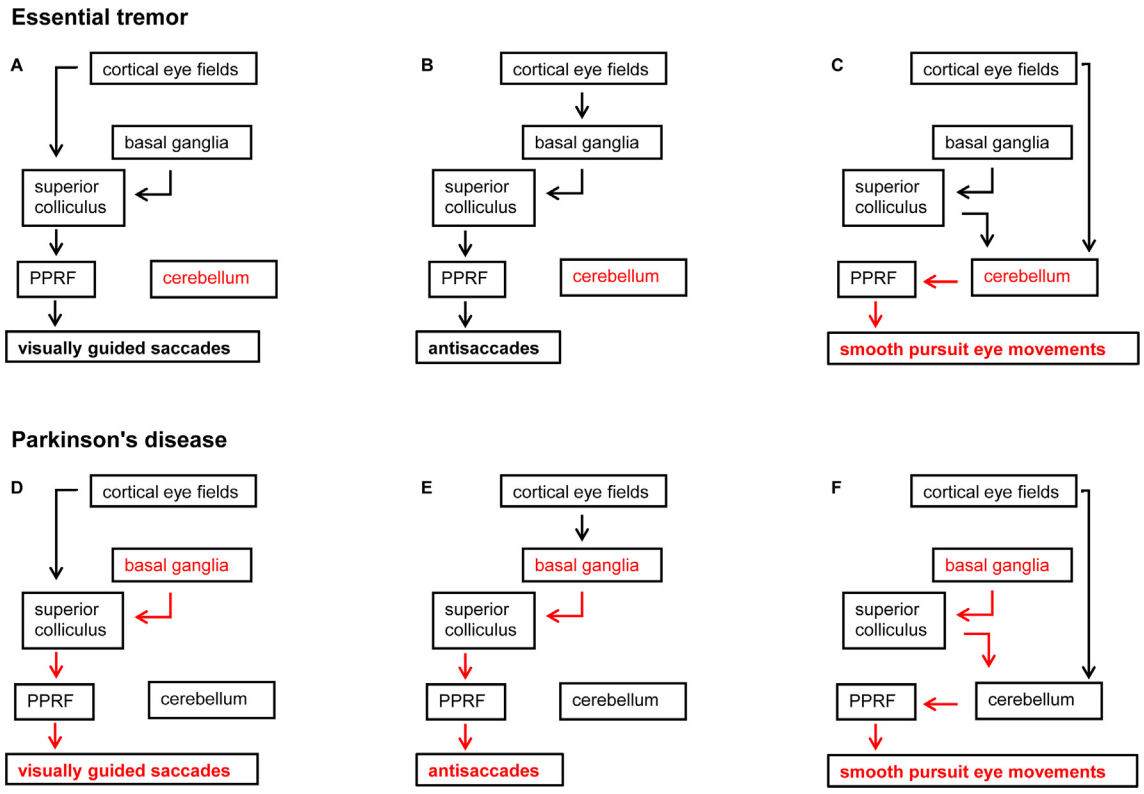

Fig. 2. Affected saccades and smooth pursuit eye movements in patient groups. The figure shows a simplified schematic representation of different types of eye movements in the essential tremor (ET) group (top row) and the tremor dominant Parkinson's disease (PD-T) group (bottom row), in which the red text and arrows represent pathologically affected structures, projections and eye movements. (A + B) Visually guided saccades and antisaccades were unaffected in ET, suggesting normal function of involved structures. Although the cerebellum does influence saccades (e.g. saccadic adaptation), we primarily investigated the gain and latency of saccades in which the cerebellum plays a less important role. (C) In ET, the reduced smooth pursuit eye movements gain, in the presence of normal saccades, may reflect cerebellar dysfunction. (D – F) In PD-T, dysfunction of the basal ganglia may have influenced all three types of eye movements represented in this figure. PPRF = paramedian pontine reticular formation.

ysis of velocity profiles of visually guided saccades and antisaccades.

The antisaccade task showed a normal latency of antisaccades and a normal error rate in the ET group. This is a novel finding; as far as we know, there are no previous studies on antisaccades in ET.

The SPEM task showed a reduced sustained SPEM gain in the ET group, which was not correlated with disease duration or disease severity. These findings are in line with previous research (Helmchen et al., 2003).

