Clinical Parkinsonism & Related Disorders 4 (2021) 100085

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

Abnormalities of smooth pursuit in Parkinson's disease: A systematic review

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ARTICLE INFO

Keywords:
Oculomotor abnormalities
Smooth pursuit eye movements
Saccadic pursuit
Parkinson's disease

ABSTRACT

Smooth pursuit eye movement (SPEM) abnormalities are commonly seen in Parkinson's disease (PD). Both reduced speed and saccades seen during SPEM, also known as saccadic pursuit (SP), have been studied in PD. A comprehensive literature review analyzed 26 studies of SPEM and PD. It appears that a greater proportion of PD patients have SPEM abnormalities consisting of reduced SPEM gain and/or SP compared to the normal population. It is not clear whether SPEM abnormalities are present early in the disease or begin sometime during disease progression. SPEM abnormalities may be correlated with disease severity but do not fluctuate or respond to dopaminergic medication in the same manner as other motor symptoms in PD. SPEM in PD is composed of normal SPEM interspersed with SP composed of both catch up and anticipatory saccades. This differs from other neurodegenerative disorders and may be related to an inability to inhibit extraneous saccades or to increased distraction reflecting executive dysfunction. Because the basal ganglia are involved in SPEM physiology, degeneration of the SNr neurons in PD may explain abnormal SPEM in this disorder. Since dementia, aging and medication effects influence SPEM, they should be controlled for in future studies of SPEM in PD. SP is easily detected on clinical exam and may be a biomarker for the disease or for disease progression. Oculomotor testing can be an important part of the Parkinson's exam.

Contents

https://doi.org/10.1016/j.prdoa.2020.100085
Received 9 September 2020; Revised 23 November 2020; Accepted 3 December 2020
Available online 17 December 2020

1. Introduction

Oculomotor abnormalities are known to occur in many neurodegenerative disorders including Parkinson's disease (PD). Corin et al (1972) reported 75% of PD patients to have some kind of oculomotor abnormality [1] which was later confirmed by Cipparrone et al (1988) [2] and Nakamura et al (1991) [3]. Predominantly, abnormalities in saccades, vergence and smooth pursuit have been described in PD. Saccades are found to be hypometric with extraneous saccades suggesting a loss of inhibition for unwanted eye movements. Convergence insufficiency is found in PD producing diplopia with near vision. Smooth pursuit eye movements (SPEM) have also been reported to be abnormal with reduced gain or speed of eye movement and saccadic pursuit (SP). SPEM gain is not easily evaluated clinically and measurement requires laboratory equipment. SP are saccadic eye movements seen during SPEM. While not reported to cause clinical abnormality, SP is easily detectable on physical exam and can be seen in PD. SPEM abnormalities have been found in early stages of PD and may be present in the prodromal stages of PD [4]. This topical review will focus on abnormalities of SPEM in PD.

SPEM are conjugate eye movements performed to keep a moving object fixated on the fovea. SPEM in PD has been evaluated for accuracy, speed and quality. SPEM abnormalities are found to be greater in the PD population with an estimated prevalence of 67% in PD compared to 20% in healthy controls [5].

The basal ganglia may be involved in efficient and automatic SPEM performance [6]. Anatomical studies showing activity in the caudate, globus pallidus and thalamus during SPEM implicates basal ganglia participation [7–9]. The Substantia Nigra pars reticulata (SNr) in particular, is thought to modulate both saccades and SPEM [10]. SNr degeneration in PD likely alters the patterns of SNr neuronal activity resulting in defects in both saccades and SPEM [9].

Further defining characteristics of SPEM abnormalities in PD were sought through this literature review. SPEM abnormalities, their prevalence, association with disease progression and medication influence on SPEM abnormalities were specific areas of interest.

