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Strain and sex differences in somatosensation and sociability during experimental autoimmune encephalomyelitis



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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease effecting around 1 million people in the US. This disease is associated with physical symptoms such as fatigue, weakness, pain and psychological symptoms such as mood problems and diminished sociability. MS also has been shown to be sexually biased toward females. In this project we have used the experimental autoimmune encephalomyelitis (EAE) and relapsing remitting experimental autoimmune encephalomyelitis (RR-EAE), the mouse model for MS. We hypothesized that EAE progression is associated with changes in muscle strength, balance, pain, and sociability and that these variations are linked to sex and/or strain. Our results indicate that strain but not sex influenced differences in muscle strength and balance during EAE, and both sex and strain have an impact on sociability and mechanical nociception, regardless of EAE disease status. Our goal is to provide some insight about the change in social behavior of MS patients and its effect on their social and day to day activities.

EXPERIMENTAL DESIGN



- Training**
1. Deacon's test
 2. Hall's test
 3. Kondziela's test

- Assessments**
1. Deacon's test
 2. Hall's test
 3. Kondziela's test
 4. Von Frey's test
 5. Crawley's test

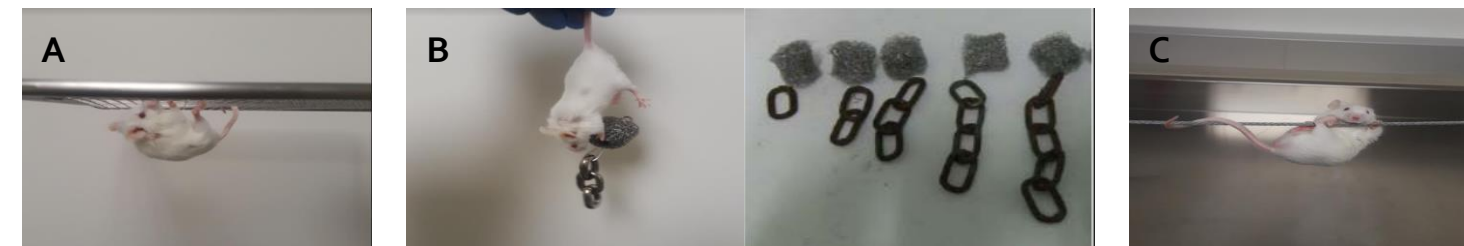
- Time-points**
1. Baseline
 2. Preclinical
 3. Clinical
 4. Recovery

- Treatment**
1. EAE immunization: C57BL/6: MOG + Ptx
SJL: PLP + Ptx
 2. Sham immunization: C57BL/6 & SJL: CFA + saline

- START (7 dpi)**
1. Body weight
 2. Clinical scoring scale: 0 = no disease
1 = limp tail
2 = hindlimb paresis
3 = hindlimb paralysis
4 = hindlimb paresis
5 = moribund/dead