Our findings support the presumed cerebellar pathology in ET. Tissue based studies in ET have shown pathological changes of Purkinje cells in the cerebellum, suggesting the cerebellum to be the site of origin of ET symptoms (Louis, 2016). The crucial role of the cerebellum in SPEM was shown in lesion studies in which complete cerebellectomy abolished SPEM, without affecting saccade amplitude (Estanol et al., 1979; Burde et al., 1975; Westheimer and Blair, 1974). In line with these studies, we found a prominent reduced SPEM gain and normal saccades in ET, see Fig. 2. Furthermore, our findings are consistent with studies in patients with late onset cerebellar ataxia (with pure cerebellar symptoms and isolated cerebellar atrophy on MRI), which showed a reduced SPEM gain and slight saccade dysmetria (mainly hypometria), increasing with increasing amplitude (Federighi et al., 2011; Wessel et al., 1998; Terao et al., 2016). These studies also showed a normal peak velocity (Federighi et al., 2011; Wessel et al., 1998), and one study in patients with pure cerebellar symptoms, and isolated cerebellar atrophy on MRI, showed a prolonged deceleration phase and duration of saccades (Terao et al., 2017). However, this prolonged deceleration and duration of saccades was found only in 30 degree saccades and not in saccades up to 20 degrees (as included in our study), explaining the normal velocity profiles we found in ET.

Historically, ET was suggested to arise from dysfunction of the olivary nucleus (Louis and Lenka, 2017), which, however, is contradicted by negative pathological findings in post-mortem studies in ET (Shill et al., 2008; Louis et al., 2007, 2013) and is also not supported by our findings. Although pathological involvement of the olivopontocerebellar pathway may cause saccade dysmetria and a reduced SPEM gain (Terao et al., 2016; Pinkhardt and Kassubek, 2011), involvement of the pontine nuclei would likely also cause a prominent decreased peak velocity (Federighi et al., 2011; Wessel et al., 1998), and peak velocity was normal in the ET patients in our study.

More recently, two post-mortem studies suggested the dentate nucleus as the origin of ET symptoms (Paris-Robidas et al., 2012; Wang et al., 2016). Impaired function of the dentate nucleus may cause an increased error rate in the antisaccade task (Kunimatsu et al., 2016; Rosini et al., 2017), which is not consistent with our findings. However, as research on eye movement abnormalities associated with dentate nucleus lesions is scarce, we cannot exclude this as a possible site of origin of the eye movement abnormalities we found in ET. A large part of Purkinje cells project through the dentate nucleus to the ventral intermediate nucleus (VIM) of the thalamus (Leigh and Zee, 2015), and pathological changes of the dentate nucleus could also be secondary to Purkinje cell pathology (Paris-Robidas et al., 2012). Involvement of this cerebellar output pathway in the pathophysiology of ET is supported by the positive effect of deep brain stimulation of the thalamic VIM on ET symptoms (Chen et al., 2018).

4.2. Parkinson's disease

The PD-T group in our study had a significantly lower gain and a significantly longer latency of visually guided saccades than the HC group, which is consistent with most previous research in patients with Parkinson's disease (without definition of tremor-dominant or non-tremor subtypes) (Chambers and Prescott, 2010; Terao et al., 2011, 2013; Pinkhardt and Kassubek, 2011). Few studies showed a normal latency of visually guided saccades in Parkinson's disease, which may be explained by the fact that these negative studies only included saccades with a small amplitude, and primarily the latency of saccades with a larger amplitude is prolonged in Parkinson's disease (Chambers and Prescott, 2010; Pinkhardt and Kassubek, 2011). The slightly more prolonged latency in larger amplitude saccades in PD-T in our study support this theory (see Fig. S2, Supplementary Information). Post-hoc analysis of accuracy of saccades showed more inaccurate saccades in the PD-T group than in the HC-group, which mainly consisted of hypometric saccades (90%). This is consistent with the lower gain we found. Post-hoc analysis of velocity profiles showed no differences between the PD-T group and the HC group, which is in line with literature (Pinkhardt and Kassubek, 2011).

The prolonged latency of antisaccades in the PD-T group, which was even more prolonged than the latency of visually guided saccades, is in line with previous research (Chambers and Prescott, 2010; Terao et al., 2011, 2013; Pinkhardt and Kassubek, 2011). The antisaccade task also showed a normal error rate in the PD-T group, which is consistent with some, but not all previous studies (Pinkhardt and Kassubek, 2011; Terao et al., 2013). Since the antisaccade error rate was previously demonstrated to increase with the advancement of Parkinson's disease, the difference in error rate between studies may be explained by a difference in disease stage (Kitagawa et al., 1994; Ewenczyk et al., 2017). In the PD-T group, the SPEM gain was significantly lower than the HC group, which is in agreement with the findings of previous studies (Pinkhardt and Kassubek, 2011).

The primary eye movement measures did not correlate with disease duration or disease severity in PD-T in this study. This is in contrast with one previous study, which, however, included patients with a more advanced disease stage (Terao et al., 2011).

