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# Ⅳ. 研究成果に関する刊行物

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# Olfactory Dysfunction and Dementia in Parkinson's Disease

Atsushi Takeda[a,*], Toru Baba[b], Akio Kikuchi[c], Takafumi Hasegawa[c], Naoto Sugeno[c], Masatoshi Konno[c], Emiko Miura[a] and Etsuro Mori[b]

[a]*Department of Neurology, National Hospital Organization, Sendai-Nishitgaga Hospital, Kagitori-honcho, Taihaku-ku, Sendai, Japan*

[b]*Department of Behavioral Neurology and Cognitive Neuroscience, Seiryo-machi, Aoba-ku, Sendai, Japan*

[c]*Department of Neurology, Tohoku University Graduate School of Medicine, Seiryo-machi, Aoba-ku, Sendai, Japan*

**Abstract**. Dementia is one of the most debilitating symptoms of Parkinson's disease (PD), but the development of dementia is still difficult to predict at early stages of the disease. We recently found that hyposmia, one of the most typical non-motor features of PD, was a predictive feature of Parkinson's disease with dementia (PDD). In that work, multivariate logistic analysis identified severe hyposmia and visuoperceptual impairment as independent risk factors for subsequent dementia within 3 years. The patients with severe hyposmia had an 18.7-fold increase in their risk of dementia for each 1 SD (2.8) decrease in scores on the odor stick identification test for Japanese (OSIT-J). We also found an association between severe hyposmia and a specific pattern of cerebral metabolic decline, which was identical to findings observed in PDD. Furthermore, volumetric magnetic resonance imaging analyses demonstrated close relationships between olfactory dysfunction and atrophy of focal brain structures, including the amygdala and other limbic structures. Our findings suggest that brain regions related to olfactory function are closely associated with cognitive decline and that severe hyposmia is a prominent clinical feature that predicts the subsequent development of PDD. We have now started a randomized, double-blind study using donepezil for the PD group with severe hyposmia. We hope that this clinical trial will allow us to establish a therapeutic intervention that can improve the prognosis of advanced PD.

Keywords: Hyposmia, Parkinson's disease with dementia, OSIT-J, PET, MRI

## INTRODUCTION

Although James Parkinson first described that intellects are uninjured in Parkinson's disease (PD) [1], it has more recently become apparent that specific cognitive dysfunctions are observed at a high rate even in early stages of PD [2]. Such dysfunction gradually worsens with disease progression and eventually leads to dementia in approximately 80% of cases [3–5]. In addition, it has been recently suggested that Parkinson's disease with dementia (PDD) is one of the biggest risk factors of mortality in PD [6], highlighting the importance of effectively managing PDD. Thus, now the complicating dementia becomes one of the most important prognostic indicators in PD. These changes are at least partly due to the fact that the long-term alleviation of motor dysfunction can be achieved by treatments including dopamine-replacement therapy. Moreover, the number of cases of elderly-onset PD, the high risk group to develop PDD, is increasing as the population ages.

We recently reported that hyposmia, one of the representative non-motor symptoms of PD, is closely associated with cognitive dysfunction [7] and that 40% of patients displaying severe hyposmia develop PDD within 3 years [8]. In this review, we elaborate on the nature of PDD, describe characteristics of hyposmia in

*Correspondence to: Atsushi Takeda, M.D., Ph.D., Department of Neurology, National Hospital Organization, Sendai-Nishitgaga Hospital, 2-11-11 Kagitori-honcho, Taihaku-ku, Sendai 982-8555, Japan. E-mail: atakeda@nishitaga.hosp.go.jp.

PD as well as the association between hyposmia and cognitive dysfunction, and comment on future directions in this area.

## PD AND DEMENTIA

In addition to motor symptoms such as tremor and muscle rigidity, other non-motor symptoms can be observed in PD. Dysautonomia is commonly associated with PD, and psychiatric symptoms such as increased depression and anxiety have recently attracted increased attention [9]. Another common symptom is cognitive dysfunction, which is often observed early in the course of PD [10]. In particular, executive dysfunction, attention deficits, and visuospatial impairments are observed in many cases. These symptoms develop gradually with the progression of PD, and impairment of memory and language also develops at later stages of the disease. The task force committee of the Movement Disorder Society (MDS) has defined such conditions as PDD when these symptoms are severe enough that they interfere with the patient's everyday life [11]. According to the task force, after excluding other diseases that are associated with cognitive dysfunction, probable PDD is defined as "the condition that presents after the onset of PD and displays cognitive disorder to the level of the patient's progressed and exacerbated everyday life becoming interfered with and is the one that is accompanied by at least 2 features out of the following 4 central cognitive dysfunctions, i.e., changing attention deficit, executive dysfunction, visuospatial cognitive impairment, and memory disorder [11]." The task force committee also recommended that PDD be diagnosed using two algorithms: a more basic level 1 algorithm for routine medical practice, and the level 2 algorithm, which is intended for research purposes at medical institutes [12].

Risk factors that are predictive of PDD include older age and more severe motor dysfunction. Some reports have identified additional risk factors, including a clinical subtype of postural instability gait difficulty (PIGD) [13], attention deficits at early stages [14], and REM sleep behavior disorder [15]. According to one cross-sectional study, approximately 20 to 40% of PD patients are classified as PDD [5]. Some differences in the rate of PDD in previous reports are most likely due to differences in the ages of PD patients included in different analyses. Some longitudinal studies have reported that the progression from PD to PDD occurs in an average of 10 years and that approximately 80% of PD cases eventually progress to PDD over the course of 20 years [3, 5]. The prevalence of PDD is approximately 1/10 that of Dementia with Lewy bodies (DLB) [5]. Assuming that there are 150,000 PD patients in Japan, it can be estimated that there are between 30,000 and 60,000 PDD patients in Japan, and that the number of DLB patients is 10 times that of patients with PDD, or between 300,000 and 600,000.

## HYPOSMIA IN PD

As mentioned above, PD is associated with a high incidence of various non-motor symptoms, including hyposmia, dysautonomia (constipation, dysuria, impotence, orthostatic hypotension, and dyshidrosis), sleep disorders, higher brain dysfunction, and psychological symptoms. These non-motor symptoms are in addition to characteristic motor symptoms such as tremor, rigidity, akinesia, and postural instability that result from degeneration of dopamine neurons in the substantia nigra [9]. Because hyposmia is already observed before the onset of motor symptoms (i.e., during the pre-motor phase), many studies have investigated this symptom as an early diagnostic marker of PD. According to these reports, it is estimated that approximately 75% of PD patients have an elevated odor detection threshold, and approximately 90% of PD patients suffer from odor identification deficits [16, 17]. These statistics suggest that hyposmia is more frequently observed than tremor, which is one of the four major motor symptoms of PD. Additionally, it has previously been reported that the degree of hyposmia is not associated with the severity of motor impairments, that hyposmia is already present bilaterally at the disease diagnosis, and that the severity of hyposmia remains essentially constant throughout the course of PD. Based on these findings, it can be inferred that the hyposmia progression is largely complete before the onset of motor symptoms of PD. Interestingly, however, patients are often not aware of their own hyposmia, and hyposmia is likely to be overlooked in the clinic unless olfactory tests are performed. It has also been reported that complete anosmia is uncommon, that the degree of hyposmia tends to be milder in women than in men, and that hyposmia is not improved by dopamine-replacement therapies [17].

Ansari and Johnson first described hyposmia in PD in 1975 [18], and subsequent, more detailed studies were conducted mainly by Doty and colleagues at University of Pennsylvania [16, 17]. It had previously been believed that the presence or absence of hyposmia in

PD was not associated with other clinical symptoms, including cognitive dysfunction. With recent advances in pathological and brain imaging analyses, it has been found that neurodegenerative changes, including the appearance of Lewy bodies, are commonly observed in regions of the brain that are responsible for olfactory perception, such as the amygdala, hippocampus, and orbitofrontal cortex [19, 20]. These changes are apparent from the earliest stages of the disease [19, 20], and the degree of atrophy in these areas is correlated with the severity of hyposmia in early PD [21]. Furthermore, clinical studies have reported that PD patients with severe hyposmia are more likely to suffer from PD-specific cognitive dysfunction, such as memory disorders and visuospatial dysfunction [7, 22]. Based on these results, it has more recently been inferred that severe hyposmia is closely associated with cognitive dysfunction in PD [23].

## SEVERE HYPOSMIA IS A PRODROMAL SYMPTOM OF PDD

As mentioned above, it is very difficult to accurately predict the onset of PDD at early stages [24]. Therefore, we conducted a 3-year longitudinal study in 82 PD outpatients without dementia to analyze factors predicting the development of PDD. Inclusion criteria were: 1) age at onset ≧40, 2) age at enrollment between 55–75, and 3) Hoehn-Yahr classification of severity from stage I to stage III. Exclusion criteria were: 1) any other history of psychological or neurological disease, 2) any abnormal head MRI finding, 3) MMSE ≦24, and 4) clinical dementia rating (CDR) ≧1. Olfactometry was performed using the odor stick identification test (OSIT-J) at the initial study visit. The OSIT-J is a Japanese modification of an odor identification test and consists of 12 microcapsules of different odorous substances that are mixed into stick-formed paraffin [25]. During testing, the examiner rubs each of the odor sticks on paper so that the microcapsules give off their smell, and the examinee is asked to judge what type of smell it is.

