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## Postural control strategy during standing is altered in patients with multiple sclerosis

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1 **POSTURAL CONTROL STRATEGY DURING STANDING IS ALTERED IN**  
2 **PATIENTS WITH MULTIPLE SCLEROSIS**

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43

44 **Abstract**

45           Disturbances in balance are one of the first reported symptoms of Multiple Sclerosis  
46 (MS), yet limited research has been performed to classify the postural control deficits in this  
47 population. This study investigated the variability present in the sway patterns during quiet  
48 standing in patients with MS (PwMS) and healthy controls. Subjects were assessed (eyes open,  
49 closed) standing on a force platform. Variability of the sway patterns was quantified using a  
50 measure of amount of variability (root mean square; RMS) and two measures of temporal  
51 structure of variability (Lyapunov Exponent – LyE; Approximate Entropy – ApEn). RMS  
52 results revealed significantly higher amount of variability in the sway patterns of PwMS. PwMS  
53 also exhibit increased regularity (decreased ApEn) and decreased divergence (decreased LyE)  
54 during standing compared to healthy controls. Removing vision resulted in significantly  
55 decreased divergence (decreased LyE) in the MS subject group. These changes in the temporal  
56 structure correspond well with the theoretical model of the optimal movement variability  
57 hypothesis and the results support using variability measures to understand the mechanisms that  
58 underline postural control in PwMS and possibly other neurodegenerative disease pathologies.

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## 62 **Introduction**

63 Multiple Sclerosis (MS) is the most common disabling neurological disease among  
64 young adults, with the majority of patients diagnosed between 20 and 50 years of age [10]. The  
65 disease specific mechanisms which contribute to impaired balance and postural control likely  
66 stem from inflammation of the CNS which results in damage to axons leading to delays in  
67 conduction [13] and can block the conduction of potentials along pathways throughout the CNS  
68 [1]. Additionally, delayed somatosensory evoked potentials are related to postural response  
69 delays in persons with MS (PwMS) [4]. These delays would affect postural control under any  
70 circumstance where somatosensory information is being utilized [15], including quiet standing.

71 To quantify balance deficits in PwMS, sway patterns have been investigated during  
72 several tasks including quiet standing [7, 34], reaching [17, 34], and under perturbation  
73 conditions [4]. All of these studies relay information regarding only the amount of sway  
74 occurring during the task. Here, we propose to enhance the existing understanding about balance  
75 in PwMS by investigating sway variability to discern characteristics about the motor control  
76 strategies used to maintain standing balance. If posture is viewed as the dynamic stability of a  
77 continuously moving body, then the temporal structure of the sway path can provide information  
78 regarding the behavior of the moving body over time. Linear methods of examining variability  
79 within a time series provide information on the amount or magnitude of variability within the  
80 signal by employing averaging procedures which assume that variations between repetitions of a  
81 task are independent of future and past repetitions which has been proven to be false in posture  
82 tasks [11]. Assessed through nonlinear measures, variability reflects multiple options for  
83 movement, providing for adaptive strategies that are not reliant on rigid programs for each task  
84 or for each changing condition encountered [11, 12]. The optimal movement variability  
85 hypothesis contends that a healthy system exhibits an optimal state of movement variability

86 characterized by maximum effective adaptability of the system to environmental stimuli and  
87 stresses. To acquire such insights, variability in postural control has been investigated previously  
88 in children and in Parkinson's disease patients [14, 21] and briefly in PwMS to measure the  
89 effects of a rehabilitation intervention which showed that postural sway variability changed  
90 (RMS increased, LyE decreased) as a result of resistance training exercise [16].

91         The purpose of this research was to investigate upright postural control in PwMS during  
92 quiet standing with eyes open and closed. It is hypothesized that 1) PwMS will demonstrate  
93 increased amount of variability due to delayed feedback from the sensory systems and due to the  
94 previously identified exaggerated sway during perturbations [4]; 2) PwMS will demonstrate  
95 more repetitive patterns in the temporal structure of variability as compared to healthy controls  
96 since PwMS have already shown less velocity scaling and more amplitude scaling in response to  
97 a translating surface perturbation due to longer latency postural responses [4]; 3) that within  
98 PwMS, differences in both the amount and temporal structure of sway variability will be found  
99 in the eyes closed compared to the eyes open condition since postural control in PwMS has  
100 previously been shown to change with altered sensory input [5].

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103

## 104 **Methods**

### 105 *Participants*

106 PwMS (n = 15, age  $45.1 \pm 10.5$ ), recruited through the University's Medical Center, and  
107 healthy controls (n = 15, age  $39.4 \pm 11.7$ ), recruited through the community, provided informed  
108 consent. PwMS and healthy controls were age, height, and weight matched (Table 1). EDSS  
109 score, the standard clinical disability scale for PwMS [18], was mean  $4.5 \pm 1.8$ , median 5.2. The  
110 research protocol was approved by the University's Institutional Review Board.