- END (28 dpi)**

Somatosensory Assessments

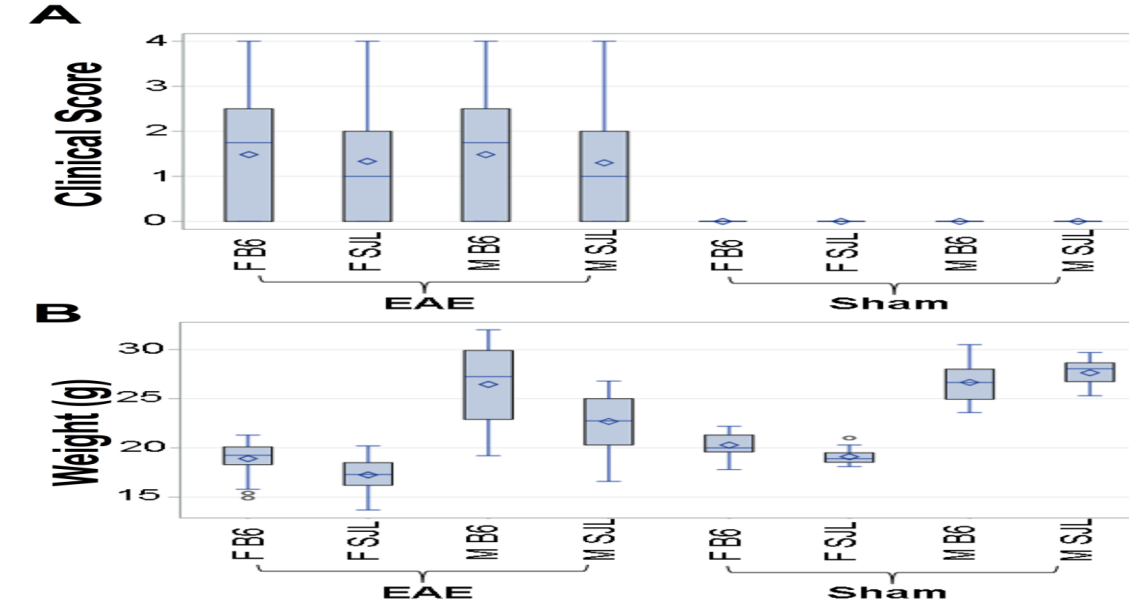


- A. Kondziela's inverted grid test
B. Deacon's weights test
C. Hall's rope grip test
D. Von Frey's mechanical nociception test