FDG-PET and brain MRIs were collected before and after the 3-year period, and 47 patients who completed both brain scans and a clinical evaluation were eventually selected for the main analysis. In the severe hyposmia group, consisting of individuals with OSIT-J score ≦4, hypometabolism in the frontal lobe and occipital lobe was observed at the time of entry, compared with the normal olfaction group or the mild hyposmia group with OSIT-J score ≧5 (Fig. 1) [8]. These differences were greater at the 3-year follow-up, such that the severe hyposmia group had not only

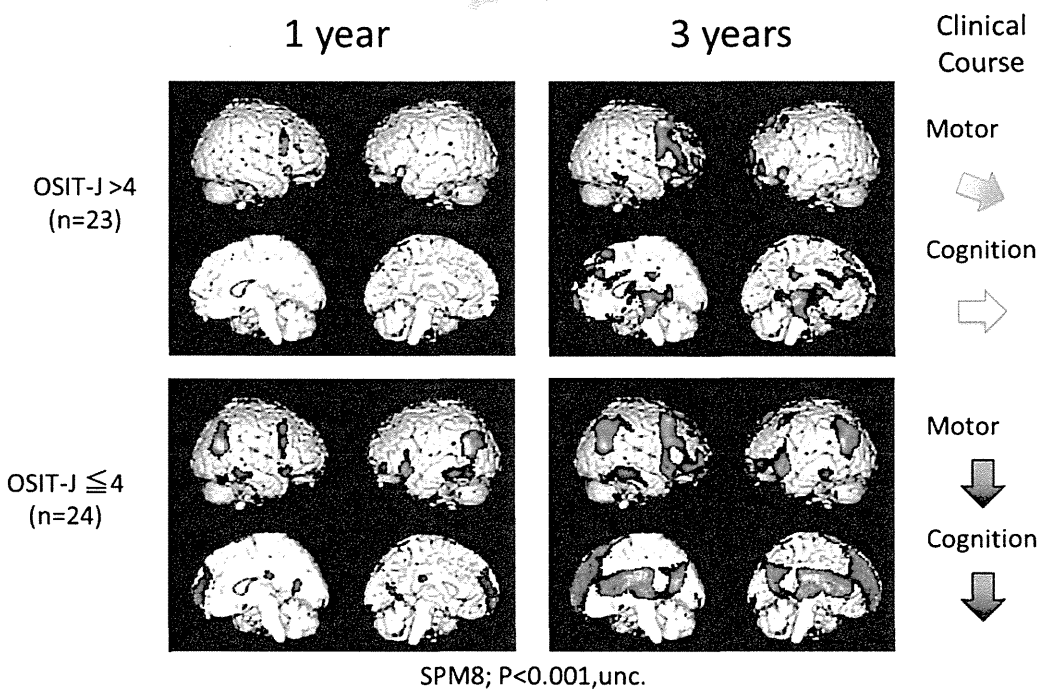



Fig. 1. Changes in brain metabolism measured by FDG-PET.

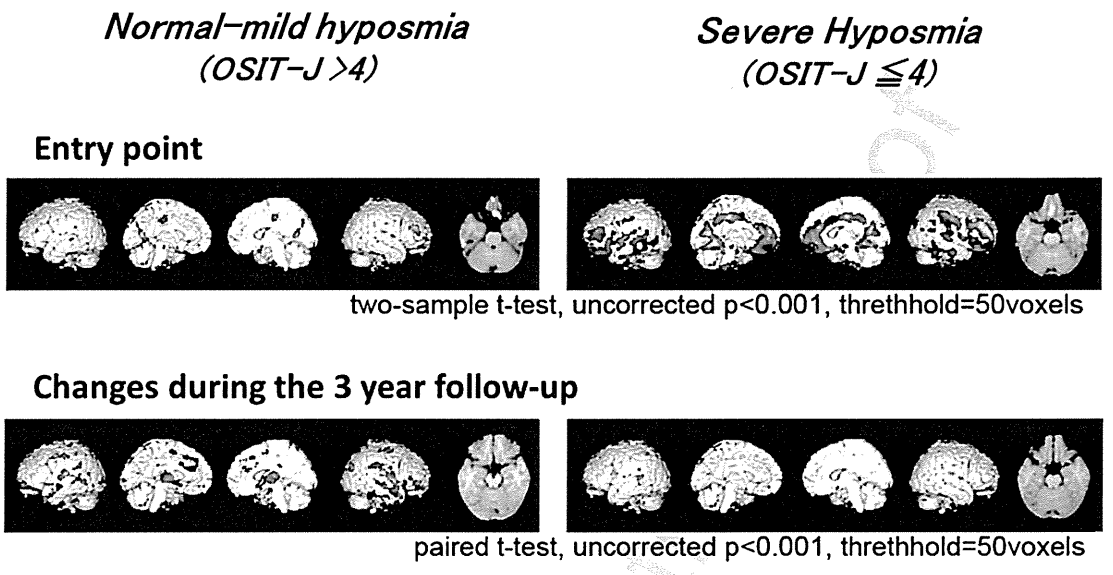



Fig. 2. Changes in brain atrophy measured by volumetric MRI.

widespread hypometabolism in the frontal and occipital lobes, but also remarkable hypometabolism on the medial surface of the brain, centered on the cingulate gyrus (Fig. 1). Volumetric MRI at the time of the initial scan revealed that the severe hyposmia group also exhibited brain atrophy centered on the cingulate gyrus and the orbital surface of the frontal lobe (Fig. 2). Interestingly, over the course of the 3-year study period, the severe hyposmia group did not show increasing brain atrophy, even though these individuals had a remarkable decline in brain metabolism (Figs. 1 and 2) [8].

Regarding clinical symptoms, the severe hyposmia group exhibited significantly exacerbated motor dysfunction as well as a remarkable decline in cognitive function; this group was thus classified as the poor prognosis group [8]. A total of 10 out of 47 cases had developed PDD by the 3-year follow-up visit. Table 1 summarizes the clinical characteristics of the cases that progressed to PDD, all of which showed an OSIT-J score $\leqq$4, but the mean scores of their cognitive or motor scales were not apparently different from the rest of the cohort. Conversely, not a single individual with an OSIT-J score $\geqq$5 progressed to PDD. Multivariate logistic regression analysis (stepwise method) was implemented to confirm that severe olfactory dysfunction was the most useful predictor of the onset of dementia. The odds ratio for the onset of dementia increased 18.7-fold for each 1 SD (2.8 points) decrease in OSIT-J scores [8].

In a recent study that investigated abnormalities of the acetylcholine system, the functional decline of acetylcholine in the amygdala and the hippocampus was correlated with hyposmia [26]. Furthermore, it has been reported in several imaging studies that hyposmia in PD is closely associated with limbic dysfunction [7, 21, 27, 28]. The association between limbic dysfunction and dementia has long been known, and olfactory tests should be particularly useful for detecting such dysfunction. In summary, it is possible that hyposmia in PD reflects limbic dysfunction, and it may be possible to predict the onset of PDD by quantitatively evaluating the level of hyposmia using olfactory tests.

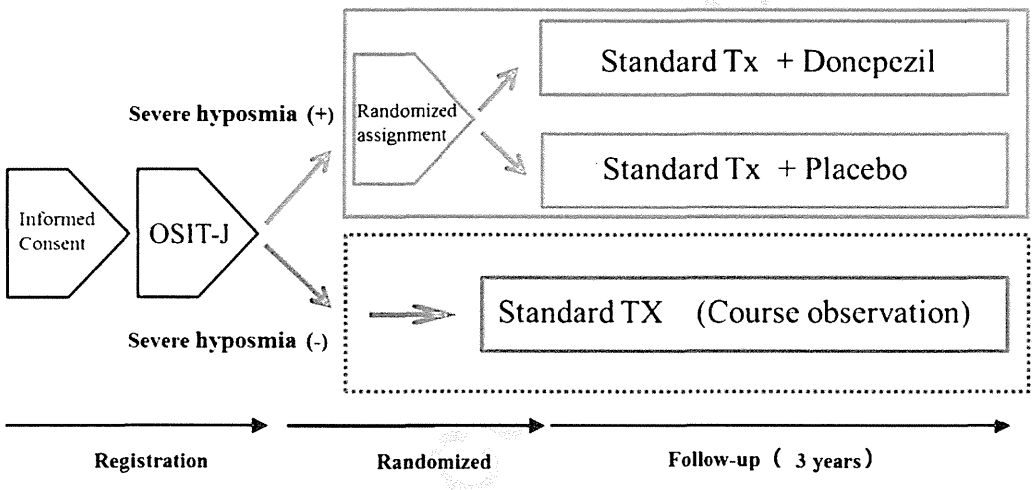
## CONCLUSIONS: FUTURE PROSPECTS

Acetylcholine function suffers in patients with PDD to a greater degree than in Alzheimer's disease [29], and cholinesterase inhibitors shows some efficacy in treating cognitive dysfunction in PDD [30]. However, as the average life expectancy after the onset of PDD is approximately 3 years [31], it is likely too late to start therapeutic interventions after the onset of dementia, thus limiting the efficacy of cholinesterase inhibitors. In addition, there are cases in which dopamine replacement therapy must be restricted and motor function sacrificed due to accompanying psychiatric symptoms such as hallucinations and delusions, which can further worsen prognoses for PDD cases. As mentioned above, no biomarkers have been found that can predict PDD onset at early stages, and the appropriate timing for therapeutic intervention has not been established.

