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Lack of Long-Trial-Improvement of Impaired Prism Adaptation in Multiple System Atrophy

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Abstract

Background: Prism adaptation (PA) is impaired in cerebellar disorders. We reported that trial number increment normalized its impairment in pure cerebellar spinocerebellar degeneration (pSCD) (long-trial-improvement). It remains to be determined whether this feature applies to multiple system atrophy (MSA).

Objectives: To clarify PA profiles in MSA.

Methods: We measured performance parameters of PA tasks with 50 or 200 trials in 26 MSA, 26 pSCD patients, and 39 healthy volunteers.

Results: With 50 trials, the adaptation ability (final error of PA) was similarly impaired in both disorders. While 200 trials normalized the PA performance in pSCD, 200 trials did not restore it in MSA. The degree of adaptation deficits correlated with clinical ataxia severity in MSA but not in pSCD.

Conclusion: No long-trial-improvement should reflect severe cerebellar adaptation circuits involvements, including middle cerebellar peduncle, dentate nucleus, brainstem nuclei and other areas, in MSA compared to mild involvements, only in cerebellar cortex, in pSCD.

Introduction

The cerebellum plays a critical role in error-based motor adaptation.[1] Cerebellar sensorimotor adaptation can be evaluated using prism adaptation (PA) tasks, in which people gradually adapt to visual perturbation induced by wedge prism with repetitive trials.[2] After prism removal, adaptations retain as an aftereffect (AE). Lesions of some parts of cerebellar cortex and cerebellar afferent pathways impair PA and reduce AE.[3] Different brain networks are suggested to contribute to different phases of PA.[4] Recently, PA has been applied to objectively detect impaired cerebellar adaptation in patients with spinocerebellar degenerations (SCD),[56] and notably the PA impairment does not directly correlate with clinical ataxia scales[4,5]. Its impairment patterns should differ among SCD subtypes reflecting pathological profiles. In multiple system atrophy (MSA), neurodegeneration affects broader regions than pure cerebellar type SCD (pSCD), namely the middle cerebellar peduncle, inferior olivary nucleus, pontine nuclei and striatum in addition to the cerebellar cortex.[7] Recently, we reported that an increased number of prism exposure trials normalized PA in pSCD (long-trial-improvement). These features of PA tasks have not been studied in MSA. Based on the above findings, in the present paper, we studied PA parameters in MSA and compared them with those of pSCD.

Materials and methods

Participants

Participants were 26 patients with MSA who met the Movement Disorder Society criteria[8] for “Clinically established MSA” or “Clinically probable MSA”.

Among the MSA patients, 25 patients had predominantly cerebellar features (MSA-C), and one had Parkinsonian features (MSA-P) (Table 1). We compared the results of MSA with those of 26 pure cerebellar type spinocerebellar degeneration (pSCD) (10 SCA6, 5 SCA31, one SCA8 and 10 IDCA [9]) (Table 2) and age matched 39 healthy volunteers (HVs). Twenty five pSCD and 35 HV were included in our previous study.[6] Clinical ataxia severity was rated using the International Cooperative Ataxia Rating Scale (ICARS)[10] and Scale for the Assessment and Rating of Ataxia (SARA).[11] Neither SARA [MSA 15.8 ± 1.4 (6–30) vs pSCD 17.3 ± 1.4 (3.5–31.5), p = 0.25)] nor ICARS [MSA 39.3 ± 3.7 (11–80) vs pSCD 45.3 ± 4.0 (6–82), p = 0.15)] differed significantly between the two disease groups. There were no significant differences in the age among three subject groups [MSA 64.8 ± 1.9 (43–81), pSCD 68.7 ± 2.0 (35–84), HV 67.5 ± 1.5 (49–86); p = 0.33].