2. Methods

A search for English language peer reviewed study articles, from inception through 2019, using the Medline database via PubMed, a service of the National Library of Medicine's National Center for Biotechnology Information (https://www.ncbi.nlmlniglgov) was performed with the following search terms: eye movement abnormalities OR oculomotor abnormalities OR interrupted smooth pursuit OR saccadic smooth pursuit OR cogwheel pursuit OR saccadic pursuit OR smooth pursuit OR catch up saccades OR saccadic intrusions during smooth pursuit AND Parkinson's disease. A total of 819 articles were found with the above search. Articles describing a study of SPEM in PD were included. Articles were reviewed by title and abstract for applicability and duplicates were removed. A total of 18 articles were identified. Eight additional articles were added based upon references from the reviewed articles. Three articles were added later for a total of 29 articles analyzed in this review. See Fig. 1.

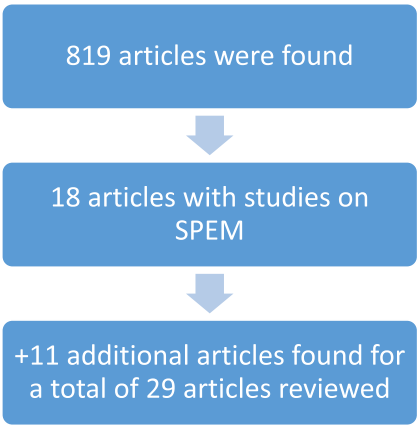

Fig. 1. Methods of SPEM literature review.

3. Prevalence of SPEM abnormalities

Not all patients with PD have SPEM abnormalities. In fact Corin et al (1972) reported from 46 to 63% of their PD patients with normal SPEM [1]. Cipparrone et al (1988) found abnormal SPEM in 61% of their PD patients [2]. Measuring the frequency at which SP began called the cogwheel pursuit threshold, Shibsaki et al (1979) found a reduced cogwheel pursuit threshold in 6 out of 19 PD patients compared to 2 out of 10 normal controls [5]. So it appears that SPEM abnormalities appear to occur more frequently in the PD population, but not everyone with PD will have SPEM abnormalities.

It is not known whether SPEM abnormalities are present early and throughout the disease course or present later in the disease. Three studies reported prevalence of SPEM abnormalities and average disease duration in their study population. Bares et al (2003) studied 21 drug naïve early PD patients with mean disease duration of 2.2 years. Approximately two-thirds of their patients had a reduction in eye displacement gain compared to controls [11]. Linder et al (2012) reported no reduction in SPEM gain in their drug naïve newly diagnosed PD patients with a mean disease duration of 1.2 years [12] and Pinkhardt et al (2009) found 4 out of 27 PD patients with reduced SPEM gain compared to controls having a mean symptom duration of 8.2 years [13]. No conclusions can be made regarding SPEM gain in drug naive early PD (Table 1).

4. Disease severity

There is controversy over whether there is a correlation between disease severity, duration and SPEM abnormalities. Eight studies found a correlation and three did not, however measurements differed between studies. See Table 2. Two studies looked at SP and found a correlation between SP and rigidity [5,14]. Three studies measured SPEM speed and found a greater reduction in SPEM velocity in more advanced stages [14–16]. Two studies of pursuit ocular movements (POM) found a correlation between the POM score and Hoehn and Yahr and Unified Parkinson's Disease Rating Scale score (UPDRS) [17,18]. Linder et al (2012) found a correlation between the axial UPDRS score and SPEM gain of their PD patients [12]. Zhang et al, 2016 found a correlation between SPEM gain and disease duration and UPDRS scores [19].

However, Machner et al (2010) found a reduction in SPEM gain only in symptomatic parkin mutation carriers but not in asymptomatic parkin mutation carriers or in early onset PD patients. Their symptomatic patients did not differ in UPDRS scores from the early onset PD, however disease duration in the early onset PD patients was not specified and it is possible that the early onset PD patients had not progressed to the point of development of SPEM abnormalities [20].