Table 1
Clinical features of cases developing dementia

| No. | OSIT-J | Age | Onset | H-Y | UPDRS3 | LED | MMSE | ADAS | Figure correct | Figure error |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 61 | 51 | 3 | 29 | 1025 | 29 | 17 | 25 | 3 |
| 2 | 4 | 63 | 56 | 3 | 16 | 451.125 | 26 | 16 | 21 | 13 |
| 3 | 4 | 63 | 59 | 3 | 27 | 301.5 | 25 | 19 | 30 | 4 |
| 4 | 3 | 59 | 55 | 2.5 | 18 | 500 | 25 | 19 | 30 | 6 |
| 5 | 2 | 72 | 70 | 2.5 | 16 | 150 | 30 | 10 | 36 | 2 |
| 6 | 2 | 72 | 70 | 2 | 14 | 200 | 25 | 15 | 28 | 7 |
| 7 | 0 | 69 | 56 | 3 | 25 | 650 | 26 | 9 | 33 | 5 |
| 8 | 0 | 73 | 71 | 2.5 | 9 | 500 | 30 | 16 | 34 | 1 |
| 9 | 2 | 70 | 70 | 2 | 18 | 225 | 26 | 23 | 34 | 3 |
| 10 | 1 | 68 | 61 | 3 | 17 | 451.25 | 27 | 15 | 29 | 3 |

Abbreviations: OSIT-J; The Odor Stick Identification test for Japanese, H-Y; Hoehn-Yahr scale, UPDRS3; Part 3 of unified Parkinson disease rating scale, LED; levodopa equivalent dose, MMSE; Mini-mental state examination, ADAS; Alzheimer's Disease Assessment Scale, Figure correct; number of correct answers in figure identification test, Figure error; number of incorrect answers in figure identification test.




- Double-blinded, Randomized, controlled-study
- 200 cases
- End-point: onset of PDD

Fig. 3. Double-blind, randomized, controlled study using 5 mg of donepezil for the PD group with severe hyposmia (The DASH-PD (Donepezil Application for Severe Hyposmic-Parkinson Disease) study).

However, under circumstances in which anticholinergic agents have been used for the improvement of motor symptoms of PD, the predominant opinion was that the use of cholinesterase inhibitor for PD should be avoided. Nevertheless, other than some tremor exacerbation, no remarkable declines in motor function have been attributed to therapeutic intervention with cholinesterase inhibitors, either in PDD or in the similar disease, DLB [32, 33]. Furthermore, activation of the acetylcholine system could potentially improve motor function in PD, based on a recent report of reduced risk of falling following the use of cholinesterase inhibitors [34] as well as another report of a correlation between reduced acetylcholine activity and a decline in walking speed in early PD patients without dementia [35].

The above results suggest that it may be possible to improve PD prognosis by intervening with cholinesterase inhibitors prior to the onset of PDD, with severe hyposmia serving as a biomarker. We have now started a therapeutic intervention study using cholinesterase inhibitor in the PD group that showed

severe hyposmia. This is a randomized, double-blind study using 5 mg of donepezil for the PD group with OSIT-J scores $\leqq$4 (Fig. 3). We hope that this clinical trial will help establish therapeutic interventions that can dramatically improve the prognosis of PD patients who suffer from declining cognitive function.

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## CONFLICT OF INTEREST

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# Deterioration of horizontal saccades in progressive supranuclear palsy

Yasuo Terao [a,*], Hideki Fukuda [b], Yuichiro Shirota [a], Akihiro Yugeta [a], Masayuki Yoshioka [c], Masahiko Suzuki [c], Ritsuko Hanajima [a], Yoshiko Nomura [b], Masaya Segawa [b], Shoji Tsuji [a], Yoshikazu Ugawa [d,e]

[a] Department of Neurology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Segawa Neurological Clinic for Children, 2-8 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan
[c] Department of Neurology, Aoto Hospital, Jikei University School of Medicine, 6-41-2 Aoto, Katsushika-ku, Tokyo 125-8506, Japan
[d] Department of Neurology, School of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan
[e] Japan Science Technology Agency, Research Seeds Program, Fukushima, Japan

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HIGHLIGHTS

- We studied horizontal saccade changes in progressive supranuclear palsy (PSP).
- This was compared with those of Parkinson's disease (PD) at various disease stages.
- Amplitudes of saccades decreased with increasing disease stage in PSP, but not in PD.
- Deterioration of horizontal saccades may be due to brainstem oculomotor pathology.

ABSTRACT

*Objective:* To investigate horizontal saccade changes according to disease stage in patients with progressive supranuclear palsy (PSP).
*Methods:* We studied visually and memory guided saccades (VGS and MGS) in 36 PSP patients at various disease stages, and compared results with those in 66 Parkinson's disease (PD) patients and 58 age-matched normal controls.
*Results:* Both vertical and horizontal saccades were affected in PSP patients, usually manifesting as "slow saccades" but sometimes as a sequence of small amplitude saccades with relatively well preserved velocities. Disease progression caused saccade amplitude reduction in PSP but not PD patients. In contrast, VGS and MGS latencies were comparable between PSP and PD patients, as were the frequencies of saccades to cue, suggesting that voluntary initiation and inhibitory control of saccades are similar in both disorders. Hypermetria was rarely observed in PSP patients with cerebellar ataxia (PSPc patients).
*Conclusions:* The progressively reduced accuracy of horizontal saccades in PSP suggests a brainstem oculomotor pathology that includes the superior colliculus and/or paramedian pontine reticular formation. In contrast, the functioning of the oculomotor system above the brainstem was similar between PSP and PD patients.
*Significance:* These findings may reflect a brainstem oculomotor pathology.


## 1. Introduction

Progressive supranuclear palsy (PSP) is a neurological disorder in which the impairment of saccades and smooth pursuit are cardinal features. Saccade measurements have been successfully used to distinguish PSP from other types of parkinsonism, especially Parkinson's disease (PD). Characteristic findings include a reduction in saccade velocity ("slow saccades"), not only in the vertical but also in the horizontal direction (Pierrot-Deseilligny et al., 1989; Rivaud-Péchoux et al., 2000; Terao et al., 2007; Pinkhardt et al., 2008; Hardwick et al., 2009).

Aside from Richardson syndrome (RS), which presents the classic findings such as vertical supranuclear palsy, prominent postural instability in the 1 year of disease and cognitive impairment, PSP has come to be regarded as a heterogenous disorder with different clinical manifestations (see Birdi et al., 2002, for review). The next common subtype, PSP-parkinsonism (PSPp), which comprises about 30% of PSP cases, is characterized by an asymmetric onset, tremor, and a moderate initial therapeutic response to levodopa (Williams et al., 2005, 2007). Patients with pure akinesia and gait freezing (PAGF) represent a subtype without rigidity, tremor, or

* Corresponding author. Tel.: +81 3 3815 5411x33783; fax: +81 3 5800 6548.
*E-mail address:* yterao-tky@umin.ac.jp (Y. Terao).

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ophthalmoplegia, and show poor response to levodopa (Imai and Narabayashi, 1974; Imai et al., 1993; Homma et al., 1987; Matsuo et al., 1991; Fachiers et al., 2008). Although clinical signs of cerebellar dysfunction are usually considered rare, some pathologically confirmed PSP patients develop cerebellar ataxia (PSPc) as the initial and principal symptom, closely mimicking spinocerebellar ataxia. This type of PSP has recently come to be established as a novel clinical subtype, recognized both neuropathologically and neurophysiologically (Kanazawa et al., 2009; Shirota et al., 2010; Jellinger, 2010). PSP subtypes presenting with progressive nonfluent aphasia and corticobasal degeneration have also been identified (Mochizuki et al., 2003; Williams and Lees, 2009).

Some recent studies have addressed the clinical and pathological heterogeneity of PSP. Functional imaging studies showed a similar but attenuated pattern of brain glucose metabolism in patients with PAGF as compared with RS patients (Park et al., 2009), pointing to the potential utility of functional measures in differentiating these subtypes. PSP that is still at an early stage is difficult to differentiate from PD on clinical grounds, but careful assessment of abnormalities in saccade velocity can often aid in making a clear diagnosis of PSP (Pinkhardt et al., 2008). However, there have been no reports on the further differentiation between PSPp and RS solely based on saccade velocity measurements, and other PSP subtypes have not been studied in this regard.

Vertical saccades are more affected than horizontal saccades in PSP patients. Physiologically, horizontal saccades are controlled by the paramedian pontine reticular formation (PPRF), whereas vertical saccades are controlled by the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the rostral midbrain reticular formation (RF). Vertical saccades are more affected due to severe neuronal loss in the midbrain RF, whereas the PPRF remains comparatively well preserved (Bhidayasiri et al., 2001; Kaneko, 1989, 1996).

