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Spatial discrimination in patients with MSA, PSP, DIP, and VP with pain

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Pain is common in Parkinson's disease and frequently observed in other diseases involving parkinsonism. Abnormal scaling function in PD has been reportedly associated with pain, but the role of this function in pain in other parkinsonism-related diseases remains unknown. We screened 127 patients with multiple system atrophy (MSA, $n=24$), progressive supranuclear palsy (PSP, $n=15$), drug-induced parkinsonism (DIP, $n=56$), or vascular parkinsonism (VP, $n=32$). After screening, 79 patients with parkinsonism (23 MSA, 10 PSP, 28 DIP, and 18 VP patients) were included in the study. We divided the patients of each group into two groups (with or without pain).The percentages of patients in those groups with pain were 73.9%, 50.0%, 67.9%, and 66.7%, respectively. There was no difference in mean SDT between patients with and without pain in any disease (all $p \geq 0.052$). The number of patients showing unmeasurable SDT did not differ between those with and without pain in any disease (all $p \geq 0.316$). Our study found no evidence of a role of scaling function in pain development in parkinsonian disorders such as atypical parkinsonism, DIP, and VP.

Keywords Pain, Atypical parkinsonism, Drug-induced parkinsonism, Vascular parkinsonism, Scaling, Spatial discrimination

Pain is common in Parkinson's disease (PD) as well as in other diseases showing parkinsonism, such as atypical parkinsonism and vascular parkinsonism (VP)[1–4]. Pain prevalence was reported to be 73% in multiple system atrophy (MSA) and 52% in progressive supranuclear palsy (PSP)[3]. The pain proportion was approximately 61–81% for MSA, 25–52% for PSP, and 60.0–61.0% for VP in previous studies[4–7]. Pain prevalence in drug-induced parkinsonism (DIP), despite being the second most common parkinsonism after PD, is not well known. Overall, pain in parkinsonism appears to be underrecognized, and its clinical features and pathogenesis are poorly understood[3].

Pain potentially has different characteristics or mechanisms among diseases showing parkinsonism. Pain is a unique non-motor symptom in PD and is considered a pre-motor symptom. In our previous study, pain occurred before motor symptoms in MSA and VP, while motor symptoms occurred before pain in PSP. In addition, pain location in the body differed among these atypical parkinsonism diseases[4]. This suggests that pain mechanisms differ among parkinsonian disorders. However, previous studies have shown similar abnormal pain mechanisms, suggesting the existence of a shared mechanism[8,9]. Furthermore, in earlier studies, researchers did not classify patients based on the presence or absence of pain. Although pain in parkinsonian disorders differs from that in healthy controls (HCs), it is unclear why pain is more frequent in patients with these disorders[8–12]. We study the differences between groups with and without pain to explain these findings.

Previously, we showed that scaling function in the sensory system was compromised in PD patients with pain compared with PD patients without pain and proposed that this abnormality contributes to the development of pain in such patients[13].

As in PD, the basal ganglia (BG) is involved in diseases that involve parkinsonism. The BG is involved in the planning of movement amplitude[14] and in timing and context-appropriate movement selection[15]. However, it is unclear whether this scaling problem exists in other diseases involving parkinsonism and if it varies by disease. In support of that, hypokinesia with progressive decrement, a typical calibration problem observed in PD, was observed in MSA but not in PSP[16,17].

In this study, we aimed to explore the existence of scaling problems in the sensory system in various parkinsonian disorders with pain, including MSA, PSP, DIP, and VP.

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Results

A total of 79 patients with parkinsonism was included in this study (23 MSA, 10 PSP, 28 DIP, and 18 VP, Table 1). The proportions of these patient groups with pain were 73.9%, 50.0%, 67.9%, and 66.7%, respectively.

The comparisons of demographic and clinical variables between patients with and without pain are shown in Table 2 by disease. Difference was not observed in clinical parameters among MSA, PSP, and VP patients with and without pain (all $p \geq 0.093$). Statistical differences between DIP patients with and without pain were observed in K-MoCA, education years, UPDRS I, and UPDRS III scores ($p = 0.026$, 0.004, 0.034, and 0.025, respectively).