111 INSERT TABLE 1 ABOUT HERE

### 112 *Quiet standing protocol*

113 Subjects stood quietly for five minutes with eyes open approximately 10 meters from a  
114 wall, while COP data was collected. Feet were placed at approximately hip width apart, toes  
115 facing forward. After a mandatory rest period of at least three minutes, subjects again stood  
116 quietly for five minutes with eyes closed. Kinetic data was collected using a force platform  
117 (Kistler Model: 9281-B11; Amherst, NY; 10 Hz) [16]. Unfiltered data was cropped to 2000 data  
118 points (approximately 3 ½ minutes) as some PwMS were unable to complete the full 5 minutes  
119 of quiet standing due to reports of discomfort and tiredness. Data was collected and analyzed  
120 unfiltered so as not to mask or remove any dynamical properties or variability present within the  
121 system [11].

### 122 *Data analysis*

123 The coordinates of the center of pressure (COP) in the medial-lateral (ML) and antero-  
124 posterior (AP) directions were calculated for each trial. Amount of sway variability was  
125 quantified using the root mean square (RMS), and was calculated from the COP time series for  
126 both directions using customized MatLab software (The Mathworks Inc., Natick, MA) [26].



127 Temporal structure of sway variability was also quantified from both directions using Lyapunov  
128 Exponent (LyE) and Approximate entropy (ApEn). Examining the temporal structure of the time  
129 series of the COP can provide information regarding the behavior of the moving body over time  
130 since even during quiet stance, the center of mass of a person is continuously moving. The  
131 largest LyE is a measure of the rate at which nearby trajectories in state space diverge and the  
132 system's sensitivity to initial conditions thereby [32]. Lack of divergence in the sway patterns  
133 will produce small values for the LyE and vice versa.

134 The LyE was calculated using the Chaos Data Analyzer Professional software [31] with  
135 an embedding dimension of 6 which was calculated using a Global False Nearest Neighbor  
136 analysis [32]. ApEn quantifies how predictable and regular are data patterns within a time series,  
137 thus evaluating the complexity of a time series [24, 25]. ApEn was calculated using customized  
138 MatLab software based upon the methodology of Pincus [24, 25] (lag = 6, m = 2, r = 0.2 were  
139 used as default parameters).

140 Group means for RMS, LyE, and ApEn were calculated for healthy controls and PwMS  
141 during the eyes open and eyes closed conditions. Because LyE and ApEn were computed  
142 separately for ML and AP [29], two separate 2x2 repeated measures ANOVA models were  
143 employed to test for effects of GROUP (MS v. Control) and CONDITION (eyes open v. closed).  
144 To compare the current dataset with previously published findings on COP sway in PwMS, 95%  
145 sway area, mean velocity, and range were calculated for the resultant COP time series for each  
146 group while standing with eyes open and compared using independent t-tests. Independent and  
147 dependent t-tests were used for post hoc analysis when significant group by condition  
148 interactions were identified. Statistical analysis was performed using SPSS 20.0 (SPSS, Inc.,  
149 Chicago, IL) with level of significance set at 0.05.

150 **Results**

151 *Linear Measures*

152 PwMS had significantly greater sway area ( $p = 0.002$ ) and greater median sway velocity  
153 ( $p = 0.004$ ) compared to healthy controls during eyes open quiet standing. Sway range increased  
154 in PwMS as compared to controls; however this increase was not statistically significant ( $p =$   
155  $0.070$ ) (Table 1).

156 In the ML direction, the RMS demonstrated a significant main effect for GROUP ( $F_{1,29}$ :  
157  $5.91$ ,  $p = 0.022$ ) where PwMS had larger RMS values. There was also a significant main effect  
158 for CONDITION ( $F_{1,29}$ :  $64.16$ ,  $p < 0.001$ ) where eyes closed resulted in larger RMS values. No  
159 significant interaction ( $F_{1,29}$ :  $0.082$ ,  $p = 0.777$ ) was found (Figure 1A).

160 In the AP direction, RMS demonstrated a significant main effect for GROUP ( $F_{1,29}$ :  $8.04$ ,  
161  $p = 0.009$ ) where PwMS had larger RMS values. There was also a significant main effect for  
162 CONDITION ( $F_{1,29}$ :  $131.94$ ,  $p < 0.001$ ) where eyes closed resulted in larger RMS values. No  
163 significant interaction ( $F_{1,29}$ :  $0.412$ ,  $p = 0.526$ ) was found (Figure 1B).