Supranuclear commands for volitional saccades reach the PPRF or the riMLF from the frontal and parietal cortices via the superior colliculus (SC), which is the final output point for volitional saccades (Krauzlis, 2005). Since vertical saccades deteriorate quickly from an early stage in PSP patients, the deleterious effects on oculomotor control caused by neurological disorders in neural structures above the brainstem level (including the basal ganglia; BG) through changes in vertical saccades may be masked. Furthermore, vertical saccade performance is asymmetric for upward and downward gazes, and normal ranges are difficult to define since they become restricted even in normal elderly people, especially in the upward direction (Yang and Kapoula, 2006). Search coil systems for recording vertical saccade movements are not available at every medical facility and, unfortunately, saccade recording using video-based eye tracking systems is hampered by the fact that the usual nine-point calibration cannot be performed in patients with vertical gaze palsy. In this study, we tried to obtain useful diagnostic information based on a measurement technique available at typical clinical facilities: electrooculography.

In contrast to vertical saccades, laterally directed saccades can be triggered until PSP is at a relatively late stage (Pierrot-Deseilligny et al., 1989), and, therefore, they may be more suitable for studying PSP pathophysiology. In patients at the earliest stage of PSP, laterally directed gap saccades show a shorter than normal latency that becomes prolonged at later stages. Concurrently, the percentage of errors in antisaccade tasks (misdirected saccades made towards a target) show a strong negative correlation with gap saccade latencies. These findings have been ascribed to a secondary imbalance between the impairment of the frontal inhibitory system and diverse excitatory pathways, but the influence of both supranuclear and nuclear influences on saccade performance has not yet been fully explored.

The present study aimed to elucidate PSP pathophysiology by recording horizontal saccades. We compared saccade parameters of PSP patients with those of normal subjects and studied how they varied during disease progression. PD patients were also studied as a disease control because similar clinical symptoms appear at the early stages of PD and yet pathological changes are primarily confined to the substantia nigra (SN), and the pathophysiology causing the oculomotor abnormalities has been extensively investigated (Terao et al., 2011). Since the pathological involvement of basal ganglia and brainstem structures are known to be more extensive in PSP than in PD, we predicted that PSP patients would exhibit more severe saccade abnormalities.

Finally, we tried to assess whether the different clinical subtypes of PSP (RS, PSPp, PSPc and PAGF) included cases differing in patholotical extent, using the saccade parameters. Due to the small sample size of each subgroup, we took the extent to which saccade parameters of individual patients deviated from the normal range as a possible indication of pathological extent in each subject.

## 2. Subjects and methods

We studied 36 patients with PSP (22 male, 14 female; age: 69.0 ± 8.4 years; mean ± SD; Table 1) who were diagnosed according to the criteria developed by the National Institute of Neurological Disorders and Stroke, and the Society for PSP (Litvan et al., 1996; Table 1). The patients stopped taking all medication (levodopa in all cases) at least 12 h before measurements were taken, as described previously (Yugeta et al., 2008; Terao et al., 2010). We also studied 66 PD patients (36 male, 30 female; age: 66.7 ± 10.6) and 58 age-matched normal subjects (28 male, 30 female; age: 68.4 ± 5.2 years). PD patients and normal subjects were also studied using the same experimental setup and procedures as described in our previous study (Terao et al., 2011a,b). Saccade recordings were conducted as part of their clinical assessment, after obtaining informed consent, following the protocols approved by the Ethics Committee of The University of Tokyo, and in accordance with the ethical standards of the Declaration of Helsinki.

PSP subtypes were classified based on previous reports (Imai and Narabayashi, 1974; Imai et al., 1993; Homma et al., 1987; Matsuo et al., 1991; Mochizuki et al., 2003; Williams et al., 2005, 2007, 2009; Fachiers et al., 2008; Kanazawa et al., 2009; Shirota et al., 2010; Jellinger, 2010). Among our 36 PSP patients, 22 were diagnosed with RS, 2 with PAGF, 6 with PSPc, and 6 with PSPp. Although autopsies were not obtained in deceased patients, these diagnoses were validated during a 5-year follow-up period by confirming midbrain atrophy on brain MRIs, frontal hypoperfusion on single-photon emission computed tomography, or maintenance myocardial uptake of $^{123}$I-metaiodobenzylguanidine (MIBG), on a case-by-case basis. Disease stage was clinically assessed using the modified Hoehn and Yahr (H–Y) staging and the Unified Parkinson's Disease Rating Scale III (motor subscale, UPDRSm). Cubo et al. (2000) reported that the UPDRSm is a reliable and applicable scale for assessing most aspects of PSP function as well as the severity of the five clinical disability domains. Since we found a good correlation between the UPDRSm and H–Y staging, we adopted H–Y staging to broadly classify patients according to their disease severity for the purpose of statistical analysis.

### 2.1. Experimental setup

The experimental setup and data analysis procedures we used have been described previously (Kato et al., 1995; Terao et al., 1998, 2011a,b; Fig. 1A). Subjects were seated in front of a black,

**Table 1**
Clinical features of PSP patients Cases 13 and 33 were recorded twice, appearing again as cases 28 and 37 (see also Fig 3A). Asterisks: patients previously diagnosed with spinocerebellar degeneration. EM: eye movement; down: downgaze; N: normal range; up: upgaze; vertical: upward and downward gazes limited.

| No | Age | Sex | Diagnosis | Duration (yrs) | H–Y stage | VerticalEM | HorizontalEM | Neck/trunk rigidity | Limb rigidity |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 60 | M | PSPp | 4 | 2 | N | N | ± | – |
| 2 | 83 | M | PSPp | 6 | | Mild down | N | +–++ | + |
| 3 | 67 | M | PSPp | 6 | | vertical | N | +–++ | + |
| 4 | 64 | M | RS | 2 | | Up (3/5), down (4/5) | N | +–++ | + |
| 5 | 60 | M | PSPp | 2 | 3 | Down (4/5) | Restriction left > right | +–++ | + |
| 6 | 81 | M | RS | 3 | | Vertical | N | – | L/E mildly spastic |
| 7 | 66 | F | PSPc | 3 | | Mild down restriction | N | + | ± |
| 8 | 80 | M | RS | 1 | | Mild up | N | – | – |
| 9 | 78 | F | RS | 4 | | Severe up > mild down | N | ++ | – |
| 10 | 63 | F | RS | 3 | | Up (1/5), down (4/5) | N | ± | + |
| 11 | 60 | M | RS | 2 | | Mild up | N | + | ± |
| 12 | 78 | F | RS | 7 | | Up (2/5), down (2/5) | N | + | + |
| 13 | 75 | M | PSPp | 2 | | Mild up | N | ± | – |
| 14* | 53 | M | PSPc | 2 | 3.5 | Up | N | – | + |
| 15 | 66 | F | RS | 1 | | Down | N | + | ± |
| 16 | 70 | M | PAGF | 8 | | N | N | Hypo | Hypotonus |
| 17* | 66 | M | PSPc | 1 | | N | N | N | Mild hypotonus |
| 18 | 79 | M | PSPp | 5 | | Mild up, nystagmus | Right (5/5), left (4/5) | + | ± |
| 19 | 67 | F | RS | 3 | | Mild vertical | N | ± | Hypotonus |
| 20 | 57 | M | RS | 1 | 4 | Up (2/5), down (3/5) | N | ++ | Mild hypotonus |
| 21 | 77 | M | RS | 8 | | Vertical | N | + | – |
| 22 | 57 | M | PAGF | 5 | | N | Right (2/5), left (2/5) | ++ | + |
| 23 | 85 | M | RS | 3 | | Up (2/5), down (2/5) | N | ± | ± |
| 24 | 84 | F | RS | 1 | | Severe vertical | N | – | – |
| 25* | 72 | F | RS | 4 | | Up (0/5), down (0/5) | N | + | ± |
| 26* | 59 | M | PSPc | 2 | | Vertical, down dominant | N | – | – |
| 27 | 78 | M | RS | 2.5 | | Up(3/5) | N | ++ | + |
| 28(13 – 2) | 76 | M | PSPp | 3 | | Up (0/5), down (0/5) | Right (2/5), left (2/5) | | |
| 29 | 63 | F | RS | 3.5 | | Up (1 – 2/5), down (1 – 2/5) | N | + | ± |
| 30 | 62 | F | RS | 2 | | Up (0/5), down (0/5) | N | + | ± |
| 31 | 67 | F | RS | 2 | | Up (0/5), down (2/5) | N | + | ± |
| 32 | 62 | M | PSPc | 3 | | Mild up | N | +–++ | + |
| 33 | 75 | M | PSPc | 4 | | Vertical | N | – | – |
| 34 | 75 | F | RS | 2 | 4.5 | Up (3/5), down (3/5) | N | ± | – |
| 35 | 61 | M | RS | 5 | | Up (0 – 1/5), down (2/5) | N | ± | – |
| 36 | 73 | F | RS | 1 | | Vertical | N | ± | Hypotonus |
| 37(33 – 2) | 64 | M | PSPc | 5 | | Up (1/5), down (1/5) | N | ± | – |
| 38 | 71 | F | RS | 7 | 5 | Up (0/5), down (0/5) | Full range but slow | +–++ | + |