Pinkhardt et al (2012) did not find any correlation between SPEM gain and UPDRS or rapid alternating hand movement score or disease duration [21]. Fukushima et al (2015) found no significant difference in Hoehn and Yahr scale, UPDRS or disease duration between PD patients with abnormal and normal initial pursuit during the simple ramp test [22]. So it is possible, but not clear as to whether there is a correlation between disease severity or duration and SPEM abnormalities.

Table 1
SPEM abnormalities and disease severity correlations.

Study	SPEM measurement	rigidity	bradykinesia	tremor	H + Y	UPDRS	PD disease duration
Shibasaki et al, 1979	SP: Cogwheel pursuit threshold	yes	no	no			
White et al, 1983	SP: % time spent in normal SPEM SPEM gain	yes	yes				
Rascol et al, 1989	SPEM gain: Peak Velocity				yes		
Leukwuwa et al, 1999	SPEM gain		yes				
Marino et al, 2007	SPEM gain: Pursuit ocular movement				yes	yes	
Marino et al, 2010	SPEM gain: Pursuit ocular movement				yes	yes	
Linder et al, 2012	SPEM gain					Axial score yes	
Zhang et al, 2016	SPEM gain					yes	yes
Machner et al, 2010	SPEM gain					No	
Pinkhardt et al, 2012	SPEM gain					No	No
Fukushima et al, 2015	SPEM gain				No	No	No

5. Correlation with motor symptoms

A single study reported a progressive deterioration in SPEM amplitude and velocity with repeated testing akin to the sequence effect characteristic of PD [16]. They attributed this to progressive bradykinesia and hypokinesia.

Sharpe et al (1987) looking at PD patients during on and off motor fluctuations did not find fluctuations in SPEM gain correlating to the motor fluctuations of akinesia and rigidity [23]. SPEM abnormalities do not appear to associate with motor symptoms and do not show fluctuations consistent with motor state.

Comparing SPEM gain in PD patients with freezing of gait (FOG), without FOG and healthy controls, Wu et al (2020) found a reduction in SPEM gain between PD patients and controls but not a significant difference between PD patients with and without FOG [24]. As FOG appears to be associated with more severe motor symptoms, SPEM does not appear to be affected to the same degree.

6. Directionality

The direction of SPEM may influence the degree of SPEM abnormality. Early observational studies found differences with greater degree of SPEM abnormality in the vertical direction as opposed to the horizontal direction. Corin et al (1972) compared SPEM in all four directions, describing abnormalities in vertical up direction in 54% and 50% in the vertical down direction compared to 37% in the horizontal direction [1]. Shibasaki et al (1979) found SP in 33.3% of PD patients in the horizontal direction and in 66.7% in the vertical direction [5].

Three studies did not find a significant difference in SPEM gain between horizontal and vertical directions despite an overall reduction in SPEM gain compared to controls [13,19,25]. Contrary to a previous study, Pinkhardt et al (2012) found significant reductions in SPEM gain in the horizontal and vertical up directions but not in the downward direction [21].

However, the majority of studies looked at the horizontal direction alone [15–18,20,22–25,27,29,30,31,34].

It may be that qualitatively SPEM abnormalities appear to be more prevalent in the vertical direction, but this is not seen using quantitative measurements such as SPEM gain.

7. SPEM speed (gain)

SPEM gain is the most frequent method of quantifying SPEM speed. Laboratory methods are required to measure it. It is defined as the SPEM velocity divided by the target velocity. The closer the gain is to 1, the closer SPEM is tracking the target at its velocity. A total of 24 articles looked at SPEM speed. Eighteen articles measured SPEM gain. (See Table 2). SPEM gain was found to be reduced in PD compared to controls in sixteen of these articles. Twoe articles did not include a control group [3,23]. Six articles measured SPEM speed by other means; eye displacement gain [11] peak velocity [15,16], pursuit ocular movements [17,18] and pursuit eye velocity [22]. In each case the SPEM speed was found to be reduced in PD compared to controls.