SDTs did not differ between patients with and without pain for any disease (Fig. 1A, ipsilateral hand, $p = 0.808$ in MSA, 0.064 in PSP, 0.227 in DIP, 0.144 in VP; contralateral hand, $p = 0.052$ in MSA, 0.643 in PSP, 0.342 in DIP, 0.223 in VP). In addition, the ratios of unmeasurable SDTs between patients with and without pain in each disease were not statistically different (Fig. 1B, ipsilateral hand, $p = 1.000$ in MSA, 0.524 in PSP, 0.630 in DIP, 0.316 in VP; contralateral hand, $p = 1.000$ in MSA, 0.524 in PSP, 0.371 in DIP, 0.600 in VP).

Discussion

Our results showed no difference in SD function between the groups with and without pain in various parkinsonian disorders (MSA, PSP, DIP, and VP), indicating that scaling dysfunction does not contribute to pain development.

A possible reason for these results is that scaling dysfunction is not the main pathophysiology of other parkinsonian disorders, unlike PD. This presumption may not be the case for MSA, in which abnormal temporal discrimination threshold and hypokinesia with progressive decrement during repetitive movements were observed[16,18,19]. However, scaling dysfunction is unlikely associated with the occurrence of pain in MSA because temporal discrimination and progressive reduction of hypokinesia were more impaired in MSA than in PD. Based on the above-mentioned studies, if scaling dysfunction is associated with pain in MSA, it would assumedly be more severe in MSA patients with pain, which was not observed in our study. The fundamental pathophysiological mechanisms of pain generation are not yet well known. Various structures in the nervous system may be involved in such pain including the anterior cingulate cortex, substantia nigra, putamen, insula, amygdala, dorsal raphe nuclei, locus coeruleus, periaqueductal gray matter, corticospinal pyramidal system, and preganglionic sympathetic cells in the thoracic intermediolateral column[8,10,20]. However, since there was a statistical trend ($p = 0.052$ in the contralateral hand), it cannot be concluded at this point that scaling dysfunction is entirely independent of pain occurrence in MSA.

Reduced pain threshold in PSP was reported[8], but the scaling of sensorimotor function was uncertain. Because progressive hypokinesia during repetitive movements was not observed in PSP, a scaling dysfunction may not be the main pathophysiology[16,17]. This was presumably associated with a more extensive lesion[17]. In addition, decreased pain threshold was suggested to be related to periaqueductal gray involvement[8,12]. Our results showed that the mean SDT values seemed to be lower in PSP patients with pain than in patients without pain (Fig. 1), but there was no statistical difference at all, probably because the sample size was too small.

Research on the pathophysiology of pain in DIP is scarce. Furthermore, the frequency of pain is contradictory and appears to be related to the research design. In one study, the frequency of pain between DIP and HC did not differ and was higher only in PD[21]. However, in another study, significantly higher frequency was observed between patients with neuroleptic drug-induced parkinsonism (NIP) those without NIP[22]. To date, pain threshold in DIP has been investigated in only one study, and no difference was observed between HC and

	MSA $n = 23$	PSP $n = 10$	DIP $n = 28$	VP $n = 18$
Age, years	61.4 ± 7.1	69.8 ± 5.9	71.9 ± 8.2	74.7 ± 6.6
Women, n (%)	10 (43.5)	5 (50.0)	19 (67.9)	9 (50.0)
Duration of disease, months	22.8 ± 18.1	16.9 ± 11.0	15.2 ± 17.3	40.4 ± 62.7
K-MMSE	27.2 ± 2.8	24.9 ± 2.4	25.2 ± 4.0	24.7 ± 3.9
K-MoCA	23.7 ± 4.5	20.9 ± 3.8	18.9 ± 5.7	19.1 ± 5.9
Education, years	10.3 ± 5.1	6.8 ± 2.7	7.7 ± 4.5	7.5 ± 5.0
BDI	12.5 ± 7.0	16.6 ± 6.6	15.4 ± 5.7	11.4 ± 7.3
HY stage	2.5 ± 0.6	2.4 ± 0.5	2.2 ± 0.6	2.3 ± 0.6
UPDRS I	2.3 ± 1.6	2.6 ± 2.3	3.8 ± 3.3	3.1 ± 2.3
UPDRS II	10.9 ± 5.3	9.7 ± 5.1	8.7 ± 5.0	9.1 ± 5.1
UPDRS III	33.6 ± 12.9	30.3 ± 13.3	32.5 ± 12.0	27.3 ± 10.4
Pain present, n (%)	17 (73.9)	5 (50.0)	19 (67.9)	12 (66.7)