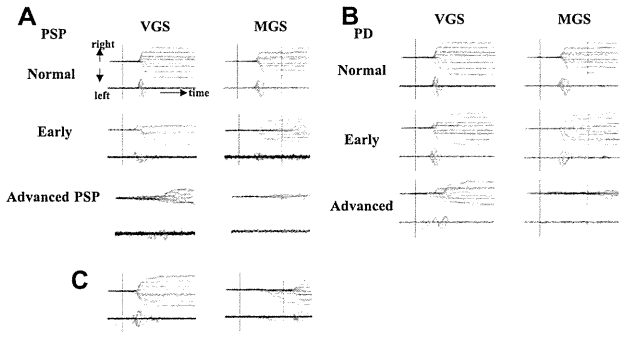


**Fig. 1.** VGS and MGS traces in PSP and PD patients. About 30 VGS and MGS traces are superimposed, time-locked to the presentation of a target (VGS) or to the offset of a central spot (MGS). Lower traces in each figure give velocity curves. (A) typical traces of PSP patients along with that of an age-matched normal subject (top figure), (B) typical traces of PD patients along with that of an age-matched normal subject (top figure), (C) saccade traces of a PSP patient (H–Y stage 4) with relatively preserved saccade velocity (case 22).

concave dome-shaped screen measuring 90-cm in diameter that contained light-emitting diodes embedded in pinholes, which served as the fixation points and saccade targets. Subjects' heads were placed on a chin rest to restrict head movements. Subjects faced the center of the screen at a viewing distance of about 66 cm. The subjects held a microswitch button connected to a microcomputer that allowed them to initiate and terminate a trial by pressing the button with their thumb (see below).

DC electrooculography (EOG) was performed using 5 Ag-AgCl gel electrodes 1.0 cm in diameter with an adhesive margin (adhesive collar H261, Nihon-Kohden, Tokyo, Japan). Two were placed horizontally on the outer canthi, 2 were placed vertically above and below the right eye, and 1 ground was placed on the forehead. The signals were fed into a DC amplifier (AN-601G, Nihon Kohden, Japan), low-pass filtered at 20 Hz, and then digitized at 500 Hz. The steepness of the low-pass filter was 48 dB/oct. The impedance was monitored and maintained below 5 kΩ throughout the measurements.

The room in which the recordings were performed was kept dark except for a small bit of ambient light around the technician, so that the unlit pinholes were not visible to the subject. After placing the electrodes, subjects were asked to sit in the dark for 20–30 min to allow them to acclimatize to the darkness. This also ensured stable time recording. There was no change in ambient illumination throughout the experiment.

Eye movement calibration was administered before each test session. EOG gain was adjusted to a target point at 20° left or right of center. While the subjects fixated on this spot, we adjusted the EOG gain so that the eye position displayed on the computer monitor matched the target position displayed on the screen. EOG gain was continuously monitored throughout the experiment, and recalibration was performed when necessary. Thus calibrated, EOG data is known to be roughly linear over a range of 5–30° and the resolution of our data was 0.5° (Kato et al., 1995). Vertical

EOG was placed to monitor the occurrence of blinks together with the video camera. Our method has been shown to correlate closely with recordings obtained with a video-based eye tracking system that is now widely used for recording saccades (Eyelink II, SR Research Ltd., Ontario, Canada; Okano et al., 2010).

### 2.2. Behavioral paradigms

We used visually guided (VGS) and memory guided saccade (MGS) tasks as behavioral paradigms. For the VGS task, a fixation point was turned on in the middle of the dome and subjects were to fixate on it as quickly as possible. It was then turned off after a period of 1500–2000 ms, and immediately thereafter, a target point was turned on at a random location 5°, 10°, 20°, or 30° horizontally to the left or right of it. We instructed the subjects to fixate on the new target as quickly as possible. After a random period of 800–2000 ms, the target point was dimmed, and the subject was required to release the hand button. When the button release was made within 3000 ms after the target dimming, a sound signaled a successfully performed trial. If the button release was made earlier or later than the allowed period, there was no sound.

For the MGS tasks, while the subject fixated a central spot, a peripheral stimulus ("cue") was provided for a brief period of 50 ms. The subjects were instructed to maintain fixation until the central spot was turned off, at which time they were to make a saccade to the spatial location where the cue had appeared. After a delay period of 600 ms, the target spot was turned on again. After a random period of 500–1000 ms, the target spot was dimmed, and the subject was required to release the hand button. Saccades unintentionally made to the cue during the delay period were called *saccades to cue*.

The subjects performed 50 trials each for the VGS and MGS tasks. For each subject, we calculated the frequency of saccades to cue among MGS trials and used these data to evaluate inhibitory control of saccades. The proportion of trials in which MGS movements were successfully initiated within 600 ms (*MGS success rate*) was calculated and used as an index of voluntary initiation of saccades. Accuracy was expressed as the ratio of saccade amplitude to target eccentricity.

### 2.3. Data analysis and statistical assessment

Four saccade parameters were determined off-line for each saccade as reported previously (Terao et al., 1998, 2011a,b): onset latency, amplitude, duration, and peak velocity. The onset of an eye movement was defined as the time when velocity and acceleration exceeded predetermined values (28°/s and 90°/s$^2$, respectively). Eye movement was accepted as a saccade based on its velocity and duration. After the onset, the velocity had to exceed 88°/s, and this suprathreshold velocity had to be maintained for at least 10 ms. The end of an eye movement was considered to have occurred when the velocity decreased below 40°/s. The total duration of the movement had to exceed 30 ms. Records contaminated by noise and those with onset latency <100 ms were excluded from the analysis. The accuracy of the first saccade amplitude was expressed as a percentage ratio with respect to the target eccentricity.

Statistical analyses were conducted using SPSS10 software (SPSS Japan, Tokyo). The determined saccade parameters were used in repeated measures analysis of variance (ANOVA) with post hoc analysis using Bonferroni's method, with group (PSP, normal control) as a between-subject factor and target eccentricity (5°, 10°, 20°, 30°, 4 levels) as a within-subject factor. Post-hoc analysis was performed using the *t*-test corrected by Bonferroni's method. The Greenhouse–Geisser correction was used to correct for sphericity.

To study variation in saccade parameters according to disease stage, and to determine whether measurement results differed between PSP and PD patients, we correlated saccade parameters with H–Y staging using the non-parametric Spearman's rank correlation test. We also performed analysis of covariance (ANCOVA) with disease stage as a covariate, and subject group (PSP, PD, 2 levels) as a between-subject factor and target eccentricity (5°, 10°, 20°, 30°, 4 levels) as a within-subject factor.

We calculated the 95% confidence interval for each saccade parameter in normal subjects (termed "normal range") and compared these results with those in each PSP subgroup. Since the number of patients in each individual subgroup was small, especially for the PAGF group, we counted the number of patients whose saccade parameters were within the normal range and the number of patients whose saccade parameters lay outside that range. The proportion of patients with normal saccade parameters and those with saccade parameters outside that range was compared between each subgroup of patients using the chi-square test.

When assessing saccade velocity, we took into account the relationship between the amplitude and the peak velocity of saccades, according to the methods of Bhidayasiri et al. (2001), a relationship that can be described by the following equation:

$$V_{max} = V_0 \times [1 - \exp(-A_s/A_0)]$$

where $V_{max}$ is the maximal saccade velocity (peak velocity) and $A_s$ is the saccade amplitude. Constants $A_0$ and $A_s$ were determined by curve fitting using a commercial software (OriginPro, version 8.0J; Lightstone, Tokyo, Japan). For all analyses, the significance threshold was set at $p < 0.05$.

## 3. Results

Among 19 subjects at H–Y stage of 3.5 or lower, only 6 patients showed typical vertical gaze palsy on neurological examinations (Table 1). In the other patients in this group, downgaze palsy was either lacking or only mildly restricted. For 17 patients at H–Y stage 4 or higher, three subjects showed only mild upgaze limitations, while the other patients showed vertical gaze palsy affecting both up- and downgazes. The six patients with PSPc showed cerebellar symptoms such as slurred and/or explosive speech, limb and truncal ataxia, wide-based gait and, in one case, nystagmus, mimicking spinocerebellar ataxia. In fact, 4 of the 7 patients with PSPc had been diagnosed with spinocerebellar ataxia before being referred to our department.

### 3.1. Saccade parameter abnormalities in PSP patients

Fig. 1A shows MGS and VGS traces recorded in a normal subject (top) and two PSP patients at early (middle row) and advanced (bottom) stages. In the early PSP patient, the traces exhibited the "slow eye movement" pattern typified by curved trajectories, giving a strong indication of PSP when clinical examination suggested parkinsonism. In the advanced PSP patient, most saccades were of very small amplitude, despite being initiated after a relatively short latency.

We compared the saccade parameters of normal controls and PSP patients (Table 2). The latency of VGS tasks was significantly longer and accuracy significantly lower than those in normal control subjects. In contrast, MGS latency in PSP patients was comparable to that in normal subjects, while accuracy was significantly reduced. The MGS success rate was lower than that in control subjects.