The maximum speed at which a target can be adequately tracked is 30 – 40 degrees/second and the speed of the target determines the final speed of tracking [32]. Two studies found the reduction in SPEM gain to be greater with higher target velocities [14,27].

It appears as if SPEM gain is reduced in PD compared to controls but not to the extent found in other forms of parkinsonism. Vidaillhet et al (1994) found reduced SPEM gain in PD compared to controls but not as much of a reduction as compared to those with progressive supranuclear palsy or corticobasal degeneration [26]. Similar findings with greater reduction in SPEM gain in multisystem atrophy compared to PD was found in two studies [12,13].

Comparing other disorders Henderson et al (2011) compared SPEM gain in PD patients to controls and in Huntington's disease (HD). They found a reduction in SPEM gain in the PD patients but not in the control or HD patients [33]. SPEM gain reduction was found in PD and ET compared to controls [34].

SPEM gain reduction was not found in every study. Machner et al (2010) found a significant reduction in SPEM gain only in symptomatic Parkin mutation carriers but not in asymptomatic Parkin mutation carriers or early onset PD patients compared to controls [20]. Rottach et al (1996) did not find any difference in SPEM gain in the five PD patients tested compared to controls [25].

Generally, it appears that SPEM speed is reduced in PD, which may reflect a form of ocular bradykinesia [5].

8. SPEM latency

SPEM latency is the time taken to initiate SPEM. Five studies looked at SPEM latency in PD patients. SPEM latency was found to be prolonged in PD in three studies [25,28,36]. No significant differences between PD and controls were found in two studies [16,29]. It is not clear whether SPEM latency is prolonged in PD.

9. SPEM accuracy

Three studies looked at SPEM accuracy – the correlation of eye movements to the target movement. Two studies found PD SPEM to

Table 2
Studies of SPEM gain in Parkinson's disease.

Study	#PD/#controls	Age Mean yrs	Mean Dx duration yrs	levodopa	SPEM Gain
White et al, 1983 [14]	14/10	NR	NR	NR	Reduced in PD
Sharpe et al, 1987 [23]	8/0	61	10	Yes	No change in gain between on and off periods
Gibson et al, 1987 [38]	15/15	58	4	none	Reduced in PD
Rascol et al, 1989 [15]	45/30	60.5	NR	20 drug naïve 25 on levodopa	SPEM peak velocity (units not defined)
Nakamura et al, 1991 [3]	24/0 no control	65	NR	yes	Reduced in PD
Vidailhet et al, 1994 [26]	14/12	61.5	11.3	yes	Reduced in PD
Waterson et al, 1996 [27]	13/13	54.7	5.3	yes	Reduced in PD
Rottach et al, 1996 [25]	5/7	67.2	7.5	yes	No change in PD
Lekwuwa et al, 1999 [16]	7/7	55.9	15.4	Yes but studied off meds	Reduced peak velocity in PD
Bares et al, 2003 [11]	21/21	59	2.2	None – given apomorphine during study	Eye displacement gain measured. 33% no change 67% reduced in PD
Marino et al, 2007 [17]	33/33	65.7	NR	Yes	Pursuit ocular movements reduced in PD 0.82 NC 1.15
Pinkhardt et al, 2009 [13]	27/23	62.1	8.2	NR	Reduced in PD
Machner et al, 2010 [20]	14 EOPD 9 symptomatic Parkin mutation carriers 13 asymptomatic Parkin mutation carriers 27 control	52 54 39	NR	NR	Reduced in symptomatic Parkin mutation carriers
Marino et al, 2010 [18]	10 drug naïve PD/10 control	58.5	NR	No – drug naive	Reduced pursuit ocular movements PD 0.84 NC 1.2
Henderson et al, 2011 [33]	16/16	61.13	1–10 yrs	yes	Reduced in PD
Pinkhardt et al, 2012 [21]	34 PD 14 PD STN DBS 23 control	63	6.9 10.5	NR	Reduced in PD and PD STN DBS compared to control
Linder et al, 2012 [12]	105/38	70	Median 1.1	NR	Reduced in PD
Helmchen et al, 2012 [28]	17/19	62.1	5.2	yes	Reduced in PD
Fukushima et al, 2015 [22]	25/14	73.5	4.7	yes	Reduced pursuit velocity in PD
Gorges et al, 2016 [30]	31/22	71	6	yes	Reduced in PD
Zhang et al, 2018 [19]	37/39	67.1	5.61	NR	Reduced in PD
Wu et al, 2018 [31]	10PD 10 control 10 young control	64.5 61.2 20	5.7	NR	Reduced in PD
Visser et al, 2019 [34]	21 PD- tremor 23 ET 19 control	65 63 64	6	yes	Reduced in PD and ET compared to controls
Wu et al, 2020 [24]	40PD 20 PD + FOG 20 PD–FOG 37 control	 66.5 66.2 NR	 4 2	Yes	Reduced in PD compared to controls but no difference between PD + FOG and PD-FOG