Table 1
Characteristics of patients with MSA

Age	Sex	Diagnosis	Disease duration	SARA	ICARS
43	M	MSA-C	28	12	29
53	F	MSA-C	48	12	21
54	M	MSA-C	60	20.5	64
54	M	MSA-C	24	22	36
57	F	MSA-C	24	13	27
58	M	MSA-C	11	6.5	27
59	M	MSA-C	42	10.5	36
61	M	MSA-C	56	23	68
62	M	MSA-C	40	12	33
63	M	MSA-C	24	20	47
64	F	MSA-C	72	18.5	46
64	M	MSA-C	48	16	36
65	F	MSA-C	20	10	23
65	M	MSA-C	20	13	33
66	F	MSA-C	12	17	44
70	M	MSA-C	48	15	38
71	M	MSA-C	12	13	31
71	M	MSA-C	22	6	19
74	M	MSA-C	48	14	35
75	F	MSA-C	60	30	80
76	M	MSA-C	60	29	71
76	F	MSA-C	48	27	69
77	M	MSA-C	72	21	N/A
77	M	MSA-C	15	16	42
81	M	MSA-C	24	8.5	16

MSA: multiple system atrophy, SARA: the Scale for the Assessment and Rating of Ataxia, ICARS: the International Cooperative Ataxia Rating Scale, N/A: not available

Age	Sex	Diagnosis	Disease duration	SARA	ICARS
49	M	MSA-P	6	6	11

MSA: multiple system atrophy, SARA: the Scale for the Assessment and Rating of Ataxia, ICARS: the International Cooperative Ataxia Rating Scale, N/A: not available

Table 2
Characteristics of patients with SCD

Age	Sex	Diagnosis	Disease duration	SARA	ICARS
51	M	SCA6	72	19	44
59	F	SCA6	96	11.5	36
60	M	SCA6	72	10.5	42
73	F	SCA6	108	13	40
73	M	SCA6	72	31.5	77
74	M	SCA6	N/A	25	65
74	M	SCA6	204	27.5	64
76	M	SCA6	180	21.5	49
78	F	SCA6	108	4	6
78	F	SCA6	216	27.5	82
73	F	SCA8	48	26.5	72
55	M	SCA31	6	7	19
64	F	SCA31	72	17	48
67	M	SCA31	252	24	70
67	M	SCA31	156	25	60
68	F	SCA31	48	12	38
78	M	SCA31	192	21	57
35	F	IDCA	60	16.5	40
61	M	IDCA	84	16	38
70	F	IDCA	96	21	43
71	F	IDCA	84	3.5	17
71	F	IDCA	36	8	22
73		IDCA	96	15.5	55
76	M	IDCA	156	16	39
78	M	IDCA	10	15	22

SCD:spinocerebellar degeneration, SARA: the Scale for the Assessment and Rating of Ataxia, ICARS: the International Cooperative Ataxia Rating Scale, SCA:Spinocerebellar ataxia, IDCA: idiopathic cerebellar ataxia, N/A: not available

Age	Sex	Diagnosis	Disease duration	SARA	ICARS
84	M	IDCA	120	14	25

SCD:spinocerebellar degeneration, SARA: the Scale for the Assessment and Rating of Ataxia, ICARS: the International Cooperative Ataxia Rating Scale, SCA:Spinocerebellar ataxia, IDCA: idiopathic cerebellar ataxia, N/A: not available

Prism adaptation task

PA task was performed in the same way as that reported in detail previously.[6] Participants sat 40 cm in front of a pressure-sensing monitor and reached the target with their right index finger. They wore wedge prism lenses and shutter goggles. Prism lenses produced a 20-diopter rightward shift during exposure periods, and 0-diopter in the pre- and post-exposure periods. Vision of the arm was occluded during reaching, and visual feedback (VF) of the final attached position was presented 300ms after target contact. In trials without VF, the shutters remained closed. All the subjects participated in two PA protocols with 50 or 200 trials separated by at least 1 month. Each protocol consisted of pre-, exposure, and post-exposure-periods (Fig. 1). Pre-exposure period comprised 30 trials without visual deviation: 10 with VF, 10 without VF, and 10 with VF. During exposure, participants performed 50 or 200 trials with VF. All the post-exposure period was without visual displacement, and VF was provided for the first 20 trials and no VF in the subsequent 50 trials. The error of each trial was defined as the horizontal distance between the target and attached position, expressing rightward errors positive and leftward errors negative. The baseline error (BE) was calculated as the mean of measured errors during pre-exposure period, and the errors of the later periods were determined by subtracting BE from the measured errors. The adaptation ability was assessed as the mean error during the final 10 exposure trials (final error: FE). The first AE was defined as the first error in the post-exposure period and recovered AE as the mean of errors during the final 10 post-exposure trials.