We then compared saccade parameters of PSP patients with those of PD patients without taking disease stage into account. On average, the latencies were comparable between PSP and PD patients; VGS latency was slightly longer in PSP patients, while

**Table 2**
Saccade parameters in PSP and PD patients as well as those in normal subjects.

| Parameter | | Normal | PSP | PD |
|---|---|---|---|---|
| VGS | Latency (ms) | 241.7 ± 58.0 | 322.8 ± 166.2* | 282.2 ± 62.6 |
| | Accuracy (%) | 97.0 ± 8.8 | 63.7 ± 24.5* | 85.6 ± 15.1 |
| MGS | Latency (ms) | 298.1 ± 83.7 | 336.7 ± 115.6 | 391.9 ± 61.2 |
| | Accuracy (%) | 81.2 ± 25.4 | 42.4 ± 28.9* | 57.4 ± 20.1 |
| Success rate of MGS (%) | | 69.1 ± 23.0 | 51.6 ± 23.7* | 69.5 ± 21.6 |
| Frequency of saccades to cue (%) | | 25.7 ± 18.7 | 47.7 ± 22.6* | 46.2 ± 23.9 |

Mean ± SD.
* Shows significant difference of PSP patients from age-matched normal control subjects ($p < 0.05$).

MGS latency tended to be slightly shorter in PD patients. In contrast, saccade accuracy in PD patients was significantly less reduced than that in PSP patients, both for VGS and MGS tasks. The MGS success rate and the frequency of saccades to cue were comparable between PSP and PD patients. However, the frequency of saccades to cue was higher in the PSP and PD groups than in the normal subject group.

### 3.2. Comparison of saccade parameter changes in PSP and PD patients

Some of the differences observed between the patient groups could be due to differences in disease stage. Thus, we compared how saccade parameters changed according to disease stage in PD and PSP patients (Fig. 2A). Saccade accuracy (amplitude divided by target eccentricity) of VGS and MGS tasks showed a significant negative correlation with disease stage in PSP patients (VGS: $r = -0.4291$, $p = 0.00639$; MGS: $r = -0.429$, $p = 0.00639$), but only a trend for correlation for the MGS task in PD patients (VGS: $r = 0.0466$, $p = 0.4073$; MGS: $r = -0.2134$, $p = 0.0878$). Although VGS accuracy was initially comparable between the two patient groups, it deteriorated more rapidly with increasing disease stage for PSP patients than for PD patients (effect of group: $F[1, 101] = 1.901$, $p = 0.1710$; effect of disease stage: $F[1, 101] = 4.303$, $p = 0.0406$; group × disease stage: $F[1, 101] = 7.933$, $p = 0.0058$). The same was true for MGS accuracy (effect of group: $F[1, 98] = 1.389$, $p = 0.2415$; effect of disease stage: $F[1, 98] = 11.728$, $p = 0.0009$; group × disease stage: $F[1, 98] = 3.962$, $p = 0.0499$).

In contrast, saccade latency was only mildly prolonged in PSP patients (Fig. 2B). VGS latency gradually increased with advancing disease (PSP: $r = 0.317$, $p = 0.01852$; PD: $r = 0.348$, $p = 0.00449$), and the rate of change was similar between PSP and PD patients (effect of group: $F[1, 86] = 0.0588$, $p = 0.4452$; effect of disease stage: $F[1, 86] = 4.981$, $p = 0.0282$; group × disease stage: $F[1, 86] = 0.446$, $p = 0.5062$). MGS latency increased only modestly but not significantly (Fig. 2C; PSP: $r = 0.111$, $p = 0.5375$, PD: $r = 0.207$, $p = 0.11309$) and tended to be slightly shorter in PSP patients compared with PD patients, at all disease stages (effect of group:

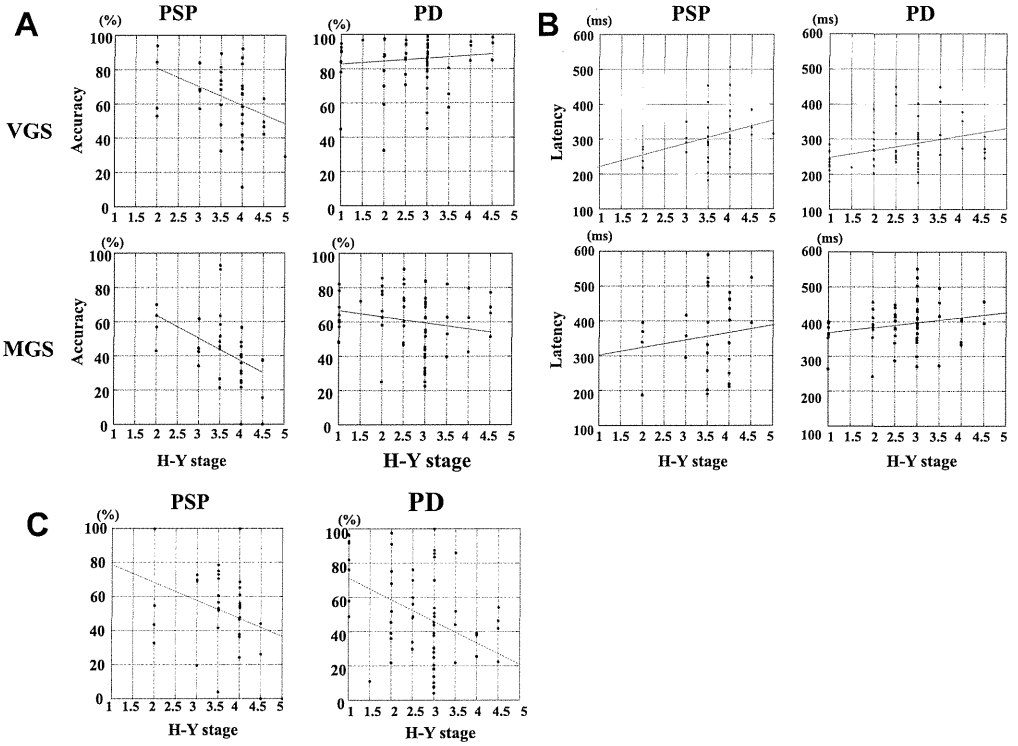


**Fig. 2.** Correlation of VGS and MGS accuracies and amplitudes with disease stage (H–Y stage) in PSP (left) and PD (right) patients. The ordinate shows saccade amplitude accuracy (A), latency (B), and MGS success rate and the abscissa shows the H–Y stage. Each dot represents a single case. The regression lines are shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

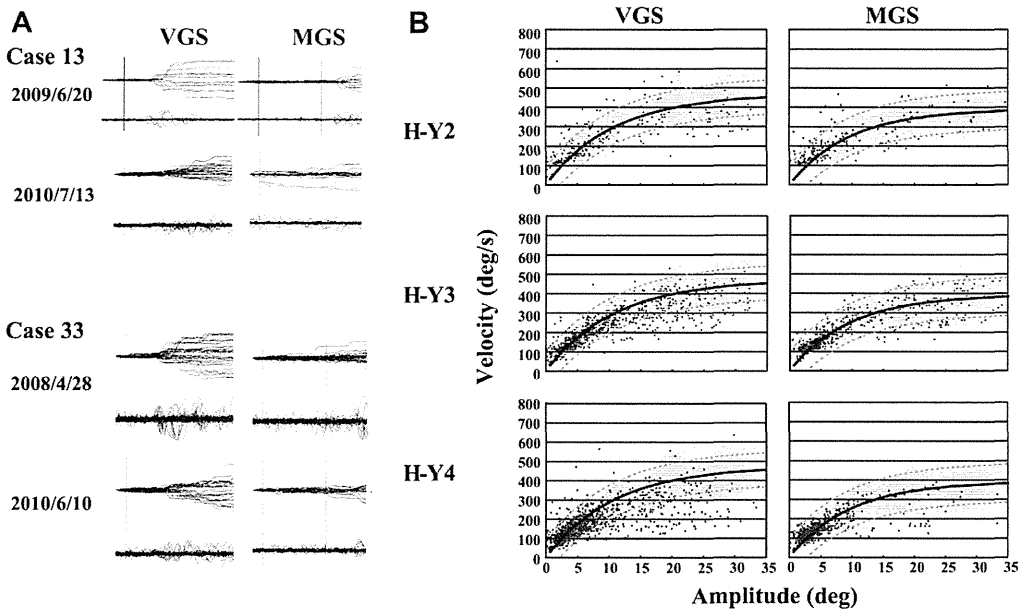


**Fig. 3.** VGS and MGS traces of two PSP patients recorded at intervals of roughly 1 and 2 years, and the relationship between saccade amplitude and velocity at different PSP stages (A) Saccade traces in two PSP patients recorded twice (dates on left). (B) Scatter plot between VGS and MGS velocity and amplitude at various disease stages. Blue dots: PSP; pink dots: normal. Dashed curves: normal 95% confidence intervals.

$F[1, 92] = 2.264$, $p = 0.1360$; effect of disease stage: $F[1, 92] = 0.961$, $p = 0.3297$; group × disease stage: $F[1, 92] = 0.087$, $p = 0.7765$).