Table 3
Saccadic pursuit in Parkinson's disease.

Study	N PD/ Controls	SPEM Gain	Measurement of SP	Results
Corin et al, 1972 [1]	70 PD 30 C	NA	Number of PD patients with abnormal SPEM = jerky or saccadic eye movements	**Severe abn:** Up 7 Down 6 **Moderate abn:** Up 9 Down 5 **Mild abn:** Up 22 Down 24 Right 26 Left 26 **Normal:** Up 32 Down 35 Right 44 Left 44
Shibasaki et al, 1979 [5]	19 PD 10 C	NA	Cogwheel pursuit threshold = frequency at which SPEM shows SP	6 PD with reduced cogwheel pursuit threshold
Teravainen and Calne, 1980 [37]	7 PD 6 C	5/7 PD had slow SPEM	Description	3/7 marked SP 2/7 mild SP 1/6 elderly C with few small amplitude saccades during SPEM
White et al, 1983 [14]	14 PD 10 C	PD Mild 0.74 Advanced 0.54 C 0.90	Description and % SPEM	SP frequent, but pts with advanced disease showed saccadic pursuit at all target velocities Reduced %SPEM in advanced PD pts compared to C
Bronstein and Kennard, 1985 [40]	8 PD 8 C	NA	Turnover velocity = target velocity at which the percentage of time SPEM is reduced by 3 dB	No difference in turnover velocity between PD and C Increased turnover velocity in PD with predictive SPEM
Cipparrone et al, 1988 [2]	36 PD	NA	Description	22/36 PD with SP 2/22 had only SP no normal SPEM (marked)
Pinkhardt et al, 2009 [13]	27 PD 11 MSAP 8 MSAC 23 C	PD Horiz 0.76 PD Vert 0.65 C Horiz 0.91 C Vert 0.77	Phase angles of saccadic component during SPEM: Onset phase angle (OPA) and End phase angle	Greater OPA = anticipatory saccades, some catch up saccades
Henderson et al, 2011 [33]	16 PD 16 C	PD 0.92 C 0.98	Frequency of saccades to distractors/total number of distracters	PD more erroneous saccades to distracters than C
Fukushima et al, 2015 [22]	30 PD 14 C	Peak pursuit eye velocity PD 5.9 C 10.2	% SPEM initial pursuit	7/29 PD pts with saccadic initial pursuit 100% C initial pursuit
Gorges et al, 2016 [30]	31 PD 32 C	PD 0.64 C 0.91	Videooculography and correlated with fMRI	1) Anticipatory saccades during SPEM reduced SPEM gain 2) Abn attributed to predominantly executive dysfunction
Wu et al, 2018 [31]	10 PD 10 C 10 young controls (YC)	PD 0.92 C 0.98 YC 1.08	Saccade rate during SPEM	PD 2.25 saccades/s C 1.4 saccades/s YC 1.2 saccades/s

be less accurate [11,40] and one did not find any significant difference in position error [38]. PD patients may have less accuracy, not following the target as closely during SPEM.