Table 1. Demographic and clinical characteristics of studied patients with parkinsonism. Values are expressed as means ± SD or number (percentage). Abbreviations: MSA, multiple system atrophy; PSP, progressive supranuclear palsy; DIP, drug-induced parkinsonism; VP, vascular parkinsonism; K-MMSE, the Korean version of the Mini-Mental State Examination; K-MoCA, the Korean version of the Montreal Cognitive Assessment; BDI, Beck depression inventory; HY stage, Hoehn and Yahr stage; UPDRS I, II, III, Unified Parkinson's Disease Rating Scale part I, II, III.

	MSA			PSP			DIP		
	Without pain $n=6$	With pain $n=17$	p*-value	Without pain $n=5$	With pain $n=5$	p*-value	Without pain $n=9$	With pain $n=19$	p*-value
Age, years	57.8 ± 5.7	62.7 ± 7.3	0.122	67.0 ± 6.4	72.6 ± 4.1	0.093	71.1 ± 10.3	72.3 ± 7.2	0.961
Women, n (%)	1 (16.7)	9 (52.9)	0.179	1 (20.0)	4 (80.0)	0.206	4 (44.4)	15 (78.9)	0.097
Duration of disease, months	20.8 ± 20.6	23.6 ± 17.8	0.622	20.2 ± 12.0	13.6 ± 10.1	0.329	15.3 ± 19.1	15.1 ± 17.0	0.654
K-MMSE	27.2 ± 1.5	27.2 ± 3.2	0.543	24.8 ± 2.2	25.0 ± 2.8	0.915	26.7 ± 2.7	24.5 ± 4.3	0.158
K-MoCA	23.3 ± 3.7	23.8 ± 4.8	0.778	21.6 ± 2.6	20.2 ± 4.9	0.600	22.1 ± 4.6	17.3 ± 5.6	0.026
Education, years	12.0 ± 5.2	9.6 ± 5.1	0.239	8.2 ± 3.0	5.4 ± 1.3	0.095	11.3 ± 4.1	5.9 ± 3.7	0.004
BDI	11.2 ± 9.3	12.9 ± 6.2	0.482	17.0 ± 7.0	16.2 ± 7.0	0.834	15.0 ± 5.2	15.5 ± 6.0	0.863
HY stage	2.3 ± 0.4	2.6 ± 0.7	0.260	2.4 ± 0.4	2.4 ± 0.5	0.910	2.1 ± 0.2	2.3 ± 0.7	0.517
UPDRS I	2.0 ± 0.9	2.5 ± 1.8	0.772	2.2 ± 1.6	3.0 ± 3.0	0.589	2.2 ± 2.1	4.6 ± 3.5	0.034
UPDRS II	9.0 ± 5.2	11.5 ± 5.4	0.194	9.6 ± 4.2	9.8 ± 6.5	1.000	6.3 ± 3.5	9.8 ± 5.2	0.092
UPDRS III	32.3 ± 13.2	34.0 ± 13.2	0.779	25.8 ± 11.9	34.8 ± 14.4	0.462	25.6 ± 10.0	35.8 ± 11.6	0.025
Pain severity	-	3.4 ± 3.0	-	-	3.0 ± 1.4	-	-	2.8 ± 1.7	-

	VP		
	Without pain n = 6	With pain n = 12	p*-value
Age, years	74.7 ± 8.6	74.8 ± 5.7	0.742
Women, n (%)	3 (50.0)	6 (50.0)	1.000
Duration of disease, months	66.0 ± 103.4	24.1 ± 4.4	0.387
K-MMSE	26.0 ± 2.2	24.5 ± 4.3	0.507
K-MoCA	22.1 ± 4.6	17.3 ± 5.6	0.186
Education, years	8.8 ± 4.2	6.8 ± 5.5	0.341
BDI	12.0 ± 10.0	11.1 ± 6.2	1.000
HY stage	2.3 ± 0.5	2.3 ± 0.7	0.653
UPDRS I	2.2 ± 2.0	3.6 ± 2.4	0.230
UPDRS II	9.5 ± 5.3	8.8 ± 5.2	0.925
UPDRS III	23.8 ± 7.9	29.0 ± 11.3	0.399
Pain severity	-	4.3 ± 2.5	-