MGS success rate showed a trend to decrease with increasing disease stage ($r = -0.321$, $p = 0.0556$), and the frequency of saccades to cue increased slightly but not significantly ($r = 0.105$, $p = 0.5537$) with disease stage, with a comparable rate of change in both groups (MGS success rate: effect of group: $F[1, 97] = 0.073$, $p = 0.7877$; effect of disease stage: $F[1, 97] = 13.103$, $p = 0.0005$; group × disease stage: $F[1, 97] = 0.092$, $p = 0.7621$; saccades to cue: effect of group: $F[1, 92] = 0.036$, $p = 0.8504$; effect of disease stage: $F[1, 92] = 2.992$, $p = 0.0869$; group × disease stage: $F[1, 92] = 0.001$, $p = 0.9795$).

In two patients, saccade performance was recorded twice, at an interval of roughly 1 or 2 years (Fig. 3A). Both cases showed mild to modest hypometria at the first recording, with relatively well preserved velocity, but amplitude reduction became evident at the second recording. Nevertheless, in Case 33, saccades were initiated with a similar latency at the first recording and at the second one performed rougly 2 years later.

### 3.3. Slow saccades in PSP patients

In some cases, especially at early disease stages, EOG traces occasionally showed relatively well-preserved velocities, mimicking those of PD patients (Fig. 1C). In order to determine whether the term "slow saccades" is fully applicable to the saccade velocities observed in PSP patients, we tried to determine if saccade velocity was genuinely slowed when compared with a normal amplitude–velocity relationship. In Fig. 3B, we plotted the velocity of saccades against their amplitudes for the H–Y stages 2 through 4. Compared to normal subjects (pink dots), saccades in PSP patients (blue dots) tended to be slightly slower for large rather than small amplitude saccades, especially in VGS tasks. Otherwise, the distributions largely overlapped, suggesting a relatively well-preserved amplitude–velocity relationship.

With advancing disease, large, but not small amplitude saccades, tended to show reduced velocities in VGS tasks. The proportions of saccades outside the normal range (dashed curves) were 9.2%, 12.5%, 12.4% at H–Y stages 2, 3, and 4, respectively. However for MGS tasks, mostly small amplitude saccades showing a normal amplitude–velocity relationship were observed, until advanced disease stages (H–Y stage of 4 or higher). Saccades outside the normal range in MGS tasks comprised 5.4%, 6.4%, 4.5% at H–Y stages 2, 3, and 4, respectively. Hypermetria, often noted in patients with cerebellar disorders, was rarely observed even in the PSPc patients.

### 3.4. Saccade abnormalities in PSP subtype patients

Fig. 4 shows a comparison of the saccade parameters for patients with different PSP subtypes. Latency (Fig. 4A) was within the normal range (gray zones) in the 2 patients with PAGF and 5 out of 6 patients with PSPp for both VGS and MGS tasks. In the 22 patients with RS, however, latency was prolonged in 10 for VGS tasks and in 6 for MGS tasks. In the 6 patients with PSPc, latency was prolonged in 4 for VGS tasks and in 2 for MGS tasks. The proportion of patients with prolonged VGS and MGS latencies was not significantly different between the RS patients and other PSP subtypes, except for a trend for difference in the PSPp subtype (chi-square test, $p = 0.0585$).

Saccade accuracy (Fig. 4B) was within normal range in the two patients with PAGF for both VGS and MGS tasks, but in the 22 patients with RS, it was reduced in 20 patients for VGS tasks, and in 19 patients for MGS tasks. Saccade accuracy was reduced in all 6 PSPc patients, and in 5 of the 6 PSPp patients, for both VGS and MGS tasks. The proportion of patients with reduced VGS and MGS amplitude was significantly larger in the RS group than in the PAGF and PSPp groups (chi-square test, $p < 0.0001$ for both groups).

The MGS success rate (Fig. 4C, left) was within normal range for 20 of the 22 patients with RS, and 6 of the 7 patients with PSPp, and normal for all PAGF and PSPc patients. Similarly, the frequency of saccades to cue (Fig. 4C, right) was normal for 21 of the 22 patients with RS, 3 of the 6 patients with PSPc, and 5 of the 6 patients with PSPp. The proportion of patients with saccade parameters within the normal range was similar for all PSP subtypes (chi-square test, $p > 0.45$).

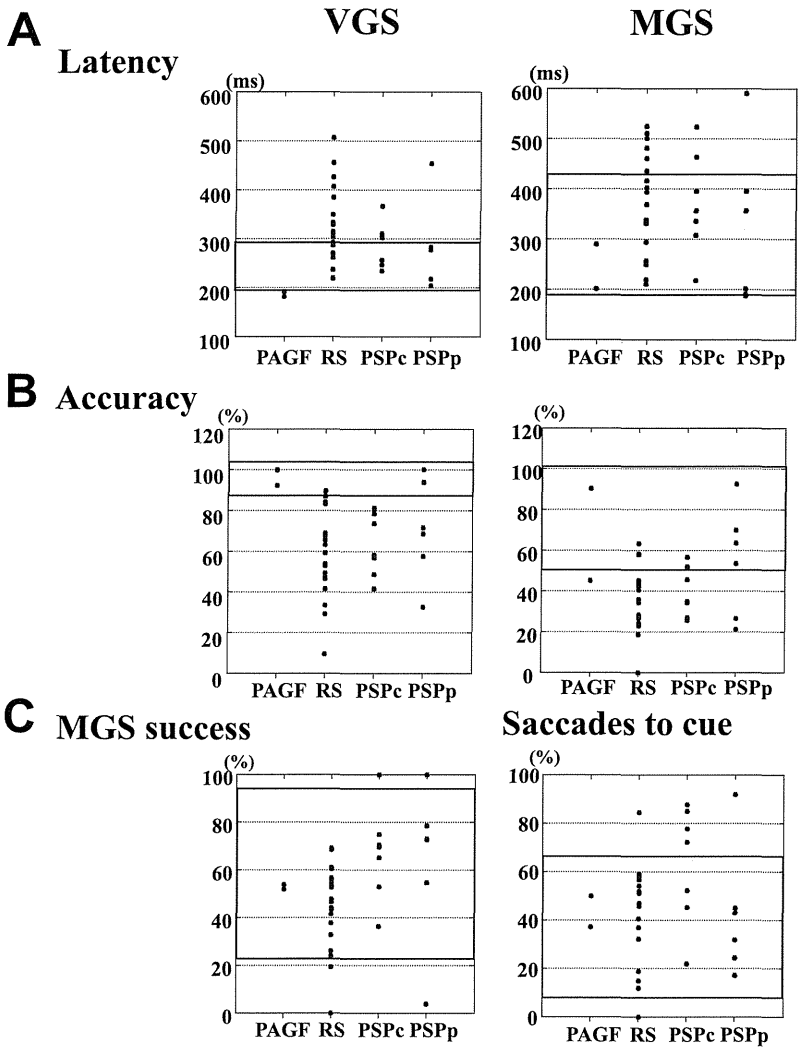


**Fig. 4.** Comparison of saccade parameters in four PSP subtypes (PAGF, RS, PSPc, and PSPp). The gray zones in each figure depict the 95% confidence interval of each parameter in age-matched normal controls. (A) Saccade latency; (B) saccade accuracy; (C) MGS success rate and frequency of saccades to cue.

## 4. Discussion

### *4.1. Changes in saccades with disease progression and pathophysiology underlying horizontal saccade abnormalities in PSP patients*

Here, we showed that not only vertical but also horizontal saccades are affected in PSP patients, usually manifesting as "slow saccades" but sometimes as a sequence of small amplitude saccades with relatively well-preserved velocities. Disease progression caused saccade amplitude reduction in PSP patients but not in PD patients. In contrast, VGS and MGS latencies were comparable between PSP and PD patients, as were the frequencies of saccades to cue, suggesting that voluntary initiation and inhibitory control of saccades is comparable in the two groups.

We were unable to reliably recognize the vertical gaze palsy typically seen in PSP patients by neurological examination until the disease was at H–Y stage 3.5. Although horizontal saccades are less affected than vertical saccades at early disease stages, we compared saccade parameters in PSP and PD patients in an attempt to find recognizable differences between the two diseases that would correlate with the disease stage. Taking disease stage into account, saccade latency in PSP patients was largely similar to that in PD patients, as were MGS success rates and frequency of saccades to cue.

Previous reports have also suggested that saccade latency is relatively mildly affected in PSP, compared with other types of parkinsonism (Pierrot-Deseilligny et al., 1989; Rascol et al., 1991; Vidailhet et al., 1994; Rottach et al., 1996). In this study, we also showed that, overall, voluntary initiation and inhibitory control of saccades were comparable to those in PD patients, implying that these two BG functions were somewhat preserved, at least to a degree similar to that in PD patients. That is, although brainstem pathology alone cannot account for all the changes observed in oculomotor performance, the present data show that performance is comparable between PD and PSP patients, even when taking the clinical stage into account. This was unexpected, considering the wide extent of pathological changes that occur in PSP patients, involving BG structures responsible for the initiation and inhibition of movements, such as the subthalamic nucleus, globus pallidus, and SN, although in advanced PD patients, widespread neuropathological changes also come to involve neural structures including the BG and brainstem areas (Murphy et al., 2008).