10. SPEM saccadic pursuit

Also referred to as "cogwheel pursuit", "interrupted smooth pursuit", "multistep" and "saccadic intrusions", SP has been described, but rarely quantified [1,2,5,11,13,15,27,30,31,33,37]. Eleven articles looked at SP (See Table 3). Not all PD patients appear to have SP and in some cases SP is present in the normal population. Corin et al (1972) reported 38 out of 70 PD patients with SPEM abnormalities described as slow and jerky [1]. Teravainen and Calne (1980) reported 5 out of 7 PD patients to have SP with 3 graded as marked and 2 with mild SP. One healthy control showed few small amplitude saccades interspersed with normal SPEM [37].

Most of the time PD patients were described to have a mixture of normal SPEM with SP. More advanced PD patients were thought to have SP alone when performing smooth pursuit [2,13,14,37]. Cipparrone et al (1988) reported 22 out of 36 PD patients to have SP with 2 out of those 22 having only SP and no normal periods of SPEM. They did not find any correlation between age at onset or disease severity and presence of SP; but disease duration greater than 10 yrs appeared to be the most significant factor [2].

Five articles attempted to quantify SP with methods ranging from measurement of the cogwheel pursuit threshold to the saccade rate during SPEM. Bronstein and Kennard (1985) measured the turnover velocity of SPEM which was defined as the target velocity at which the percentage of time spent in normal SPEM was reduced by 3 dB.

They did not find any difference in the turnover velocity between the PD patients and normal controls [40].

Two studies looked at the percentage of time spent in SP or normal SPEM. White et al (1983) noted a reduction in the percentage of time spent in normal SPEM in PD patients compared to controls. This was dependent upon the target velocity with a greater amount of SP occurring at greater target velocities. PD patients spent less time in normal SPEM exhibiting a greater amount of time in SP with advanced disease patients having SP even at the lowest target velocities [14]. Wu et al (2018) found PD patients to have higher saccade rates during pursuit (2.2 saccades/s) compared to both age matched and young controls (1.4 and 1.2 saccades/s) [31].

SP has been thought to be compensatory for slow SPEM. As such SP was thought to represent "catch up" saccades performed to correct the eye position to align with the target [1,2,5,14,15,27,37]. Because it was related to slower eye movements, SP was proposed to be a measure of oculomotor bradykinesia [5]. However, further analysis of the saccades performed during SPEM has brought this into question. Saccades occurring ahead of target were designated as anticipatory and saccades occurring behind the target were designated as catch up. Analysis of the phase angles of the saccades during SPEM showed anticipatory saccades interspersed with catch up saccades [13]. They proposed SP to be the cause rather than a result of lower gain. Anticipatory saccades during SP have been found in additional studies [14,30,33,35]. Likewise, Wu et al (2018) found the increased saccades in SP were not triggered by spatial offset stimuli implicating factors other than correction [31]. Analyzing catch up saccades during SPEM in healthy controls compared to saccades, de Brouwer et al (2002) found catch up saccades to be in both forward (catch up) or reverse (anticipatory) directions which differed in amplitude. Both types of saccades during SPEM differed from saccades physiologically [35].

But are the anticipatory saccades truly predictive or are they part of randomly occurring saccades? Predictive or anticipatory saccades are reduced in PD. Patients follow rather than anticipate the target which is thought to be due to increased reliance on vision [40]. Ladda et al (2008) found PD patients impaired in using static visual information as a cue for predictive SPEM [36]. Additionally, PD patients were impaired in predicting target motion onset [28]. Moreover, anticipatory saccades did not improve SPEM; either in accuracy or gain.

