

Physical activity and dentate gyrus volume in pediatric acquired demyelinating syndromes

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Abstract

Objective

To assess the association between daily moderate-to-vigorous physical activity (MVPA) and dentate gyrus volume (DGv) in pediatric patients with acquired demyelinating syndromes (ADSs) of the CNS.

Methods

Cross-sectional analysis of accelerometry (7 days) and research protocol MRI data from 12 pediatric MS and 18 children with monophasic ADS (monoADS). Total brain and DGv were quantified using standardized methods. The association of daily minutes of MVPA with normalized DGv (nDGv) was assessed using multivariable generalized linear models.

Results

Median (interquartile range) MVPA was lower in MS patients [9.5 (14)] and exhibited less variation than in monoADS patients [24.5 (47)]. nDGv did not differ significantly between groups [mean nDGv (SD) [cm^3]: MS 0.34 (0.1); monoADS 0.4 (0.1); $p = 0.100$]. In the monoADS group, every 1-minute increase in MVPA was associated with a 2.4- mm^3 increase in nDGv ($p = 0.0017$), an association that was independent of age at incident demyelination, time from incident demyelination, sex, and brain white matter T2 lesion volume. No significant association was found between MVPA and nDGv ($-2.6 \text{ mm}^3/\text{min}$, $p = 0.16$) in the MS group.

Conclusions

Higher MVPA associates with greater nDGv in children who have recovered from monophasic demyelination. Larger studies are required to determine whether MVPA can promote regional brain development, or limit tissue damage, in youth with MS.

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Glossary

ADS = acquired demyelinating syndrome; **CES-DC** = Centre for Epidemiological Studies Depression Scale for Children; **CPM** = counts per minute; **DG** = dentate gyrus; **DGv** = dentate gyrus volume; **DMT** = disease-modifying treatment; **EDSS** = Expanded Disability Status Scale; **LV** = lesion volume; **monoADS** = monophasic ADS; **MVPA** = moderate-to-vigorous physical activity; **nDGv** = normalized DGv.

The hippocampus is responsible for memory and spatial processing. Hippocampal atrophy is observed in adults and children with MS and is associated with impaired visuospatial and episodic memory.¹ Recently, moderate-to-vigorous physical activity (MVPA), via its pleiotropic effects, has been associated with improved memory performance and increased hippocampal volume in healthy adults^{2,3} and adults with MS.⁴ Evidence in mice and humans further supports the notion that physical activity selectively increases dentate gyrus (DG) volume (DGv), perfusion, and neurogenesis.⁵ Currently, information is lacking regarding the association between MVPA and DGv in children with acquired demyelinating syndromes (ADSs), 20% of whom are diagnosed with MS. Accelerometry is used widely in the pediatric population, including in children as young as 3 years of age, for objective documentation of physical activity.^{6,7} It is important to note that having patients wear an accelerometer for 7 days has been shown to be a reliable metric of usual physical activity in both healthy children and children with various chronic conditions.^{8,9} We investigated the association between MVPA levels, quantified as average minutes per day of MVPA using 7-day accelerometry, and the DGv of pediatric patients with ADS, including those ascertained as having MS and those who remain as monophasic ADS (monoADS). We hypothesized that higher levels of MVPA would be associated with greater DGv. We also explored whether more modest physical activity intensities (sedentary and light physical activity) were associated with DGv in children with MS and monophasic demyelination.

Methods

Study population

This was a cross-sectional analysis of prospectively collected data on MS or monoADS patients recruited between 2014 and 2015 attending a specialized Pediatric MS Center. Standard definitions of MS and monophasic demyelinating disorders were followed.¹⁰ Patients with research MRI scan and accelerometry acquired within 30 days of one each other that passed quality assurance, and who had been followed up for a minimum of 2 years after incident demyelination, were enrolled. Patients who experienced a relapse or received corticosteroids within 30 days from study start were excluded from the present analysis.

Clinical factors

Demographic and clinical variables were collected using a standardized case report form. Disability (Expanded Disability Status Scale [EDSS]) and depression status (Centre for Epidemiological Studies Depression Scale for Children [CES-DC]),¹¹ 2

factors that may influence physical activity levels, were evaluated within 30 days of the accelerometry measure. CES-DC scores ≥ 15 were considered suggestive of major depression.¹¹

Physical activity measurement

Physical activity was measured according to a standardized 7-day protocol with accelerometry (ActiGraph 7,164 accelerometer; ActiGraph, Pensacola, FL) as described.¹² Because physical activity levels are fairly stable in children within the same season,^{13,14} we assumed general stability of patterns of behavior over a period of 30 days in the absence of a specific intervention. To further mitigate concern regarding change in physical activity in the interval between accelerometry and imaging, we performed MRI scanning and accelerometry in close temporal relation.