The eye movement abnormalities we found in the PD-T group reflect basal ganglia dysfunction, as the latencies of antisaccades were even more prolonged than the latencies of visually guided saccades (Terao et al., 2013). In the generation of saccades, as is illustrated in Fig. 2D and E, the basal ganglia play a prominent role in the generation of volitional saccades, which may explain why antisaccades were most affected in the PD-T group (Terao et al., 2013). Furthermore, basal ganglia dysfunction has been suggested to cause excessive inhibition of the superior colliculus, influencing all saccades and SPEM (Krauzlis, 2001; Terao et al., 2013). The excessive inhibition of the superior colliculus may have resulted in slow initiation and a low gain of visually guided saccades as well as a low SPEM gain in the PD-T group in our study (see Fig. 2D to F). The combination of hypokinesia of all investigated eye movements (i.e. visually guided saccades, antisaccades and SPEM) with the volitional saccades (i.e. antisaccades) being most affected, is typical for basal ganglia dysfunction (Terao et al., 2013; Basso and Liu, 2007). Moreover, basal ganglia dysfunction, resulting from degeneration of dopaminergic neurons in the substantia nigra, pars compacta, is the hallmark of the pathophysiological process in PD-T, supporting the theory that basal ganglia dysfunction caused the oculomotor abnormalities we found in PD-T (Lees et al., 2009). In the pathophysiological process in PD, the frontal cortex may also become affected (Lees et al., 2009), and frontal eye field dysfunction may be an alternative explanation for the prolonged latency of volitional saccades more than of visually guided saccades we found in PD-T (Dias and Segraves, 1999). However, frontal eye field dysfunction may also cause a higher antisaccade error rate, while the normal antisaccades error rate we found in PD-T is more consistent with basal ganglia dysfunction (Guitton et al., 1985; Condy et al., 2004). Dysfunction of the superior colliculus itself may also cause increased saccade latencies, yet with a prominent decreased peak velocity (Hikosaka and Wurtz, 1985), which is not in line with our findings.

4.3. Limitations

Clearly, there are limitations of the present study. First, most patients with PD-T were investigated while on levodopa treatment, and this treatment might have affected the initiation and amplitude of saccades and SPEM in the PD-T group. However, slow initiation and small amplitude of movements are common symptoms of Parkinson's disease and levodopa treatment is presumed to improve these symptoms (Tolosa et al., 2006). The precise effect of levodopa treatment on eye movement parameters is controversial and has yet to be established (Pinkhardt and Kassubek, 2011). Future research comparing PD-T patients on and off medication could give insight on the influence of levodopa on eye movement parameters. Furthermore, in addition to patients with ET and PD-T, including a patient group with cerebellar disease and a group of patients with non-tremor dominant PD, would be of value in the interpretation eye movement parameters as indicators of pathophysiological affected structures. It could be worthwhile to investigate also larger amplitude saccades, as these may reveal abnormalities otherwise missed, and to include hypometria and hypermetria for the evaluation of dysmetria, which may be averaged out in the calculation of the saccade gain.

A second limitation is the fact that the diagnosis of ET and PD-T was a clinical diagnosis. Misdiagnosis, however, would likely have led to an underestimation rather than an overestimation of the differences between ET and PD-T.

Another potential limitation of our study is that blinding of researchers for the diagnosis of subjects was not possible due to the specific symptomology of ET and PD-T. This might have led to a risk of confirmation bias, which was attempted to prevent by automatic detection of outcome measures.

It also may have been of possible influence on our findings that the ET group had a significantly longer disease duration than the PD-T group. However, since the PD-T group had the abnormal saccades and the shortest disease duration, this would likely have made the differences in eye movements smaller between ET and PD-T.

We did not find correlations between eye movement abnormalities and disease duration or disease severity in ET, nor in PD-T, possibly due to the little group variance for disease duration and disease severity in both patient groups in our study. Furthermore, the small sample size and the exploratory nature of this study preclude the denial of such correlations.

Noteworthy, our HC group had a higher mean antisaccade error rate than some HC groups in previous research (Ewenczyk et al., 2017; Kitagawa et al., 1994). This could be explained by a higher mean age in the HC group in our study, as previous research showed a higher antisaccade error rate in older subjects (Abel and Douglas, 2007). Possibly, a shorter time interval between antisaccade trials in the present study also contributed to the relatively high antisaccade error rate.

4.4. Conclusions

In ET, SPEM gain was reduced in the presence of normal saccades, whereas in PD-T, the reduced SPEM gain was accompanied by delayed saccade initiation and hypometric saccades, in line with cerebellar dysfunction in ET and basal ganglia dysfunction in PD-T.

These findings support the presumed cerebellar pathology in ET. In addition, the difference in saccade features may contribute to the groundwork for a quantitative diagnostic test to differentiate between these disorders.

5. Disclosures

None of the authors have potential conflicts of interest to be disclosed.

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