SP anticipatory saccades have been proposed to be the result of an inability to suppress extraneous saccades which can be explained by neuroanatomy. When triggered by abnormal firing patterns mediated by the basal ganglia, the superior colliculus which in involved in the release of saccades allows unwanted saccades to occur [30].

Increased distractibility or reduced attention as a result of executive dysfunction may also explain increased SP of PD patients. [13,21,30,33] Using functional MRI, Gorges et al (2016) found reduced functional connectivity in the default mode network to be correlated with poor SPEM performance and increased SP. Specifically the angular gyrus and the superior temporal gyrus appear to be involved with the unwanted release of saccades during SPEM. In fact all of the PD associated oculomotor deficits tested were found to be attributed to executive dysfunction rather than to ponto- cerebellar circuits or to oculomotor brainstem nuclei [30]. Henderson et al (2011) looked at SPEM with distractor stimuli. They found PD patients to have increased error saccades (15.94%) to the distractors especially when appearing distant and ahead of the target compared to controls (5.49%). They concluded difficulty inhibiting automatic responses and distractibility across multiple tasks and modalities were responsible [33].

SP is found not only in PD but in other neurodegenerative conditions, with aging and even in normal controls under conditions of higher target velocities. Genetic conditions such as Hallorvorden-Spatz and Gaucher type 3 have SP [56]. Analyzing the saccades in SP may help to differentiate PD from other conditions. SP is composed of both anticipatory and catch up saccades in PD while only catch up saccades are found in MSA, normal control and the normal aging population [13,31].

In summary, PD patients appear to have increased SP composed of both catch up and anticipatory saccades interspersed between periods of normal SPEM. An inability to suppress extraneous saccades [21,31,33] and possibly attentional or executive dysfunction [13,30,33] are thought to be underlying SP.

11. Medication effects on SPEM

Medication effects on SPEM is not as clear. Ten articles mentioned medication effects. Five articles found improvement in SPEM with dopaminergic medication [1,3,11,18,38] and three did not find any difference [15,27,36]. One article found patients performed worse following levodopa [27]. Two articles compared medication effects with DBS stimulation on and off [21,29]. Three studies reported a fraction of patients with improvement in SPEM with levodopa [1,3,38]. The improvement did not mirror the degree of limb motor improvement. Gibson et al (1987) found an improvement in SPEM gain after treatment with either levodopa or dopamine agonist in half of their patients and no change in gain in the other half. They speculated that the non-improved patients may have had an insufficient dose [38].

Apomorphine was found to improve eye displacement gain in 18 patients with 2 having no improvement and a single patient had worsening of the eye displacement gain [11]. This is in contrast with the findings of Friedman et al (1994) who found a reduction in SPEM gain and an increase in SP following apomorphine injections in healthy controls [41].

Additionally, some medications influence SPEM. The influence of benzodiazepines, antipsychotics and antidepressants among other classes of medication on eye movement were reviewed extensively. Benzodiazepines reduce SPEM gain, increase SP and error. Antipsychotics do not appear to adversely affect SPEM gain, however they may increase SP. Selective serotonin receptor inhibitors may actually improve SPEM gain and reduce SP [42]. Some of the studies reviewed showed an effort to screen for these medications excluding patients taking them from the study [11,15,27,28,34,38].

12. DBS effects on SPEM

Two articles studied the effects of DBS on SPEM [21,29]. Both studies compared DBS on and off states. One study compared PD DBS to PD medication only and controls in the medication on state. The second study compared PD DBS off medications. Only the second study found an improvement in SPEM gain and accuracy and a reduction in SPEM latency in the DBS on/off medication state. It was thought that there may be some influence of medication effect on SPEM which may explain the different outcomes of the two studies. While it is not clear as to whether DBS has an effect on SPEM or not, DBS is thought to have overall beneficial effects on eye movements [43].