Physical activity was classified based on the accelerometer counts as sedentary to vigorous, depending on the rate of energy consumption [1 Metabolic Equivalent of Task (MET) = 3.5 ml/kg/min of O₂ consumption] estimated for a given count, sex, and age range. We followed validated accelerometry cutoff points calibrated with energy expenditure in children and youth aged 6 years and older.¹⁵ MVPA was measured in minutes per day and defined as physical activity exceeding 3,199 counts per minute (CPM).¹² Sedentary and light physical activity were defined as activities below 100 and 3,199 CPM, respectively.¹⁵

MRI

The MRI protocol included (1) a sagittal T1-weighted, 3D spoiled gradient recalled echo sequence (1.5 × 1 × 1 mm; repetition time (TR) = 22 ms; echo time (TE) = 8 ms; flip angle = 30°); (2) a 2D axial dual-echo proton density-/T2-weighted fast spin-echo sequence (1 × 1 × 2 mm; TR = 3,500 ms; TE1/TE2 = 15/63 ms; echo train length = 8); and (3) an axial 2D multislice fluid-attenuated turbo inversion recovery sequence (1 × 1 × 5 mm; TR = 9,000 ms; TE = 100 ms; TI = 2,250 ms). After a 9-parameter linear registration based on intensity, cross-correlation was performed as a similarity measure between each native T1-weighted volume and the ICBM152 template; a brain mask was extracted using a multiresolution nonlocal segmentation technique. Each brain mask was warped back onto each T1-weighted native space using the inverse transformations and used to compute the brain volume.^{16,17} T2 lesion volume (LV) were measured according to established pipelines.¹⁷ The manual tracing of the DG within the hippocampal body and tail was performed according to a standardized protocol¹⁸ (itksnap.org) by a single observer blinded to patients' clinical data, with computation of total (right + left) DGv normalized for brain size (normalized DGv [nDGv]). To test intraobserver reproducibility of DG segmentation, the scans of 10 randomly

selected patients were evaluated twice, 2 weeks apart; the intraclass correlation coefficient was 0.89.

Statistical analysis

SPSS (SPSS Inc, Release 23.0) was used to compute descriptive statistics based on the Fisher exact test, independent samples *t* test, or Mann-Whitney *U* test, where appropriate. Modeling was performed using Python (python.org) and the R (R Team, 2015) package lme4.

A general linear model was used to model the nDGv in each group (monoADS or MS):

$$\begin{aligned} \text{nDGv} \sim & \text{MVPA} + \text{Group} * \text{MVPA} + \text{Group} + \text{Sex} \\ & + \text{Age at incident demyelination} \\ & + \text{Time from incident demyelination} + \text{LV} \end{aligned}$$

Our model takes into account multiple fixed factors and covariates including the daily minutes of MVPA, group (MS and monoADS), age at incident demyelination, time from incident demyelination, sex, and T2-LV. In particular, the term MVPA estimates the magnitude of the association between MVPA and nDGv in the MS group, whereas the interaction Group * MVPA estimates the additional effect in monoADS vs MS. We also tested separately the sum MVPA + Group * MVPA, which estimates the magnitude of the association in the monoADS group (table 1). We refit the model with the EDSS or depression status replacing LV to assess the effect of these factors, which are potentially correlated with each other. EDSS was treated as a categorical variable. Depression status was coded as a binary variable, equal to 1 if the CES-DC score was ≥ 15 and

0 otherwise. Finally, we refit the model with sedentary activity or light physical activity replacing MVPA. Results were corrected for multiple comparisons (Bonferroni correction for 5 independent tests: adjusted *p* = 0.01).

Standard protocol approvals, registrations, and patient consents

Ethics approval was received from the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada (REB# 100005356 and 1000042743). Written informed consent was obtained from all guardians and informed assent from all patients.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Eighteen patients with monoADS [acute disseminated encephalomyelitis = 8, monofocal monoADS = 9, and polyfocal monoADS = 1] and 12 with MS (phenotype of initial presentation: transverse myelitis = 2, optic neuritis = 3, hemispheric syndromes = 3, and brainstem syndromes = 4) were included in the analysis. The median time between MRI and accelerometry was 1 day (interquartile range 1.3). Seven patients were excluded because of the elapsed time between accelerometry and research MRI exceeding 30 days. Pediatric MS patients were older at the time of incident demyelination, had a shorter elapsed time from incident demyelination, higher LV (as measured at the time of accelerometry), and lower daily MVPA with limited