Table 2 . Clinical characteristics of parkinsonian patients without pain and with pain. Values are expressed as means ± SD or number (percentage). Pain severity was evaluated with a visual analog scale with scores ranging from 0 to 10. $^*p < 0.05$ indicates significant differences. Abbreviations: MSA, Multiple system atrophy; PSP, progressive supranuclear palsy; DIP, drug-induced parkinsonism; VP, vascular parkinsonism; K-MMSE, the Korean version of the Mini-Mental State Examination; K-MoCA, the Korean version of the Montreal Cognitive Assessment; BDI, Beck depression inventory; HY stage, Hoehn and Yahr stage; UPDRS I, II, III, Unified Parkinson's Disease Rating Scale part I, II, III.

DIP[23]. However, since our study showed no difference in pain threshold between HC and PD, the results should be interpreted with caution.

Knowledge regarding pain in VP is limited, and there is no research on sensory function or pain mechanisms in VP. Currently, the pain mechanism in VP remains unknown. However, because abnormal sensorimotor integration occurs in VP[24–26] and sensory dysfunction such as olfactory function has also been reported[27], we hypothesize an involved sensory dysfunction.

Our study had several limitations. First, the sample size for each disease was small, especially for PSP. It's hard to say precisely, but it may require a much larger number of patients. For example, our previous research investigated 90 PD patients (18 patients without pain, and 72 patients with pain, Kim et al., 2023)[13] Second, although JVP domes are a standardized grating tool for spatial discrimination evaluation, a more sophisticated and comprehensive evaluation method may be required.

In conclusion, the results of our study did not show any evidence of scaling dysfunction in association with pain in MSA, PSP, DIP, and VP patients. This indicates that the pain mechanisms of these disorders differ from that of PD. Further investigations to confirm the results of the present study are warranted.

Methods

Patients.

We consecutively investigated patients experiencing parkinsonism in our hospital from September 2015 to September 2021 (24 MSA, 15 PSP, 56 DIP, and 32 VP). These patients were diagnosed according to the current international diagnostic criteria[28–31]. We included only VP patients who underwent[18] F-N-(3-fluoropropyl)-2b-carbon ethoxy3b-(4-iodophenyl) nortropane (FP-CIT) PET scan to exclude those with neurodegenerative dopaminergic deficits[4]. DIP was diagnosed based on the following criteria: (1) the presence of at least two of