Sociability Assessment-Crawley's test

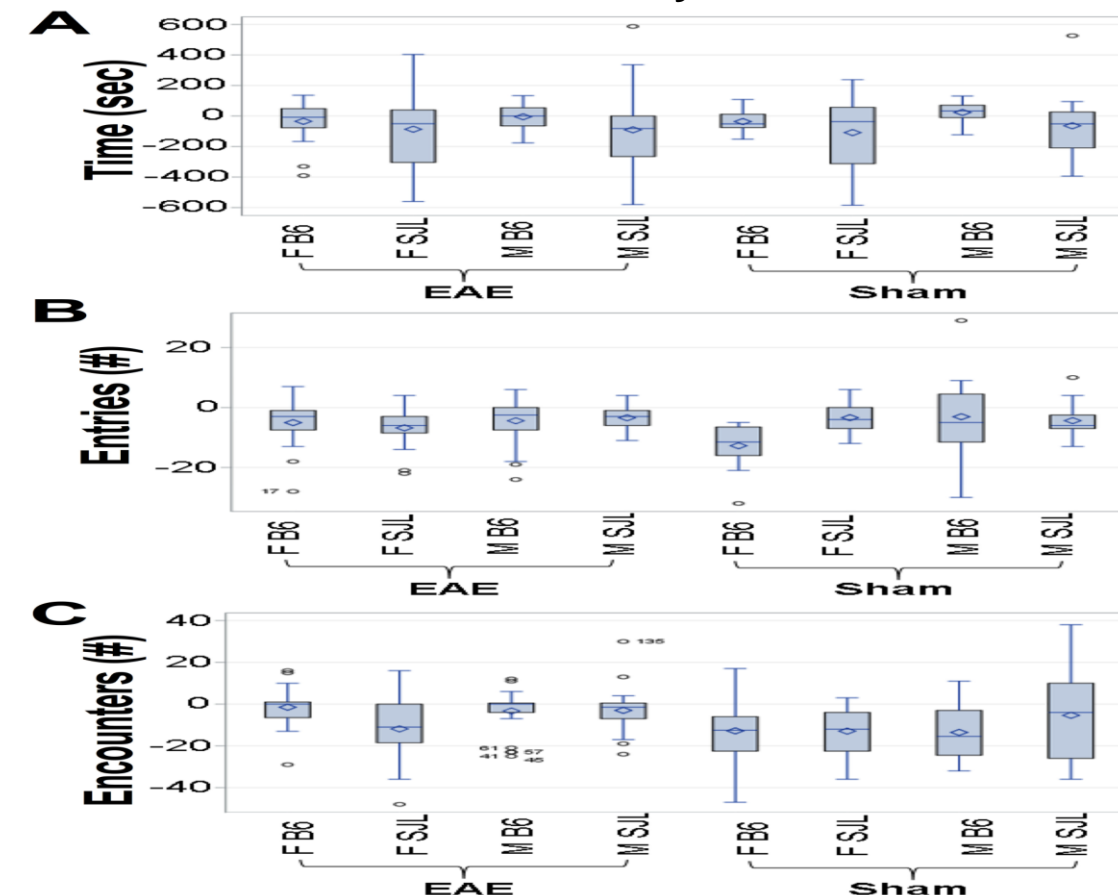


Clinical Scoring and Body Weight



Clinical scoring and change in body weight, (Mean ± Std Dev) The pattern of change in clinical score and percentage of body weight relative to baseline was consistent with the expectation for EAE and sham group in both sexes and strains (n = 6 for EAE and n = 4 for sham).

Sociability



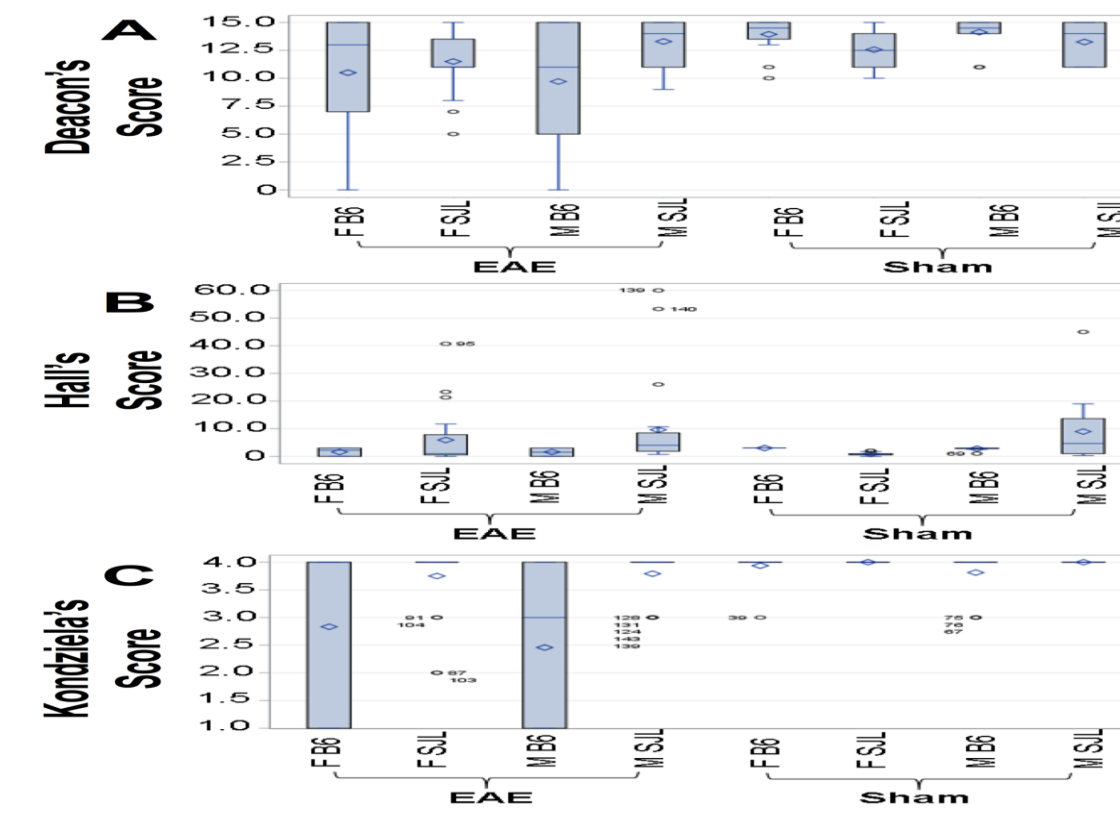
Time spent with empty cylinder and novel object (Mean ± Std Dev)

Data was analyzed by ANOVA Type I/II/III SS for disease stage and it was adjusted for baseline measurements.