Statistical analysis

FEs and AEs were compared using two-way ANOVA with TRIAL (50 vs. 200) and GROUP (MSA, pSCD, HV) as factors, followed by Tukey's HSD post-hoc test for significant effects. Correlations between clinical variables (age, disease duration, SARA/ICARS) and PA parameters were also studied. Statistical analyses were performed using SPSS version 27.0.1 (IBM, Armonk, NY, USA). A two-sided P value < 0.05 was used as statistical significance. Data are presented by mean ± SEM.

Results

Figure 1 shows error time courses. In 50 trials session (A), FEs were larger and first AEs were smaller in both patient groups than HVs. In 200 trials, the FE was normalized in pSCD but remained larger in MSA. Additionally, both AEs were almost the same as those of HVs. Figure 2A shows comparisons of PA parameters. GROUP [$F(2, 135) = 30.1$, $p < 0.001$] has a significant effect on BE. Post-hoc analysis

showed BEs of MSA and pSCD were larger than that of HV (MSA: 13.88 ± 0.76, pSCD:12.84 ± 0.81, HV: 8.08 ± 0.35, $p < 0.001$]. Two-way ANOVA on FE revealed an effect of TRIAL [$F(1,135) = 13.35$, $p < 0.001$] and GROUP [$F(2,135) = 12.27$, $p < 0.001$], and there was interaction [TRIAL x GROUP: $F(2,135) = 3.49$, $p = 0.03$] (Fig. 2B). In 50-trail session, the FEs of MSA and pSCD were larger than that of HV (MSA: 24.60 ± 3.50 vs pSCD: 24.00 ± 4.03 vs HV: 7.50 ± 1.97, $p < 0.001$) (Fig. 2Ba). On the other hand, in 200 trails, the FE of MSA remained larger than that of HV, while it was normalized in pSCD (MSA: 16.03 ± 3.29 vs pSCD: 7.90 ± 3.79 vs HV: 6.20 ± 1.18, $p = 0.018$) (Fig. 2Bb).

ANOVA analyses showed that both the first AE and recovered AE were significantly affected by the factor of TRIAL [first AE: $F(1,135) = 4.84$, $p = 0.03$, recovered AE: $F(1,135) = 15.03$, $p < 0.001$] and unaffected by the factor of GROUP [first AE: $F(2,135) = 2.07$, $p = 0.13$, recovered AE: $F(2.135) = 2.35$, $p = 0.10$], and there was no interaction between the two factors [$F(2,135) = 1.14$, $p = 0.32$]. The 200-trail-sessions induced larger AEs than the 50-trial-sessions.

Correlation between PA parameters and clinical scores

In MSA, 50- trial FE correlated with total ICARS ($r = 0.48$, $p = 0.05$), ICARS upper limb scores ($r = 0.51$, $p = 0.038$) or finger-finger test ($r = 0.69$, $p = 0.002$) in MSA (Fig. 2Ca). FE of the 200-trial in MSA also correlated with the total ICARS ($r = 0.41$, $p = 0.045$) (Fig. 2Cb). These correlations were not observed in pSCD (Fig. 2D). No other parameters correlated with clinical scores.

Discussion

Here, we showed the details of PA profiles in MSA for the first time. 1) In the 50-trial protocol, the main adaptation performance shown by FE was similarly impaired in MSA and pSCD. The long-trial (200 trials) protocol normalized the FE in pSCD but not in MSA. 2) The degree of FE correlated with clinical ataxia severity in MSA, but not in pSCD even though the clinical severity was almost the same in both groups. 3) The AEs were increased by the long-trial protocol in all subject groups.

