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1 **A new approach to identifying the effect of diabetic peripheral neuropathy**
2 **on the ability to drive safely**

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29 **Abstract**

30 The purpose of this study was to estimate the potential for impaired driving performance
31 in current drivers with diabetic peripheral neuropathy compared to healthy controls. We
32 analysed, using a driving simulator, three important aspects of driving - use of the
33 accelerator pedal, steering wheel and eye-steering coordination - to test for any
34 differences, and then to integrate these findings to identify a unique pattern of changes in
35 people driving with diabetic peripheral neuropathy. Patients with diabetic peripheral
36 neuropathy displayed differences in use of the accelerator pedal compared to healthy
37 control drivers ($p < 0.05$) which could be a direct consequence of their sensorimotor
38 impairment due to diabetic peripheral neuropathy. Drivers with DPN used the more
39 extreme high and low positions of the pedal to a greater extent than the Control group
40 who exhibited a more graded use of the accelerator pedal over the mid-range. Eye-
41 steering coordination was also different in drivers with diabetic peripheral neuropathy
42 ($p < 0.05$) and, as it improved during the second drive, becoming closer to healthy drivers'
43 values, the occasional loss of control experienced during driving reduced. These insights
44 demonstrate that diabetic peripheral neuropathy affects multiple aspects of driving
45 performance suggesting the need for an integrated approach to evaluate the potential for
46 driving safely in this population.

47 **1. Introduction**

48 Driving can be considered as a sensorimotor process in which multiple streams of
49 information are combined and processed in order to produce an adequate motor output
50 (Siegler et al., 2001). The speed at which sensory information is processed and the motor
51 reaction times are crucial factors for successfully negotiating difficult or dangerous traffic
52 situations and for avoiding collisions (Anstey et al., 2005).

53 Different perceptual, cognitive, and motor factors have been associated with driving
54 difficulties and crash incidence (Marmeleira et al., 2009). Primarily, it has been

55 recognized that age-related changes in sensory, cognitive, and physical abilities, impair
56 driving capability (Kua et al., 2007), and in particular health status (e.g. cardiovascular
57 illnesses, diabetes mellitus, depression, and dementia) can be directly linked to the
58 occurrence of crashes in older drivers (McGwin Jr et al., 2000).

59 Diabetes leads to a wide range of complications that could impair driving performance
60 (Inkster and Frier, 2013; Seeger and Lehmann, 2011): 1) hypoglycaemia has been
61 recognized as one of the most important risk factors in causing accidents (Cox et al.,
62 2006); 2) diabetic retinopathy leads to visual deficits that can make it impossible to
63 control a vehicle; 3) diabetic peripheral neuropathy (nerve damage and loss of sensation
64 in the feet) may affect the ability to feel the pedals when driving (Inkster and Frier, 2013).
65 The International Diabetes Federation estimated that in 2017 there were 451 million
66 people with diabetes worldwide. These figures were expected to increase to 693 million
67 by 2045 It was estimated that almost half of all people (49.7%) living with diabetes are
68 undiagnosed (Cho et al., 2018). Public Health England estimates that 3.8 million people
69 in England, around 9% of the adult population, now have diabetes (Public Health England
70 press release, September 2016). Up to 50% of these (so 4.5% of all UK adults) will have
71 diabetic neuropathy (Diabetes UK Facts and Stats, October 2016). An estimated 45.5
72 million people in England hold a full car driving licence (Driver and Vehicle Licencing
73 Agency, 2015). These figures suggest that 2.047.500 individuals, a large number, are
74 driving with diabetic peripheral neuropathy, and if present trends continue, this number
75 will substantially increase. Despite the fact that peripheral neuropathy affects up to 50%
76 of patients, and diabetic peripheral neuropathy (DPN) has been recognized to be one of
77 the most common presentations of diabetes, only a few studies have addressed this
78 complication as a potential factor in impairing driving performance (Meyr and Spiess,
79 2017; Sansosti et al., 2017; Spiess et al., 2017) so, for these reasons in our research we

80 tried to offer objective quantitative measures of driving performance impairment while
81 also evaluating the potential for improving (Perazzolo et al., 2019).

82 Diabetic peripheral neuropathy leads to irreversible diffuse nerve damage (Mendez, 2002;
83 Schaumburg and Spencer, 1979); the progressive loss of both sensory and motor fibres
84 causes a subsequent decrease in neural sensitivity, proprioception and muscle strength
85 (Andreassen et al., 2009; Chiles et al., 2014; Sénéchal et al., 2015; Shun et al., 2004;
86 Simoneau et al., 1995; Vaz et al., 2013). To assess fitness to drive with DPN, considering
87 the wide spectrum of clinical manifestations for this condition, an integrated approach is
88 required covering the different aspects of driving and assessing both sensory and motor
89 system variables. The first important aspect is the control of the pedals. The cutaneous
90 and proprioceptive sensory loss together with the motor dysfunction seen in DPN start
91 from the feet and progressively affect more proximal parts of the lower limbs (King, 2001;
92 Said, 2007); it has already been shown that DPN patients present altered (longer) brake
93 response times compared to diabetic patients without neuropathy and healthy controls
94 (American Diabetes Association, 2013) Another fundamental aspect of driving is eye-
95 steering coordination (Chattington et al., 2007; Land and Lee, 1994). The degree of
96 coordination between eye and steering wheel movements, and their relative timing,
97 substantially determines driving performance (Marple-Horvat et al., 2005), and impaired
98 coordination, for example during alcohol intoxication, is associated with crash incidents
99 (Marple-Horvat et al., 2008). Appropriate eye-steering coordination reflects the way in
100 which the central nervous system has solved the problem of steering, using and combining
101 all available information, including that arriving from the peripheral nervous system
102 (sensory information), but there have been no studies of the effect of diabetic peripheral
103 neuropathy on eye-steering coordination to date.