A) There were no significant differences in time spent in the chamber with the novel conspecific versus the time spent in the opposite chamber, B) There were significant interactions between sex and strain for distributions in the number of entries into the chambers (p < 0.01) and between treatment, sex, and strain (p < 0.01). C) Variation between phases for number of interaction with the novel conspecific's cylinder showed a trend for strain, p=0.0882.

RESULTS

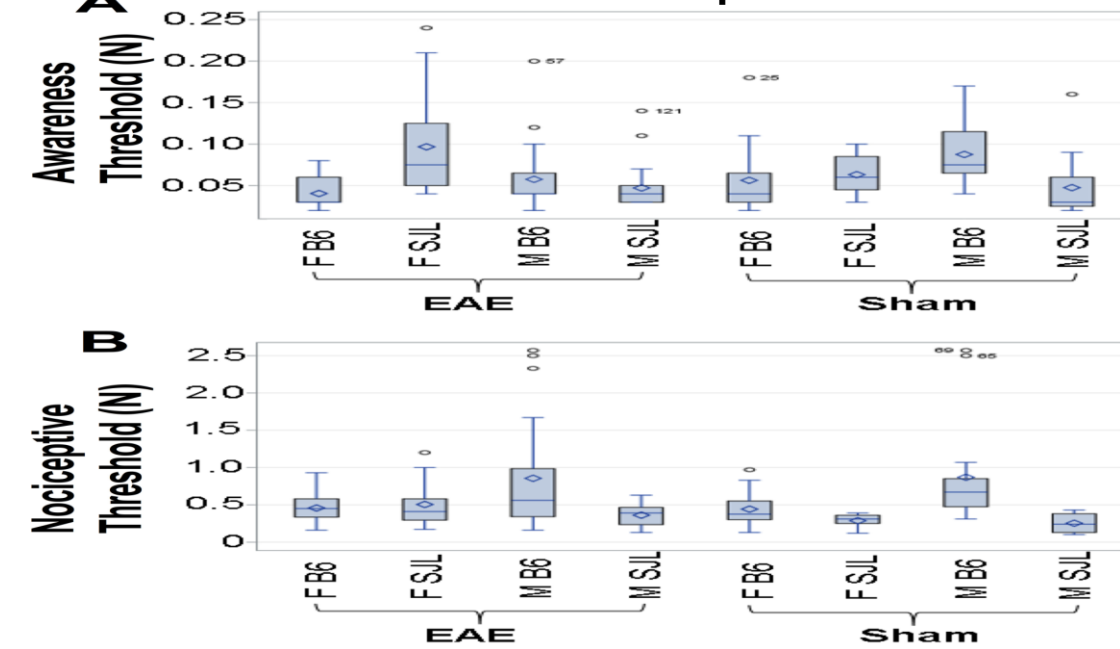
Balance & Muscle Strength



Score of somatosensory assessments (Mean ± Std Dev).

Data was analyzed by ANOVA Type I/II/III SS for disease stage and it was adjusted for baseline measurements. Distributions in Deacon's weight lift scores showed a significant interaction between treatment and strain (p < 0.01). B) There were no significant differences in the distributions of scores for the Hall's rope grip test. C) Variations in Kondziela's inverted grid over the course of disease were significantly affected by the interaction of treatment and strain (p < 0.0001).

Mechanical Nociception



Performance on the Von Frey's test (Mean ± Std Dev)

Data was analyzed by ANOVA Type I/II/III SS for disease stage and it was adjusted for baseline measurements. A) "Awareness" threshold: the lowest force needed to elicit a startle response. There were significant main effects of sex (p < 0.05) and strain (p < 0.01), as well as interactions between treatment and strain (p = 0.001) and between sex and strain (p < 0.001) B) Nociceptive threshold: the lowest force needed to induce nociceptive responses. There was a significant main effect of strain (p < 0.0001) and a significant interaction between sex and strain (p < 0.01). There was a trend towards a significant interaction between treatment and strain (p = 0.0906).