Table 1 Results of the general linear model (reference group: MS)

nDGv			
Model goodness of fit: <i>F</i> = 4.159; <i>p</i> = 0.0047; adj. <i>R</i> ² = 0.433			
Effect	Effect estimate (mm ³)	95% CI	<i>p</i> Value
Intercept	473	259–688	
MVPA (MS)	–2.6	–6.1 to 9.0	0.16
Group (monoADS) * MVPA	5.0	1.6–8.4	0.008
Group (monoADS)	–117	–237 to 2.9	0.069
Sex (F)	–24.5	–94 to 45	0.50
Age at incident demyelination [y]	–4.0	–15 to 7.2	0.47
Time from incident demyelination [y]	–0.9	–19 to 17	0.92
LV [cm ³]	–4.1	–12 to 3.7	0.31
MVPA + group (monoADS) * MVPA	2.4	1.1–3.8	0.0017

Abbreviations: CI = confidence interval; monoADS = monophasic acquired demyelinating syndrome; MS = multiple sclerosis; nDGv = total (left + right) normalized dentate gyrus volume; F = female; MVPA = moderate-to-vigorous physical activity per day; LV = brain lesion volume. The effect estimate is the amount in mm³ of additional nDGv expected with a 1-unit increase in the effect, and the *p* measures the significance of that change. The “*” indicates an interaction. Patients with monoADS experienced an average 2.4 mm³ increase in nDGv with a 1-minute increase in MVPA [Group (monoADS) * MVPA interaction]. The term MVPA gives the estimated effect on nDGv in the MS group, whereas the interaction Group * MVPA is the difference between the MS and monoADS groups. The sum of these terms is the estimated effect in the monoADS group and is provided in the last row.

Table 2 Demographic and clinical characteristics

	MS	monoADS	<i>p</i> Value ^a
No. of patients	12	18	—
Median clinical follow-up (IQR) [y]	4.4 (2.2)	6 (2.5)	0.001
Females/males	9/3	7/11	0.072
Mean age at incident demyelination (SD) [y]	12.8 (2.3)	8 (3.3)	0.001
Median time from incident demyelination (IQR) [y]	2.5 (2)	4.1 (2.5)	0.001
Median no. of clinical attacks (IQR)	1.5 (2)	1 (0)	0.022
Median MVPA (IQR) [min/d]	9.5 (14)	24.5 (47)	0.017
Median EDSS (IQR)	1.3 (1.3)	1 (1.1)	0.346
Depressed/nondepressed	4/12	3/18	0.392
Mean nDGv (SD) [cm ³]	0.34 (0.1)	0.4 (0.1)	0.100
Median LV (IQR) [cm ³]	2.5 (10.8)	0.1 (0.01)	0.001
No. of patients with >1 gadolinium-enhancing lesions (%)	3/12 (25)	—	— ^b

Abbreviations: monoADS = monophasic acquired demyelinating syndrome; IQR = interquartile range; MVPA = moderate-to-vigorous physical activity per day; nDGv = normalized dentate gyrus volume; LV = brain lesion volume; SD = standard deviation.

^a Fisher exact test, independent samples *t* test, and Mann-Whitney *U* test, where appropriate.

^b Unenhanced MRI scans were performed in all except one monoADS patients, who did not show any contrast enhancement after gadolinium administration.

variance compared with monoADS patients. nDGv did not differ significantly between groups (table 2). Ten of the 11 MS patients were being treated with a first-line disease-modifying treatment (DMT) at the time of the study (glatiramer acetate = 4, interferon β -1a = 2, interferon β -1b = 1, and dimethyl fumarate = 3). Three of them received previous treatment with another injectable DMT (glatiramer acetate, interferon β -1a, or interferon β -1b). One MS patient, on natalizumab at the time of the study, previously received cyclophosphamide pulses. Our general linear model controlling for age at the time of incident demyelination, time from incident demyelination, sex, and LV showed that in the monoADS group, each one-minute increase in MVPA was associated with 2.4 mm³ larger nDGv ($p = 0.0017$). The estimated mean effect in the MS group was negative (-2.6 mm³/min increase in MVPA); however, this association was not significant ($R^2 = 0.19$, $p = 0.16$), likely a result of the small sample size and one outlying value. Consequently, our data do not allow the direction of an effect, if any, to be confidently ascertained. However, when we compared the magnitude of the association of MVPA with nDGv between groups, patients with MS showed significantly less increase in nDGv with increased MVPA than did those with monoADS (5.0 mm³ smaller nDGv increase per minute of MVPA in MS vs monoADS, $p = 0.008$) (table 1, figure).