In contrast, saccade accuracy showed significantly quicker deterioration with disease progression in PSP patients than in PD patients, as exemplified by the two cases shown in Fig. 4A. This

feature was not seen in any of our PD subjects. The slowing of horizontal saccades in PSP patients may reflect either the loss of the excitatory burst neurons in the PPRF or the involvement of burst neurons in the SC (Bhidayasiri et al., 2001). Inactivation of the primate mesencephalic RF, the PPRF (Waitzman et al., 2000; Barton et al., 2003) or the SC (Aizawa and Wurtz, 1998) in monkeys induced curved saccade trajectories, increased saccade duration, and increased number of saccades falling below the normal amplitude–velocity relationship, similar to what has been observed in PSP patients. Thus, the rapid reduction in horizontal saccade amplitude may also reflect progressive pathological changes in these brainstem structures for oculomotor control (see below).

In view of the extensive pathological changes that occur in the BG, we believe that oculomotor control may be influenced more by the functional changes in these structures than by the brainstem oculomotor structures that directly issue motor outputs, or structures closely related to these (Steele et al., 1964). In terms of functional performance, our findings suggest that for horizontal saccades, the involvement of brainstem structures such as the SC and/or the burst neurons in the PPRF is more responsible for the saccade changes in PSP patients than the BG drives reaching the SC from above the brainstem level, and it has been pathologically demonstrated that PSP affects several subcortical and brainstem areas (Collins et al., 1995; Hardman et al., 1997). Impaired oculomotor motility is consistent with the pathological involvement of the SC and brainstem RF in PSP patients (Blumenthal and Miller, 1969; Malessa et al., 1991), although the oculomotor and vestibular nuclei are somewhat spared (Juncos et al., 1991). Of course, the impaired oculomotor initiation cannot be solely ascribed to the brainstem pathology, since BG above the brainstem level are also involved. However, our results suggest that brainstem pathology is prominent in determining the oculomotor abnormalities in PSP.

There have been several reports showing brainstem reflex abnormalities in patients with PSP. Vidailhet et al. (1992) found that in PSP, the auditory startle response (ASR) was absent or severely reduced, consistent with a loss of neurons in the lower pontine reticular formation. They speculated that this might be related to the disappearance of facilitatory input to brainstem centers and reticulospinal pathways from the BG. Abnormalities of facial reflexes in response to electrical stimulation to the median nerve were detected in patients with PSP (Valls-Solè et al., 1997). This finding is a distinctive feature of PSP, which can be used to differentiate it from other parkinsonian syndromes. It is ascribed to a functional involvement of the circuits mediating orbicularis oculi responses to median nerve electrical stimuli. Abnormal voluntary, spontaneous and reflex blinking has also been found in patients with PSP (Bologna et al., 2009), reflecting the widespread cortical, subcortical and brainstem degeneration related to this disease. Although Williams et al. (2008) found that the lack of ASR and other auditory brainstem responses (ABR) does not appear to be useful in differentiating PSP from PD, the strength of the ASR reveals the extent of the pathology, which is known to be more severe in RS than in PSPp and PAGF. Our results are in agreement with this suggestion. We believe that our findings are important because they help reveal the extent of brainstem pathology in the different clinical subtypes of PSP. We furthermore expect that they will be useful in making a differential diagnosis between the subtypes of PSP when used in combination with ASR and ABR, which we will discuss in the following section.

### 4.2. Relative preservation of small amplitude saccades in PSP patients

We found that, in PSP patients, traces often depict "slow eye movements" with curved trajectories, giving a strong indication of PSP when clinical examination suggests parkinsonism. This characteristic pattern agrees with previous studies showing that even small saccades, horizontal or vertical, are slower in PSP patients than in controls (Garbutt et al., 2003; Otero-Millan et al., 2011). This is all the more remarkable when we note that even at advanced stages, PD patients showed small saccades at normal velocity with respect to amplitude, as shown in Fig. 1B (bottom row).

However, despite exhibiting an apparently "slow saccade" pattern, some PSP patients in our cohort did show small amplitude saccades with a relatively a well-preserved amplitude–velocity relationship (Hardwick et al., 2009; Averbuch-Heller et al., 2002). In such cases, differentiating PSP from PD on the basis of saccade traces can be difficult. This was especially true for small horizontal saccades, especially in MGS tasks (Fig. 3B).

Even in these patients, large amplitude saccades tend to show a slightly reduced velocity for their size. Small saccades may be represented more redundantly within the brainstem RF than are large saccades, and, therefore, may be less susceptible to pathological changes (Hepp and Henn, 1983). With disease progression, the velocity of large saccades may become reduced, or large saccades may degenerate into small multi-step saccade sequences that have relatively normal velocity with respect to their size.

It is possible that the low-pass filter used in the present study (20 Hz) limited the detection of differences in speed for small saccades. However, this would not completely explain the largely normal amplitude–velocity relationship in PSP patients, because saccades in normal subjects, PD, and PSP patients were recorded under the same conditions in our study. Although this possibility warrants further investigation, we also inspected the individual saccade traces visually, and checked for a possible failure to detect small saccades. Actually, with the procedure described in the Subjects and Methods section, the rate of detection failure was <2% of the total trial number, depending on the patient. Previous studies reported an absence of decreased horizontal saccade velocity regardless of the disease stage, possibly because only small amplitude saccades were studied (Vidailhet et al., 1994; Rottach et al., 1996; Rascol et al., 1991). Moreover, our EOG technique is of sufficient quality that it shows an excellent correlation with eye movement data acquired using a video-based eye tracking system, and we have conducted quantitative analyses of EOG data for several hundred patients to date.

In any case, the prominent reduction in saccade amplitude within a relatively short period of time stood in marked contrast with the saccade performances of PD patients. The EOG method and repeated recordings of saccades during the disease course may therefore be especially useful for the diagnosis of PSP, although an accurate measurement of the vertical saccade velocity and gain would allow PSP patients to be differentiated from PD at an earlier phase.

### 4.3. Saccade parameters in different types of PSP patients

Saccade parameters differed in patients with different PSP subtypes. As stated in the Introduction, we took the extent to which saccade parameters of individual patients deviated from the normal range as a possible indication of the pathological extent in each subject. Saccade latency was normal for patients with PAGF, mostly within normal range for PSPc and PSPp patients, but markedly deteriorated for RS patients, although there was a substantial overlap in distribution of the saccade parameters. The relative preservation of saccade parameters in PAGF and PSPp patients is consistent with the smaller burden and more restricted distribution of tau pathology in PAGF and PSPp patients than that in RS patients. On the other hand, we rarely observed hypermetria in PSPc patients (Terao et al., 2007). Hypermetria may have been masked, either because cerebellar involvement was mild, or because large saccades had degenerated into a number of smaller amplitude

saccades with disease progression. In our experience, hypermetria in cerebellar disorders is more often observed for saccades initiated at short latencies after the go-signal, and overshoots are considered evidence of a delay in the fastigial nucleus to signal the end of contralateral saccades (Goffart et al., 2003; Robinson et al., 1993). However, in the PSP patients we measured, saccades were slow to reach their end position, and this choking by the fastigial nucleus was too fast to come into play.

Saccade accuracy was markedly reduced in most patients, but not in those with PAGF, again reflecting pathological changes in the PPRF and/or SC. Nevertheless, the voluntary initiation of MGS and the frequency of saccades to cue reflecting inhibitory control were relatively well preserved in most cases, regardless of PSP subtype. With further investigation of patients with various subtypes of patients, saccade accuracy may be used to indicate the degree of involvement of the brainstem in each subtype of PSP.

The progressively reduced accuracy of horizontal saccades in PSP patients suggests a brainstem oculomotor pathology that includes the SC and/or the paramedian pontine reticular formation. Thus, recording horizontal saccades may prove useful in differentiating PSP from PD, especially when measurements are repeated over a period of several years. In contrast, the voluntary initiation of MGS and the frequency of saccades to cue, which reflect the inhibitory control of saccades, were relatively preserved in most of the cases in the present cohort, regardless of the PSP subtype. This was an unexpected finding, considering the widespread pathological changes observed in PSP patients, and suggests that saccade abnormalities in PSP are characterized by a predominantly brainstem pathology.

Finally, although EOG is a very practical technique in the clinical setting, we must acknowledge that it also has some limitations. Above all, EOG does not allow fully accurate assessment of velocity, especially of small-amplitude saccades, even failing to detect some of them with the low-pass filtering used in the present study. While the general conclusions obtained in this study are still valid despite these limitations, future studies should also consider the use of alternative methods such as the very accurate electromagnetic method as described by Bour and Aramideh, (2000); Bour et al., (2008), which is far less invasive and cheaper than the search coil method and much more suitable for clinical use. Such novel techniques would allow these characteristic saccade features of PSP to be assessed clinically with sufficient quality. For example, the combination of reduced peak velocity of vertical saccades in addition to the occurrence of horizontal square wave jerks is a very strong argument for the diagnosis of PSP. The technique of Bour et al. will enable us to evaluate both these features.

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