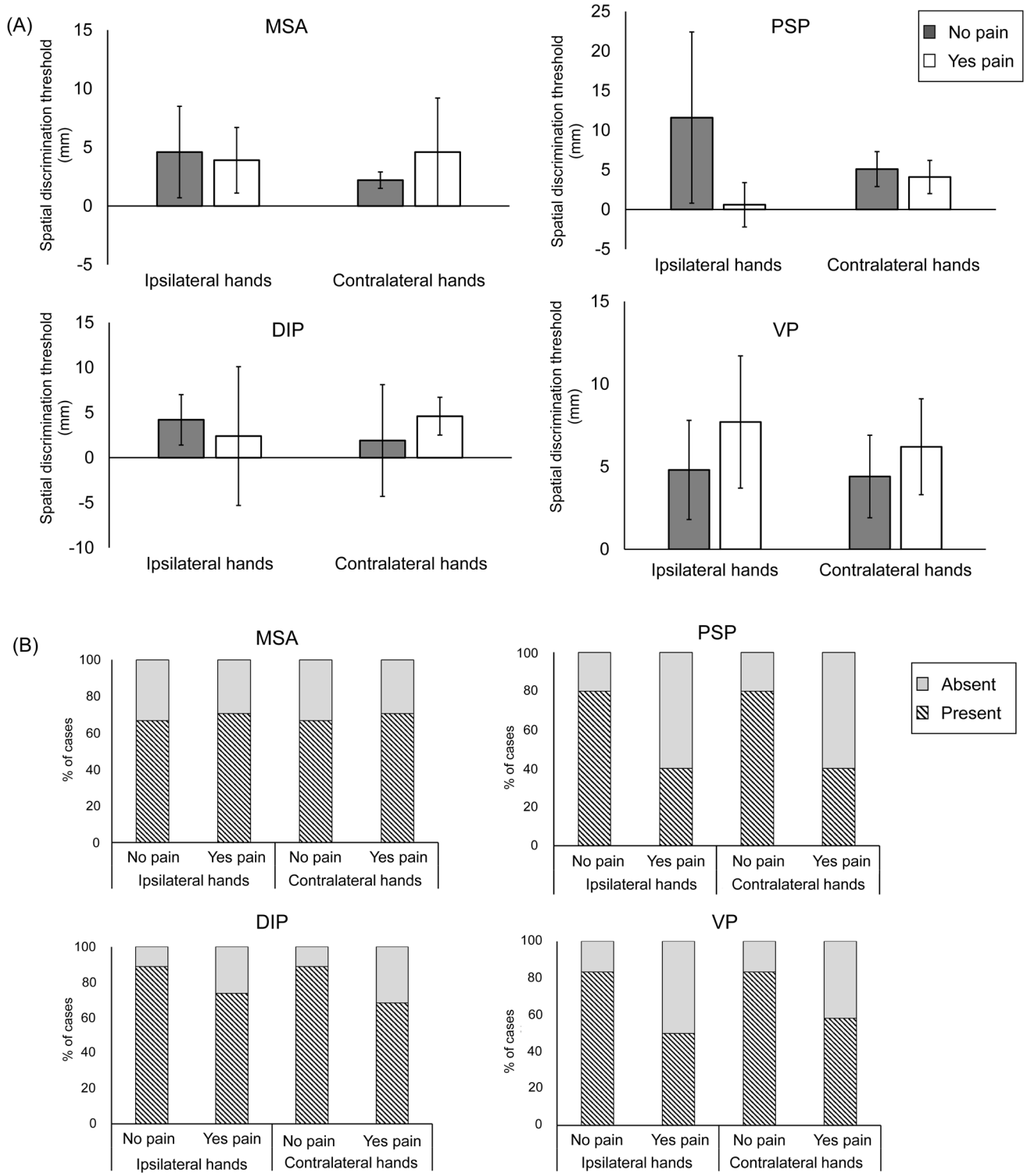

Fig. 1. Comparison of SDT between patients with and without pain in various parkinsonian disorders. The ipsilateral SDT represents that at the more affected hand, while the contralateral SDT represents that at the less affected hand. (**A**) Bar graphs illustrate the mean and standard deviation (error bars). The mean SDT values were not different between patients with and without pain by disease (ipsilateral hand, $p = 0.808$ in MSA, 0.064 in PSP, 0.227 in DIP, 0.144 in VP; contralateral hand, $p = 0.052$ in MSA, 0.643 in PSP, 0.342 in DIP, 0.223 in VP). (**B**) The percentage of patients showing unmeasurable SDT did not differ between patients with and without pain by disease (ipsilateral hand, $p = 1.000$ in MSA, 0.524 in PSP, 0.630 in DIP, 0.316 in VP; contralateral hand, $p = 1.000$ in MSA, 0.524 in PSP, 0.371 in DIP, 0.600 in VP). SDT = spatial discrimination threshold; MSA = multiple system atrophy; PSP = progressive supranuclear palsy; DIP = drug-induced parkinsonism; VP = vascular parkinsonism

the four cardinal symptoms of parkinsonism; (2) no parkinsonism prior to exposure to offending drugs; (3) resolution of or significant improvement in parkinsonism within 12 months after withdrawal of offending drugs; (4) no alternative explanation for parkinsonism; (5) normal symmetric dopamine transporter (DAT) binding in the caudate nucleus and putamen on[18] F-FP-CIT PET[32,33].