Neither the EDSS (37 mm³/min of MVPA for the EDSS score 1 vs 0, $p = 0.25$; -12.5 mm³/min of MVPA for the EDSS score 2 vs 0, $p = 0.83$) nor the presence or absence of depression (56 mm³/min of MVPA, $p = 0.073$) was associated with the nDGv. None of the models for sedentary or light

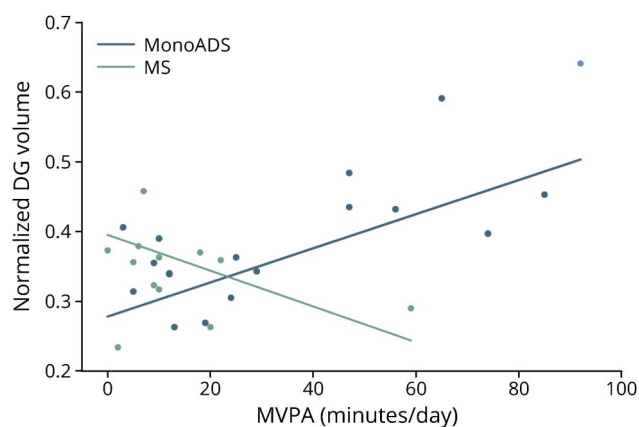
physical activity was significant (sedentary physical activity: model goodness of fit: $F = 0.794$; $p = 0.60$; adj. $R^2 = -0.052$; light physical activity: model goodness of fit: $F = 1.194$; $p = 0.35$; adj. $R^2 = 0.045$).

Discussion

Higher levels of MVPA in children with monophasic demyelination are associated with greater DG size, after adjusting for age at the time of incident demyelination, time from incident demyelination, sex, T2 lesion burden, physical disability, and depression. Children with monophasic demyelination recover well neurologically, have a very low rate of depression, and typically have a low burden of residual T2 lesions; thus, although these factors were considered, they did not influence our findings.

Previous studies have documented an association between MVPA and preservation of global hippocampal volume^{4,19–21} and improved memory function^{4,22} in adult MS patients. We did not find a statistically significant association between MVPA and nDGv in our pediatric MS patients (-2.6 mm³ for each 1-min increase in MVPA, $p = 0.16$), likely in part due to the limited amount and level of physical activity. This is consistent with previous data indicating lower participation in physical activity in children with MS compared with both monoADS and healthy youth.¹² However, our results leave open the possibility that the correlation between MVPA and DGv is, in fact, negative. Previous studies in adult relapsing-remitting MS have shown hippocampal morphological changes consistent with increased DGv; this effect was not present in primary or secondary progressive MS.²³ This

Figure Comparison between minutes of MVPA/day and nDGv in patients with MS (green) or monoADS (blue)



Patients with monoADS demonstrated a range of MVPA levels that correlated positively with nDGv ($R^2 = 0.32$; $p = 0.0016$). Although the green line suggests an adverse effect of MVPA on nDGv, this association was not significant in the MS group ($R^2 = 0.19$; $p = 0.16$), likely a result of the small sample size and one outlying value. However, patients with MS showed significantly less increase in nDGv with increased MVPA than did those with monoADS ($p = 0.008$). monoADS = monophasic acquired demyelinating syndrome; MVPA = moderate-to-vigorous physical activity; nDGv = normalized dentate gyrus volume.

observation suggests that the volume of the DG might increase in MS in response to inflammation. Our observation of a nonsignificant negative correlation between MVPA and nDGv may thus hint to an anti-inflammatory effect of physical activity within the DG of patients with MS. We computed that a study with 37 patients with MS would be required to confirm a negative correlation between MVPA and nDGv of the magnitude we observed (one-tailed t test, $\beta = 0.8$).²⁴ In future studies, more specific MR measures than DGv may be required. Possibilities include evaluation of changes in cellularity and water content²⁵ or tissue microstructure.²⁶ Of note, the MS group did not differ from the monoADS patients in terms of physical disability (maximum EDSS score = 2 in both the MS and monoADS groups). Thus, the limited amount of MVPA in the MS group and, arguably, the lack of a statistically significant association between MVPA and nDGv were not due to greater physical disability. Flu-like symptoms are a common side effect of beta interferons therapy, which may have limited physical activity engagement in our MS patients. However, only three of 11 were receiving such treatment at the time of the study. A study of 29 adult MS patients with depression demonstrated an association between depression and smaller DG/Cornu Ammonis 2–3 volume.²⁷ We did not detect depression as a significant contributing factor in our patients, probably because of the low sample size and the low frequency of depression within our MS group. Other studies have shown an association between depression and reduced participation in physical activity in adolescents with MS.¹² Future studies are needed to sort out the complex relationship between depression, physical activity, and DGv in this population.