164 INSERT FIGURE 1 HERE

165 *Nonlinear measures*

166 For LyE in the ML direction, a significant main effect for GROUP was found ( $F_{1,29}$ :  
167  $14.98$ ,  $p = 0.001$ ) where PwMS had lower LyE values compared to healthy controls. No  
168 significant main effect was found for CONDITION ( $F_{1,29}$ :  $3.57$ ,  $p = 0.070$ ). A significant  
169 interaction was found for GROUP x CONDITION ( $F_{1,29}$ :  $6.52$ ,  $p = 0.017$ ). Post-hoc tests  
170 revealed that within the MS patient group, the LyE was significantly decreased ( $t$ :  $2.50$ ,  $p =$   
171  $0.026$ ) in the eyes closed condition compared to eyes open. Within the healthy control group,  
172 there was no difference ( $t$ :  $-0.66$ ,  $p = 0.516$ ) in the LyE values due to CONDITION. PwMS had

173 significantly lower LyE values compared to controls during the eyes closed condition (t: 4.59, p  
174 < 0.001) but not during the eyes open condition (t:-1.57, p = 0.128) (Figure 2A).

175 In the AP direction, LyE analysis revealed a significant main effect for GROUP ( $F_{1,29}$ :  
176 10.13, p = 0.004) where PwMS had significantly lower LyE values. No significant main effect  
177 was found for CONDITION ( $F_{1,29}$ : 0.014, p = 0.906). A significant interaction was found for  
178 GROUP x CONDITION ( $F_{1,29}$ : 7.74, p = 0.010). Post-hoc tests revealed that within the MS  
179 patient group, the LyE was significantly decreased (t: 2.167, p = 0.049) in the eyes closed  
180 condition compared to eyes open. Within the healthy control group there was no difference (t:  
181 1.81, p = 0.092) in LyE values due to CONDITION. PwMS had significantly lower LyE values  
182 compared to controls during the eyes closed condition (t: 3.67, p = 0.001) but not during the eyes  
183 open condition (t: 0.846, p = 0.405) (Figure 2B).

184 INSERT FIGURE 2 HERE

185 The ApEn in the ML direction revealed a significant main effect for GROUP ( $F_{1,29}$ :  
186 8.284, p = 0.008) where PwMS had significantly lower ApEn values. There was no significant  
187 main effect for CONDITION ( $F_{1,29}$ : 0.821, p = 0.373) and no interaction ( $F_{1,29}$ : 0.614, p = 0.440)  
188 (Figure 3A).

189 ApEn in the AP direction there was no significant main effect for GROUP ( $F_{1,29}$ : 0.591, p  
190 = 0.449) or for CONDITION ( $F_{1,29}$ : 0.837, p = 0.368). No significant interaction ( $F_{1,29}$ : 0.723, p  
191 = 0.111) was found (Figure 3B).

192 INSERT FIGURE 3 HERE

193

194 **Discussion**

195 Our results indicate that PwMS have altered COP sway variability during quiet stance in  
196 both the ML (RMS, LyE, ApEn) and AP (RMS, LyE, ApEn) directions. Results also indicate  
197 that removing vision causes changes in COP sway variability with PwMS in the ML (RMS, LyE)  
198 and AP (RMS, LyE) directions. Increased sway area and sway velocity in PwMS indicate that  
199 the current dataset is in agreement with previously published data [2, 5, 34]. These findings  
200 support our first hypothesis and agree with previous studies which reported that people with MS  
201 have increased amount of sway variability while standing quietly [7, 30, 34]. The increased RMS  
202 observed in the PwMS is possibly the result of slowed somatosensory feedback [4].  
203 Somatosensory information has been suggested as the most critical sensory mechanism for  
204 control of posture and the increase in RMS may reflect a deficiency in the somatosensory  
205 feedback loop [28]. Adequate postural control occurs as a function of somatosensory information  
206 being integrated with vestibular information necessary for an adequate motor response to  
207 maintain control of stance [8]. In MS, it is possible that the integration of vestibular and  
208 somatosensory information is disrupted and leads to the increased amount of sway variability.  
209 The increased RMS could also be attributed to the effects of spasticity since up to 80% of PwMS  
210 report problems with spasticity, the velocity-dependent increase in tonic stretch reflexes and  
211 exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex[20, 27]. While the  
212 present study did not measure spasticity, it has been reported that PwMS who have high  
213 spasticity, as measured soleus Hoffman reflex, exhibit increased COP sway area [30]. Thus, it is  
214 also possible that a combination of deficits in sensory information processing and motor  
215 impairment such as spasticity contribute to increased COP sway RMS. Fatigue is also a heavily  
216 reported symptom in PwMS [9] and because some of the subjects in the present study could not

217 stand for the entire 5-minute trial length, it is likely that they were affected by fatigue. Chung et  
218 al [7] reported that in PwMS, reported fatigue was moderately correlated with COP variability in  
219 the ML and AP direction. Thus, it is possible that in the present study, fatigue also contributed to  
220 the increased COP sway RMS in PwMS compared to controls.