Our present result of large 50-trial FE in MSA are consistent with previous reports.[12] Purkinje cells and cerebellar afferent pathways were known to play important roles for PA[3], and those all regions are involved in MSA.[13] In the previous paper[5], PA impairment with 100 trial was severer in MSA than in those with the other types of SCD (SCA3, SCA6 and SCA31). In the present protocol with 50 trials, the FE was almost the same in between MSA and pSCD. In contrast, in the protocol with 200 trials, the FE was normalized in pSCD but was not normalized in MSA despite showing slight improvement by trial number increment in both disorders. Based on the above results, abnormally large FE was improved by the trial number increment from 50 to 200 in pSCD. This final normalization is compatible with the finding that the cooling of the cerebellar cortex reduced adaptation speed in animals but did not abolish it[14]. Because the cerebellar cortex is primarily involved in pSCD, [15–17] slow adaptation accomplished an

adaptation with long trials. No normalization in MSA with 200 trials may be explained by the widespread pathology of MSA and consistent with poorer rehabilitation efficacy.[18]

In previous papers, the parameters of PA did not directly correlate with clinical symptoms of ataxia such as dysmetria or decomposition.[5,19] Here, we showed that the FE correlated with ICARS, particularly upper limb coordination and finger-finger test scores in MSA but not in pSCD. How do we explain this dissociation? The FE should reflect an ability for immediate or short-term adaptation mediated by the cerebellum. The clinical ataxia symptoms reflect overall cerebellar dysfunction, which is compensated for a long disease duration by several neuronal circuits including cerebellum, brainstem nuclei, cortices and other areas. This compensation is expected to be less effective in MSA than in pSCD because cerebellar connections and other neural systems are also involved in MSA, whereas the cerebellar cortex is purely involved in pSCD. The ability for adaptation (FE) must parallel clinical ataxia scores with less compensation in MSA, but not with long-term compensated clinical ataxia in pSCD.

Another issue to be assessed is the dissociation between the FE and AEs. The FE should reflect an ability for immediate adaptation to the present task, while the AEs should indicate how much subjects can retrieve adaptation information from the stored memory. This memory is thought to be stored during the adaptation process within the cerebellar cortex, deep cerebellar nuclei such as the dentate nucleus, posterior parietal cortex (PPC), motor cortex, premotor cortex and other areas.[3,20–22] The present finding that the AEs were larger after 200 trials than after 50 trials may be explained by the longer duration of memory process in the former. The compensation for poor adaptation ability by retrieval of adaptation information from the stored memory in areas other than the cerebellar cortex would explain no differences in AEs between the subject groups.

We often have difficulty in differentiating MSA-C from other cerebellar degenerations, especially at the early stage. [23] The present results suggest that the long duration PA protocol (200 trials) may help us to differentiate MSA from pSCD.

Limitations

There are several limitations in the present study. They are relatively small sample size, no pathological confirmation, inclusion of mainly MSA-C patients. Finally, longitudinal evaluation was not performed. These issues are currently being addressed in an ongoing prospective study.

Conclusion

In conclusion, the long duration PA protocol could reveal different sensorimotor adaptation profiles between MSA and pSCD, which should reflect the difference in pathologically involved areas between the two disorders.

Declarations

Acknowledgments

We would like to thank all the participants of this study.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

RH received grants from Sumitomo Pharma CO on the prism adaptation in ASD patients, and it has no relation with the present paper.

Ethics approvals

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tottori University (No. 18A033).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Data availability

No datasets were generated or analyzed during the current study

Author's contributions

K.T. contributed to the design of the study, acquisition, analysis, and interpretation of data, execution of the statistical analysis, and writing of the first draft; T.S. contributed to the design of the study, acquisition, analysis, and interpretation of data, execution of the statistical analysis, review, and critique; Y.M, T.N, N.T. and S.M. contributed to the data acquisition, review, and critique; T.M. and Y.U. contributed to the discussion on the interpretation of the data, review, and critique; R.H. contributed to the study conception and design, review, and critique; All authors have approved the final submission.