In addition to consideration of patient-based experiential factors, we also evaluated relationships between nDGv and MS disease activity (LV). Both in adults²⁸ and children,¹ moderate direct correlations have been documented between LV and morphological changes of the DG surface suggestive for DG hypertrophy of uncertain significance.^{1,23} Our analysis did not reveal a significant association between LV and DGv. This may have been due to the different techniques applied (DG segmentation and volumetry vs radial mapping analysis) or the smaller sample size of our study.

The cross-sectional, observational nature of this study did not allow us to draw a causal or mechanistic relationship between increased MVPA and nDGv in children with monophasic demyelination. However, many studies support the biological plausibility of this finding. On a histologic level, animal studies have shown that voluntary wheel running selectively increases neurogenesis,^{5,29,30} angiogenesis,^{5,31} and dendritic complexity^{32,33} within the DG. Within the hippocampus, voluntary wheel running is also known to increase the secretion of neurotrophic factors^{2,34} and anti-inflammatory cytokines.³ Increased MVPA levels may thus reduce inflammatory injury and/or promote repair after acute demyelination. In children with monophasic demyelination, the absence of ongoing inflammation may lead to a permissive environment for MVPA to supply a trophic stimulus. In the context of MS, however, the ability of MVPA to modulate inflammation-related injury may be challenged by persistent pathologic processes, both inflammatory and degenerative. Our finding of significantly less increase in nDGv with increased MVPA in the MS patients compared with the monoADS group seems to support this notion. In particular, recent work suggests a pattern of microglial activation within the DG, which is associated with selective neurodegeneration, alteration in synaptic transmission, and memory impairment in mice with early experimental MS.³⁵ It is thus possible that increasingly effective immune-modulating therapies, which lead to a reduction in MRI and clinical burden of inflammatory disease, may facilitate the benefit of physical activity in patients with MS.

As an alternative explanation for the different strength of the association of MVPA with nDGv between groups, the effect of MVPA on DGv may occur in the context of higher levels of daily MVPA (similar to that observed in our monoADS group), or increments in DGv may proceed in a nonlinear fashion, with smaller increases for patients with lower daily MVPA. Therefore, the limited participation in MVPA in our MS group may have limited our ability to detect its relationship with nDGv. Importantly, the hippocampus is involved in the complex cognitive processing associated with certain kinds of physical activity and exploratory behavior.³⁶ To follow this argument, we cannot exclude reverse causality—specifically, the possibility that MS-related insult to hippocampal structure and function led to reduced engagement in physical activity in our MS group.

Hippocampal subfield segmentation is feasible in children and adolescents using the 3D-T1 1.5T sequences acquired,³⁷ but

our DG measures would have been enhanced by hippocampal-targeted high-resolution sequences. Future longitudinal studies should evaluate the effects of physical activity levels on age-expected regional and whole brain growth over time, which has been recently found to be affected even in children with monophasic demyelination.³⁸

We show that moderate to vigorous exercise associates with increased size of the DG in children who have recovered from monophasic demyelination. Our results also show that the relationship between MVPA and DGv in MS may be more complicated, possibly confounded by other factors, such as inflammation or therapy; more specific imaging techniques may be required to quantify these factors. Longitudinal design with controlled intervention would also reduce confounding factors.

Author contributions

G. Longoni: study concept and design, analysis and interpretation of data, and drafting of the manuscript. R. A. Brown: analysis and interpretation of data and critical revision of the manuscript for intellectual content. B. Aubert-Broche: analysis and interpretation of data. S.A. Grover: data acquisition and critical revision of the manuscript for intellectual content. H. Branson: data acquisition and critical revision of the manuscript for intellectual content. D. Fetco: analysis of data and critical revision of the manuscript for intellectual content. A. Bar-Or, critical revision of the manuscript for intellectual content and funding for the research. R.A. Marrie: critical revision of the manuscript for intellectual content and funding for the research. R. W. Motl: critical revision of the manuscript for intellectual content. D.L. Collins: critical revision of the manuscript for intellectual content. S. Narayanan: critical revision of the manuscript for intellectual content. D.L. Arnold: critical revision of the manuscript for intellectual content and funding for the research. B.L. Banwell: study concept and design, critical revision of the manuscript for intellectual content, and funding for the research. E.A. Yeh: study concept and design, critical revision of the manuscript for intellectual content, and funding for the research.

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