Summary of Data Analysis

Table 1. Effect of treatment, sex and strain on EAE score, muscle strength and balance, mechanosensitivity, and social responses. Estimates of mean differences were adjusted for clinical stages of disease, and each outcome was adjusted for baseline response; p values. Significant differences are in bold.

Outcome	Treatment	Sex	Strain	Treatment*Sex	Treatment*Strain	Sex*Strain	Treatment*Sex*Strain
	EAE vs. Sham	Female vs. Male	B6 vs. SJL				
EAE Score							
Clinical Score (0-5)	1.835; <0.001	0, 1.00	0, 1.00	0.042; 0.9303	0.229; 0.6305	0, 1.00	-0.042; 0.9507
Weight (g)	-5.917; <0.0001	-8.675; <0.0001	-0.863; 0.2105	3.858; 0.0002	4.563; <0.0001	2.309; 0.0385	-4.429; 0.0005
Somatosensory Integration							
Muscle strength & balance							
Deacon's Score	-0.389; 0.7499	0.750; 0.5749	-0.500; 0.7083	-0.917; 0.5954	-5.389; 0.0022	0.333; 0.8600	2.000; 0.1430
Hall's Score	3.417; 0.2791	-3.617; 0.2668	-2.526; 0.4618	3.022; 0.4950	-5.847; 0.1881	3.275; 0.4997	-2.258; 0.7183
Kondziela's Score	-0.277; 0.2935	0, 1.00	-0.250; 0.3877	-0.056; 0.8816	-1.528; <0.0001	0.167; 0.8835	0.3889; 0.4616
Mechanosensitivity							
Awareness Threshold (N)	0.019; 0.2291	0.041; 0.0223	0.047; 0.0093	0.037; 0.1124	-0.078; 0.0010	-0.093; 0.0003	0.055; 0.0916
Nociceptive Threshold (N)	0.063; 0.6787	0.099; 0.5529	-0.967; <0.0001	0.220; 0.3048	-0.364; 0.0006	0.678; 0.0050	0.240; 0.4002
Social Interaction							
Time (sec)	-26.667; 0.6630	-44.813; 0.5040	87.25; 0.1942	48.583; 0.5746	-1.648; 0.9848	-14.813; 0.8758	-18.833; 0.8777
Entries (number)	0.959; 0.6712	1.000; 0.6859	1.313; 0.4691	-4.375; 0.1719	-2.313; 0.4691	-10.688; 0.0026	14.438; 0.0033
Encounters (number)	2.375; 0.6983	-7.563; 0.1150	-8.188; 0.0882	-1.313; 0.8315	7.896; 0.2018	8.32; 0.2199	2.354; 0.7873

All analyses were performed using SAS software, version. Somatosensory, mechanosensitivity, and social scores variation across time was calculated, and this value was compared among groups according to treatment, sex, and strain. Single and multiple linear regression were used to relate each outcome to treatment, sex, and strain. All regression were baseline normalized and adjusted for each outcome and severity of disease. For all tests, p < 0.05 was deemed statistically significant.

DISCUSSION

- To our knowledge this is the first attempt to assess the effects of strain, sex, and disease stage on muscle strength and/or balance, pain, and sociability during EAE and RR-EAE.
- B6 and SJL mice performed differently on the Deacon's weight lift and Kondziela's inverted grid tests thus, these tests can be valuable assays to elucidate motor and balance capabilities during EAE neuropathology.
- Notably, there significant differences for the number of entries during the sociability test but not for time and number of encounters. Likewise, there were no differences for self-focused behaviors (data not shown).
- One limitation of this study was that we did not investigate the performance of female SJL after a relapse. Therefore, future studies should include the observation during relapses and chronic stage (~42 dpi) to evaluate the efficacy of using these tests to assess strain and sex differences after a relapse or at the chronic stage.