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Figures

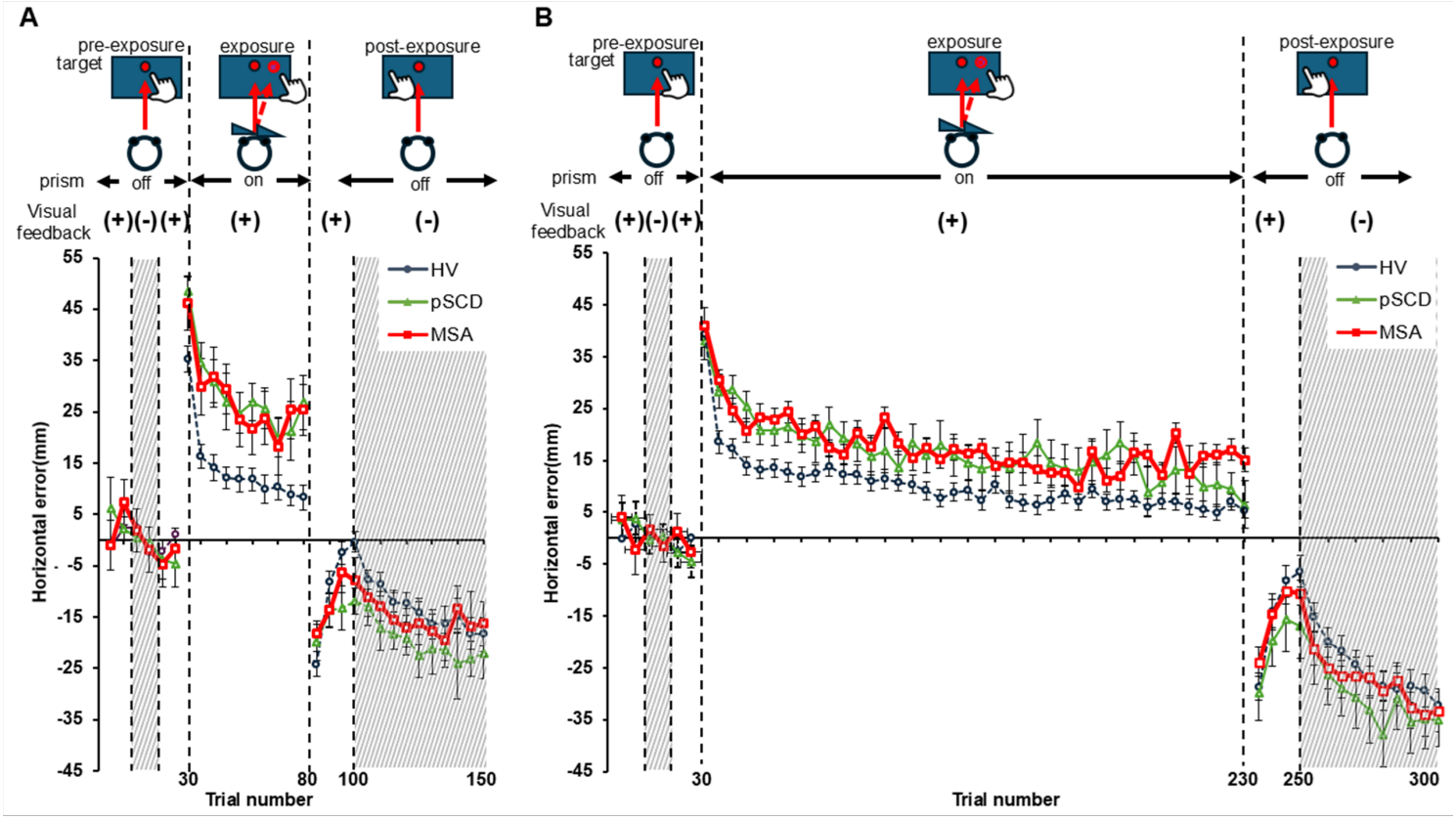


Figure 1

Time course of horizontal errors in 50 (A) and 200 (B) trials. Each point represents an average of five trials. The ordinate represents horizontal error. Abscissa indicates number of trials. Data are represented as means and SEs. Lines indicate data of healthy volunteers (HV, blue), pure cerebellar spinocerebellar degeneration (pSCD, green), and Multiple system atrophy (MSA, red).