We collected Hoehn and Yahr (H&Y) stage, Unified Parkinson's Disease Rating Scale (UPDRS) parts I–III, disease duration, the Korean Version of the Mini-Mental State Examination (K-MMSE), the Korean Version of the Montreal Cognitive Assessment (K-MoCA), education years, Beck Depression Inventory (BDI), the presence of pain, and pain severity at diagnosis for all patients. We evaluated the pain using a systematic questionnaire. The systematic questionnaire included detailed information about pain type. Using this questionnaire, we classified patients who did not have any type of pain into the pain-free group. Pain severity was measured using a visual analog scale (VAS) scored from 1 to 10 (1 = no pain, 10 = the worst pain). The exclusion criteria were cognitive dysfunction (K-MMSE < the 2.5th percentile for age and educational-appropriate norm)[34]; severe depression (BDI score ≥ 29)[35]; and a co-morbid pain condition such as rheumatic disease, severe osteoarthritis, or traumatic, orthopedic, or peripheral nerve injury[36]. The Institutional Review Board of Hallym University Dongtan Sacred Heart Hospital approved this study. All methods were performed in accordance with the Declaration of Helsinki and followed relevant guidelines and regulations. Informed consent was obtained from all participants.

Spatial discrimination measurement.

We used plastic John-Van Boven-Philips (JVP) domes (Stoelting, Wood Dale, IL, USA) to measure spatial discrimination (SD). JVP domes are a commercially available, standardized grating task set, and SD threshold (SDT) was determined as described in other studies[13,37].

Participants were asked to sit comfortably with their eyes closed and hold their palms in a supinated position. Both hands were tested. Handedness was determined based on self-report, and all participants were right-handed. We applied eight plastic JVP domes with gratings of various widths (3.0, 2.0, 1.5, 1.25, 1.0, 0.75, 0.5, 0.35 mm). Twenty vertical or horizontal orientations per dome (10 times for each of the two possible orientations) were applied to the distal fat pad of the index finger for approximately 1–2 s, beginning with the largest groove width and progressing through narrower widths in a predetermined random order. The participants were asked to report the orientation of the grooves. The SDT was determined by calculating the grating width corresponding to a 75% correct response using a linear interpolation technique[13,38]. Unmeasurable SDT was defined as a case in which the participant reported pressure but could not determine the orientation of the widest groove. The ipsilateral SDT was measured at the more affected hand, and the contralateral SDT was that of the less affected hand.

Because diseases involving parkinsonism do not always show marked motor asymmetricity, the method was a slightly modified version of that used to determine the more and less affected sides of Parkinson's disease in our previous study and was based on UPDRS part III (items 18–31)[13]. The side of disease onset was used if the more affected side could not be determined with UPDRS part III (i.e., if the sides did not differ based on UPDRS part III). If one side experienced axial symptoms, the more affected side was regarded as that with the first lateralized symptoms in medical history[39]. This is generally based on the observation that the side on which symptoms appear first in the medical history is usually the side with more severe motor symptoms on neurological examination. If the more affected side could not be determined using these methods, the right side was considered the more affected side.

Statistical analysis

We analyzed patients with MSA, PSP, DIP, and VP for each disease. Demographic and clinical variables in the groups with and without pain were compared. Data are expressed as mean ± standard deviation. The chi-square test or Fisher's exact test were used for categorical variables, and the unpaired *t*-test or Mann-Whitney *U* test was used for continuous variables, as appropriate. Patients with MSA, PSP, and VP showed no difference in clinical variables between those with and without pain, and the Mann-Whitney *U* test was used to determine the difference in SDT between these groups. In DIP patients, one-way ANCOVA was used to compare SDT between DIP patients with and without pain after adjusting UPDRS III scores and education years. The normality test was performed using skewness and kurtosis, and the acceptable values were < 3 and < 10, respectively[40]. Although there were statistical differences between DIP patients with and without pain in education years, K-MoCA, UPDRS I, and UPDRS III scores, only UPDRS III and education years were adjusted. In DIP patients, one-way ANCOVA was used to compare SDT between DIP patients with and without pain after adjusting UPDRS III scores and education years… This lack of adjustment was due to K-MoCA and UPDRS I overlapping with other variables (i.e. K-MMSE and BDI) and reflecting similar clinical features such as cognition and mood. A p-value < 0.05 was considered statistically significant in IBM SPSS 28 statistics (IBM Corp., Armonk, NY, USA).

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Author contributions
M.S.K. and S.Y.K. designed the study, collected the data, and wrote the manuscript. J.H.K. reviewed the manuscript. All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
This protocol was approved by our Institutional Review Board of Dongtan Sacred Heart Hospital. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants and/or their legal guardians. This study was performed in accordance with the Declaration of Helsinki. The study conducted in accordance with good clinical practice.

Additional information
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