221         The results also support our second hypothesis since both LyE and ApEn were  
222 significantly lower in PwMS. LyE quantifies separation between continuous paths of movement  
223 and whether these paths will expand or contract within a dynamical system [32]. ApEn is a  
224 probability measure that can quantify the predictability of vectors identified within a dynamical  
225 system [32]. Decreased LyE and ApEn values of PwMS compared to controls indicate a sway  
226 pattern with less divergence and a more repeatable and predictable pattern. This direction of  
227 change for LyE and ApEn compared to controls could indicate an inability to adapt to  
228 perturbations in PwMS. Since the sway patterns of PwMS are restricted, PwMS could exhibit an  
229 increased dependence on repeatable movement patterns in order to maintain upright balance. In  
230 other words, if the task demands or environmental conditions were to change, PwMS could be  
231 less able to adapt and maintain task performance. This breakdown of task performance has been  
232 exhibited in PwMS [4]. When exposed to a surface translation during standing, PwMS responded  
233 with delayed and excessive scaling of postural response amplitude. This scaling was related to  
234 the patient's spinal somatosensory evoked potential latencies [4], indicating a relationship  
235 between response to perturbation and somatosensory conduction speed. During quiet standing, it  
236 has been reported that the dynamics of muscle firing patterns do not necessarily map directly to  
237 the dynamics at the movement task level [25]. Thus, for PwMS, normal muscle firing patterns  
238 are likely disrupted due to delayed somatosensory information receipt and due to axonal damage  
239 which could influence the dynamics of the standing task. This conclusion is speculative but it has

240 been reported that neural circuitry which is successful in producing a desired outcome has a  
241 higher probability of being accessed again for similar tasks [19]. This would indicate an  
242 increased reliance on past patterns of movement that have proved successful regardless of the  
243 received somatosensory information or the muscle firing activity. For PwMS, if a novel or  
244 unexpected task was necessary, reliance on past patterns of movement without the ability to  
245 adapt to the presented scenario could result in failure to maintain postural control.

246 Our final hypothesis was partially supported since LyE also showed a significant group  
247 by condition interaction and RMS showed an effect of condition, but ApEn was not affected by  
248 removing vision. The interaction identified for LyE indicates that when vision was removed in  
249 PwMS, the divergence of the sway trajectories decreased in PwMS only. One possible  
250 explanation for this interaction is an impaired ability to properly perform sensory re-weighting in  
251 the MS group. Control of posture requires complex integration of sensory information which is  
252 weighted based upon accuracy or availability of the information and/or environmental conditions  
253 [23]. It's possible that when vision was removed, PwMS couldn't account for the loss of sensory  
254 input by relying more heavily on somatosensory and vestibular input, so LyE decreased further  
255 in both the ML and AP directions. Previous studies have also demonstrated that PwMS have  
256 altered postural control with the alteration of one sensory input [5, 34]. To confirm the effect of  
257 sensory alteration on balance in PwMS, it is necessary to examine a variety of sensory alteration  
258 conditions and determine under which conditions the patients are most or least affected.

259 Employing nonlinear measures of variability to examine COP sway allowed us to gain a  
260 unique perspective on postural control in PwMS. The COP time series reflects the net motor  
261 control signal output and encompasses the position of the whole body center of gravity and the  
262 muscle activity involved in maintaining balance [6]. In PwMS, the COP time series showed

263 decreased LyE and ApEn values which indicate less behavioral complexity in the sway paths as  
264 compared to controls. The decrease in complexity in the PwMS corresponds well with the  
265 optimal movement variability model. The theory states that optimal movement variability has a  
266 highly complex structure and is associated with healthy movement patterns which reflect a rich  
267 behavioral state allowing for diverse movement strategies [33]. Conversely, a more rigid system  
268 has reduced adaptive capability [22] which indicates that a system may be less able to produce a  
269 physiological response to a particular task or to a system perturbation [6]. Compared to healthy  
270 controls, PwMS are less complex, more rigid, and have less movement strategies available to  
271 them. Future studies should also investigate treatments that help PwMS return to a state of  
272 optimal variability, possibly by introducing variability into the process of learning a new motor  
273 task [3]. Additionally, an investigation of the relationship between postural control and specific  
274 system (sensory, pyramidal, cerebellar) disability could provide insight regarding whether there  
275 is a common source of disability which relates to postural control deficits.

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361 *Figure Legends*

362 **Figure 1A.** RMS of the ML direction. Significant main effect for \*GROUP ( $p < 0.05$ ) and  
363 §CONDITION ( $p < 0.05$ ).

364

365 **Figure 1B.** RMS of the AP direction. Significant main effect for \*GROUP ( $p < 0.05$ ) and  
366 §CONDITION ( $p < 0.05$ ).

367

368 **Figure 2A.** LyE for the ML direction. Significant main effect for \*GROUP ( $p = 0.001$ ).  
369 Significant interaction for CONDITION x GROUP ( $p < 0.05$ ); †Post hoc test significant  
370 difference ( $p < 0.05$ ).