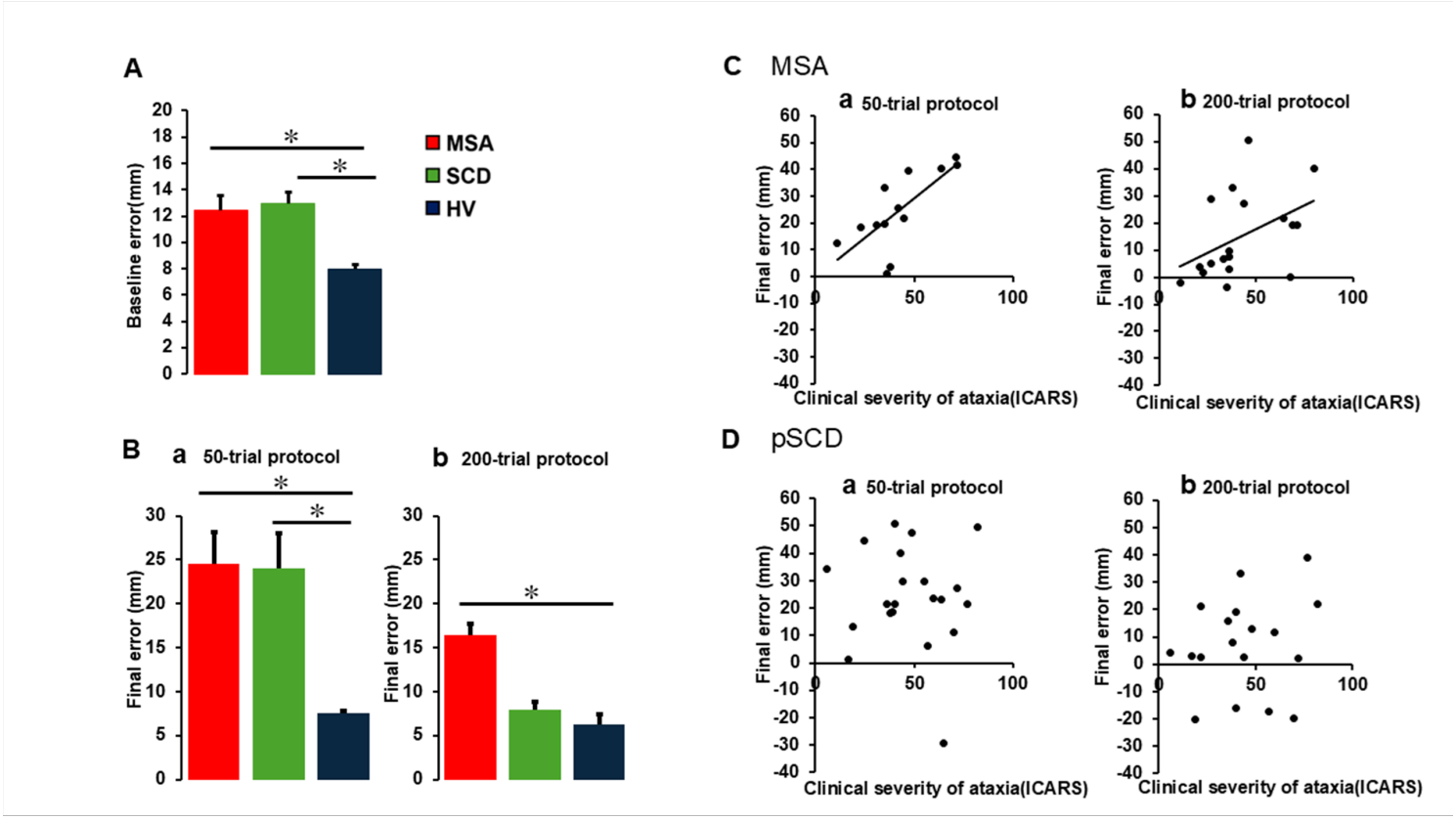


Figure 2

A.B. Comparison of each parameter between the groups. Data are represented as means±SE . Bars indicate data of healthy volunteers (HV, blue), pure cerebellar spinocerebellar degeneration (pSCD, green), and Multiple system atrophy (MSA, red).

C.D. Correlation between the ICARS score and final error in MSA (Ca, Cb) and in pSCD (Da, Db) during the 50-trial task (a) and 200-trial task (b)Each dot represents a single patient.