13. Other effects on SPEM

13.1. Cognitive performance and attention

Cognitive processes including attention, selection, learning and prediction are all important to SPEM performance. Although visual input is needed to drive SPEM, cognitive control exerts a strong influence over the manner in which that information is used to control eye movements. Selective attention is required to track a specific moving object and to ignore or suppress motion information from other sources [44].

It is well accepted that dementia can affect SPEM. Three studies found a reduction in SPEM gain along with an increase in SP in patients with Alzheimer's dementia [45,46,47]. Because dementia

can coexist with PD, it is important to exclude dementia to be able to see SPEM abnormalities due to PD alone. Many studies excluded patients with significant cognitive difficulties and dementia [12,23,24,27,31,33,34,38]. Four studies looked at measures of cognitive function on SPEM [19,21,22,30]. There was no correlation was found in two studies. Gorges et al (2016) used the battery of neuropsychological tests used by the Consortium to Establish a Registry for Alzheimer's disease (CERAD) which is a measure of executive function. They found a significant correlation between the CERAD score and SPEM gain. They concluded the oculomotor performance worsened with cognitive decline as seen by the CERAD score [30] confirming prior study results.

14. Age

Because of cell loss and changes in the oculomotor systems observed in aged animals and humans it has been thought that advancing age affects SPEM. In a large cross sectional study of healthy people aged 7–82 years, it was found that the SPEM gain and positional precision followed a U shaped curve with the best performances between 20 and 50 years of age [52]. Sharpe and Sylvester (1978) found smooth pursuit to be affected by aging. They reported restriction in upgaze and convergence in addition to an increased frequency of saccades during SPEM and reduced gain in their normal elderly population aged 65–77 years compared to the younger normal population aged 19–32 years [48]. Additional studies confirmed these findings [49,50].

Moreover, Wu et al (2018) compared SPEM gain in PD to age matched controls and to younger aged controls and found the lowest SPEM gain to be in PD patients. The highest SPEM gain was found in young controls with an intermediate value in age matched controls. Saccade rates during pursuit (SP) were found to be higher in PD patients but not in age matched or young controls. There was no difference between SP rates in the aged matched and young controls. This would indicate a reduction in SPEM gain with age and a significantly reduced SPEM gain in PD patients compared to age matched controls. SP appears not to be affected by age [31].

However, in a longitudinal study of healthy elderly over 75 years of age, Kerber et al, (2006) found no change in SPEM gain over nine years [51]. Compensatory mechanisms may be responsible as no difference in SPEM tracking gain in the elderly normal population was found in the natural setting which suggests a difference between the laboratory and natural setting [53].

Because aging most likely has an effect on SPEM, the majority of studies compared PD patients with an age matched control population.

15. Conclusions

Oculomotor abnormalities are common in neurodegenerative movement disorders. They may precede or follow motor symptoms and evaluation of oculomotor function may provide valuable information regarding early disease detection or disease progression [58]. Bedside testing of oculomotor function is mostly sufficient with laboratory testing for subtle abnormalities [58].

There are definite abnormalities of SPEM in PD with a greater proportion of PD patients having reduced SPEM gain and/or SP. It is not clear whether SPEM abnormalities are present early in the disease or begin sometime during disease progression. SPEM abnormalities may be correlated with disease severity but do not fluctuate or respond to dopaminergic medication in the same manner as other motor symptoms in PD. SPEM is composed of normal SPEM interspersed with catch up and anticipatory saccades in PD. This differs from other neurodegenerative disorders and may be related to an inability to inhibit extraneous saccades or to increased distraction reflecting executive dysfunction [59]. SP worsens with disease progression [57]. Because dementia, aging and medication effects influence SPEM, they should be controlled for in future studies of SPEM in PD. SPEM pathways linking the cortex to the basal ganglia with the SNr mediating SPEM may be the basis for abnormalities of SPEM seen in PD [10,54,55,56].

Declaration of Competing Interests

Nothing to declare.

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Further reading

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