371

372 **Figure 2B.** LyE for the AP direction. Significant main effect for \*GROUP ( $p < 0.05$ ).  
373 Significant interaction for CONDITION x GROUP ( $p < 0.05$ ); †Post hoc test significant  
374 difference ( $p < 0.05$ ).

375

376 **Figure 3A.** ApEn for the ML direction. Significant main effect for \*GROUP ( $p < 0.05$ ).

377

378 **Figure 3B.** ApEn for the AP direction.

379

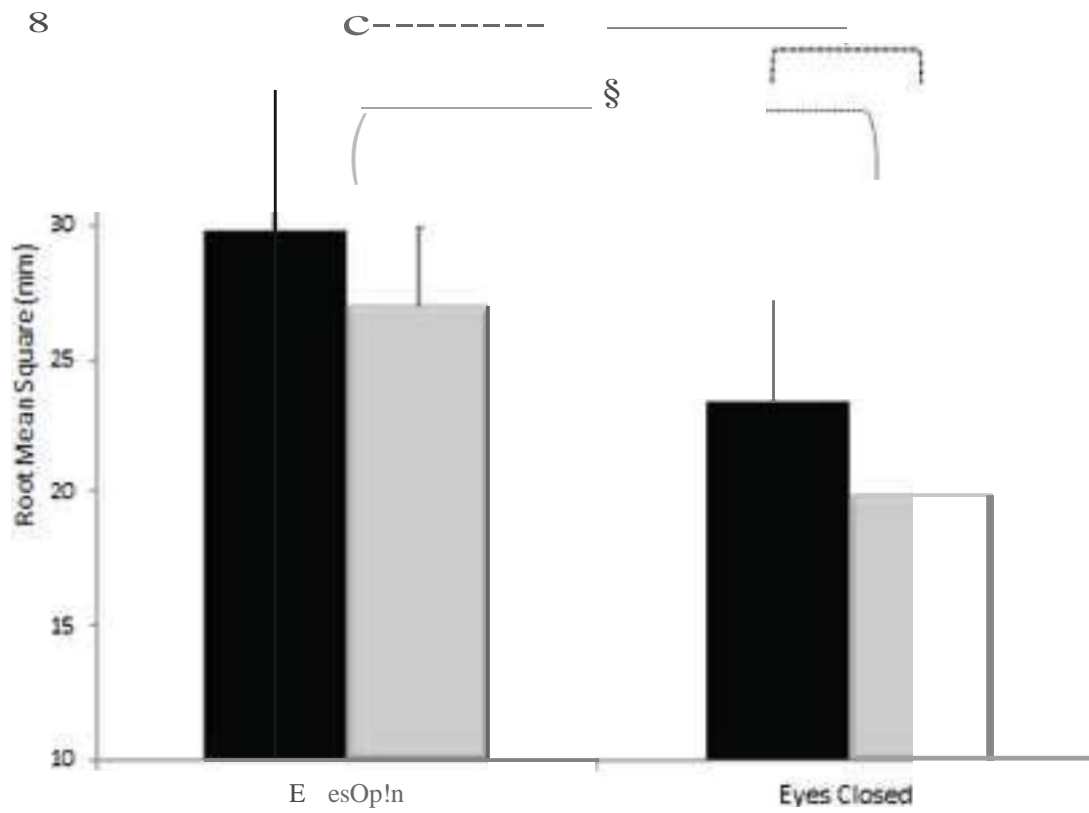
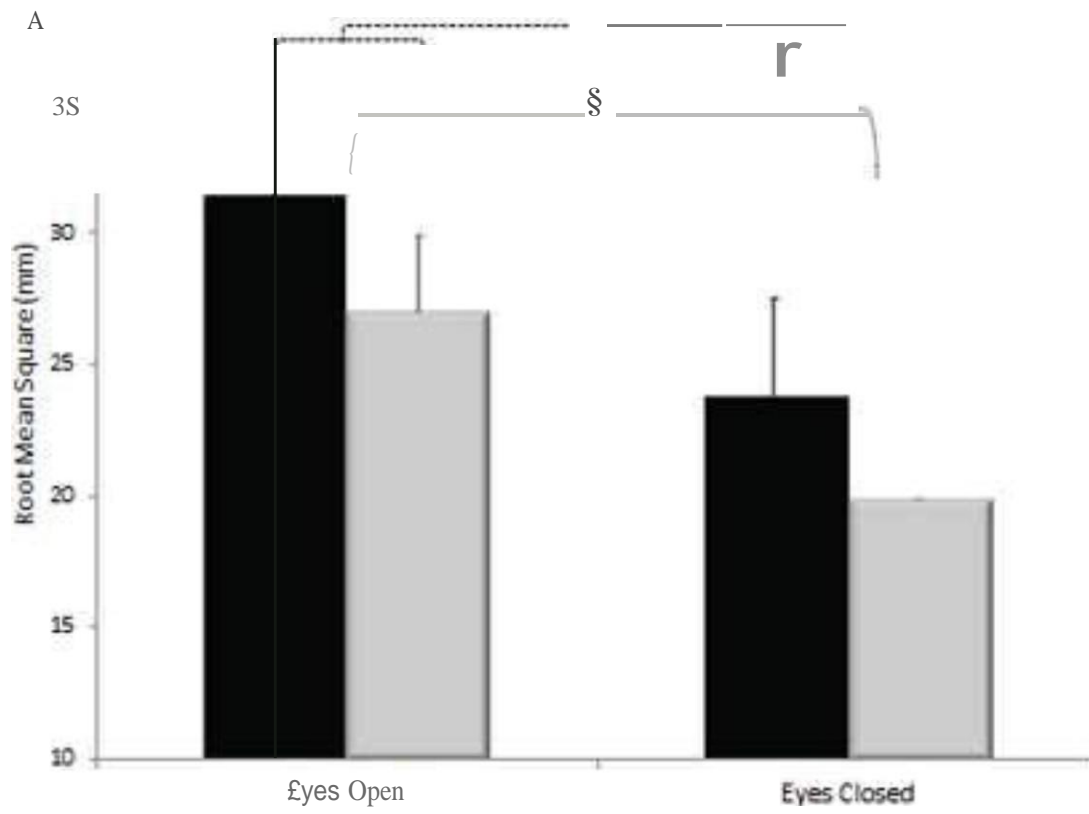


Figure  
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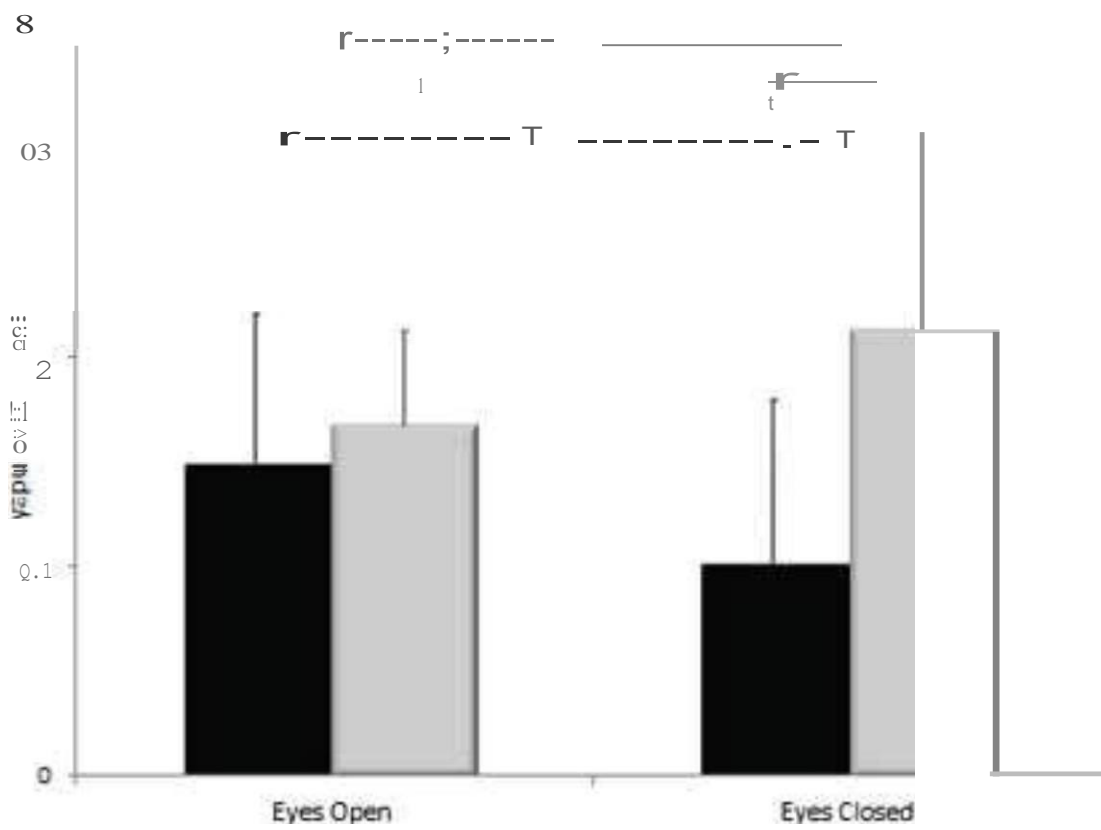
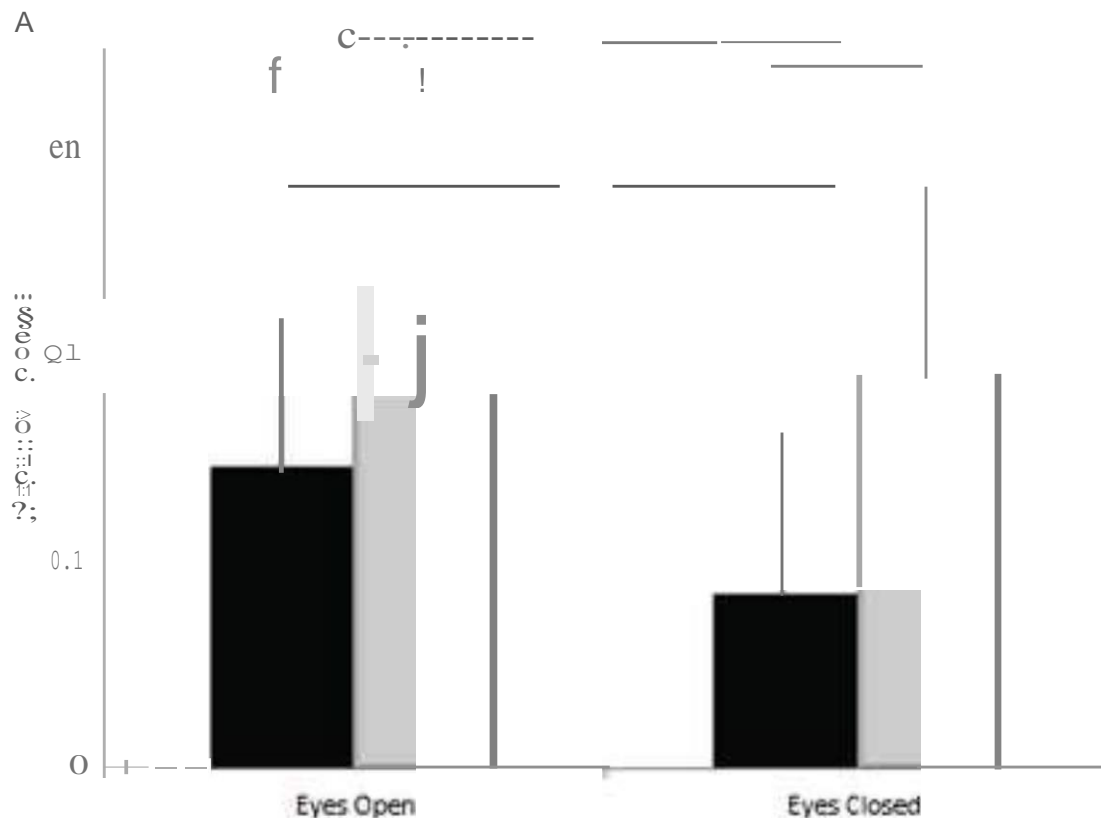
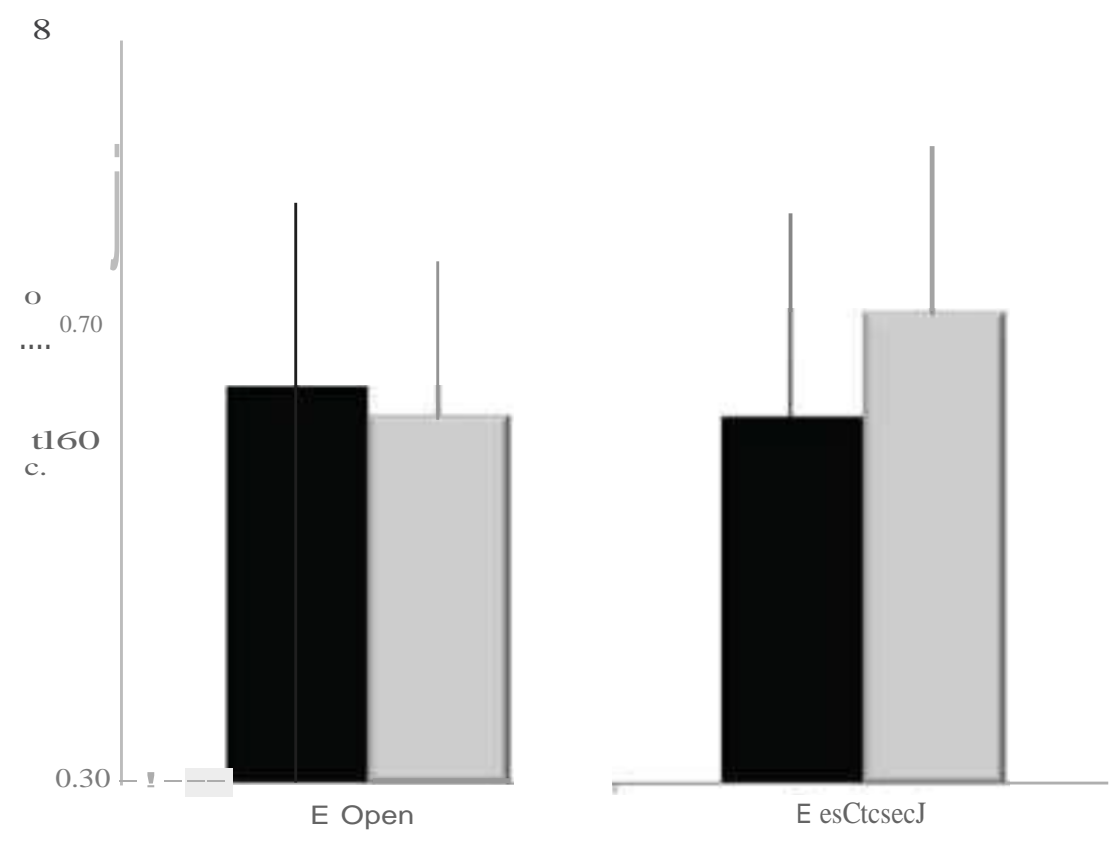
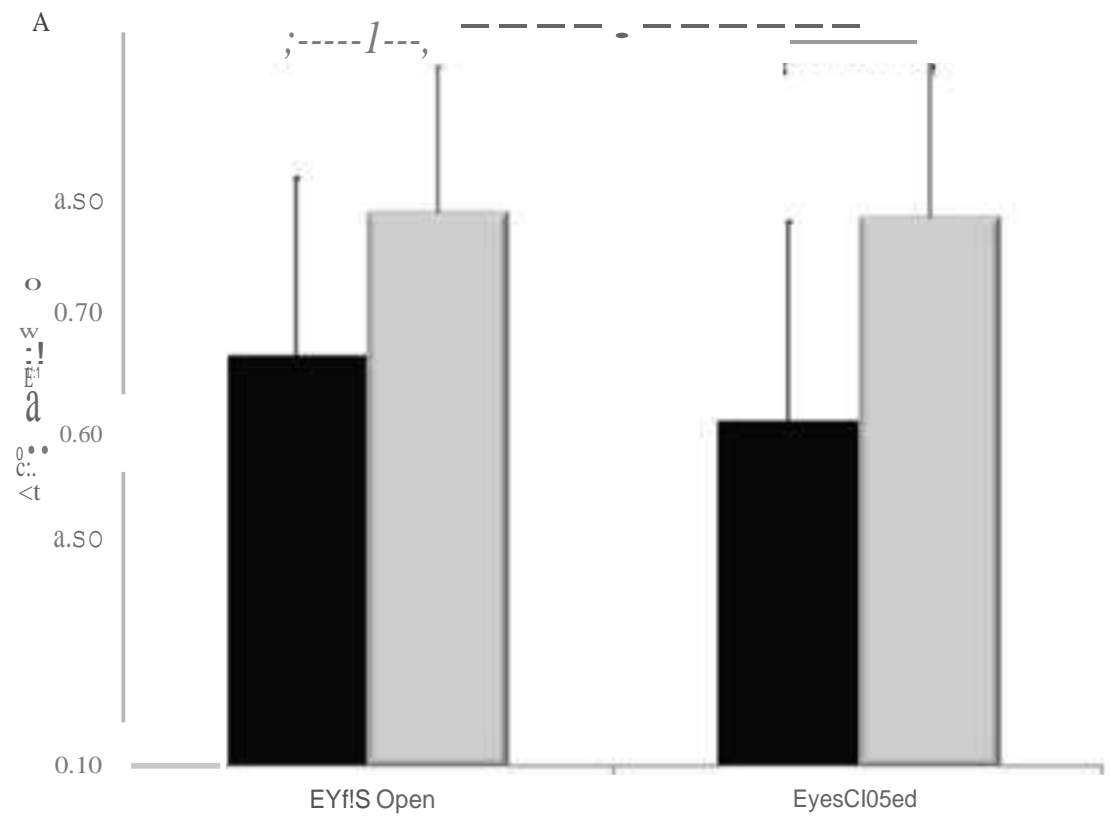


Figure3  
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1 **Table 1.** Demographic information (mean  $\pm$  std dev) for healthy controls and MS subjects. EDSS  
 2 = Expanded Disability Status Scale.

3	Characteristics	Control (n=15)	MS (n=15)	p-value
4	Age (years)	39.4 $\pm$ 11.7	45.1 $\pm$ 10.5	0.233
5	Height (cm)	157.4 $\pm$ 10.6	166.7 $\pm$ 8.9	0.903
6	Weight (kg)	66.2 $\pm$ 7.5	75.9 $\pm$ 13.1	0.104
7	EDSS Score Mean	-	4.5 $\pm$ 1.8	
8	EDSS Score Median	-	5.2	
9	Female/Male	12/3	13/2	
	95% Sway Area (mm <sup>2</sup> )	3.53 $\pm$ 2.92	12.23 $\pm$ 9.14	0.002*
	Median Sway Velocity (mm/s)	0.98 $\pm$ 0.56	3.12 $\pm$ 2.44	0.004*
	Sway Range (mm)	4.21 $\pm$ 3.64	6.91 $\pm$ 3.91	0.070

\*Significant (p < 0.05) difference between groups