104 Until now, literature on driving with diabetes has mainly focused on the risk of
105 hypoglycaemic events during driving and the associated incidence of crashes. This
106 current research is an extension of a study in which we demonstrated that motor function
107 impairment due to diabetic peripheral neuropathy can affect driving performance. People
108 with diabetic peripheral neuropathy reduce their overall driving speed for example
109 (Perazzolo et al., 2019). In this report, we present analyses of several fundamental aspects
110 of driving - use of the accelerator pedal, steering, and eye-steering coordination – that can
111 be used in an integrated way to identify any uniquely different pattern of driving in people
112 driving with DPN. The innovative approach of this study consists of assessing whether
113 there are differences in both central (eye-steering coordination) and peripheral (pedal
114 control) components that could potentially have a negative impact on driving
115 performance. Once the risk associated with hypoglycaemic events has been excluded, are
116 there other potential factors that we should consider in order to assess driving fitness in
117 this population?

118 **2. MATERIALS AND METHODS**

119 **2.1 Participants**

120 Twenty-two UK active drivers were recruited into two groups: 11 participants with
121 diabetic peripheral neuropathy, DPN (DPN group mean \pm SD, age 67 ± 5.0 years, BMI
122 32 ± 4.2 kg/m², n= 9 males; 2 females), and 11 healthy age-matched controls without
123 diabetes (Control group aged 60 ± 11 years, BMI 27 ± 4.4 kg/m²; 9 males, 2 females). In
124 terms of ethnicity all participants were white British. All participants gave their written
125 informed consent to participate in the study, which received ethical approval from all
126 relevant bodies. The inclusion criteria were: diagnosis of diabetes and diabetic peripheral
127 neuropathy for the DPN group, or absence of diabetes and diabetic peripheral neuropathy
128 in the Control group (confirmed via random blood glucose test <7.8 mmol/l); holding a

129 current full UK driving licence; driving a car at least once per week. The exclusion criteria
130 were: 1) active foot ulcers on either foot, 2) lower limb amputation involving more than
131 two toes on the right foot, 3) dementia, 4) visual acuity worse than 20/50, 5) proliferative
132 diabetic retinopathy.

133

134 **2.2 Procedure**

135 Before starting to record we obtained a medical history. We used the modified
136 Neuropathy Disability Score (mNDS), a composite test of multiple sensory modalities,
137 together with the detection of the vibration perception threshold (VPT), using a
138 neurothesiometer (Bailey Instruments Ltd. Manchester, U.K.), to assess the presence and
139 the severity of diabetic peripheral neuropathy (Boulton et al., 2004). Patients were defined
140 as having moderate-severe diabetic peripheral and accepted into the DPN group if they
141 demonstrated a mNDS score of ≥ 25 and/or a VPT of ≥ 25 Volts, on either foot. A random
142 blood glucose test was used to confirm the absence of diabetes in controls and to avoid
143 any hypo- or hyperglycaemic influence during the driving task in the DPN group. Blood
144 glucose levels needed to be within a range of 4.5 to 20 mmol/l to progress to the simulated
145 driving task.

146 Visual acuity was assessed using a Snellen Chart (23 X 35.5 cm) with traditional
147 optotypes. Visual acuity range from 20/200 to 20/20 was tested at 3 meters distance
148 (McGraw et al., 1995). Corrected visual acuity had to be $\geq 20/50$ since this is defined by
149 the World Health Organization as “moderate visual impairment”.

150 **2.3 The driving simulator session**

151 The driving simulator consisted of a 42-inch plasma screen, a force feedback steering
152 wheel, accelerator and brake pedal system and car seat. Analogue signals of accelerator

153 pedal position, horizontal eye movement (calibrated to 1° accuracy), and steering wheel
154 rotation were digitized at 200 Hz using a CED 1401A/D converter (Cambridge Electronic
155 Design, Cambridge, UK). Eye movements were recorded using a remote infra-red eye
156 tracking system (ASL 504, Applied Science Laboratories, Bedford, MA, USA) mounted
157 at dash panel height.

158 Participants were invited to find a comfortable driving position with adjustment of the
159 simulator construct as needed for individual preference. Specific instructions were given
160 to participants: “drive safely, as you would in a real car on the road”. Verbal instruction
161 concerning the car controls was given, including that the car was an ‘automatic’ so there
162 were only accelerator and brake pedals. The route consisted of a driving environment
163 simplified by the absence of other vehicles and pedestrians, taken from the Colin McRae
164 Rally 2 simulation (Codemaster, Leamington Spa, Warwickshire, UK). The duration of
165 the driving session varied depending on the participant’s own chosen speed to travel along
166 a winding country road 3.1 miles long, which included gentle and sharp bends with few
167 straight sections. At the end of the driving session we asked some questions about the
168 experience and about participants’ driving habits in real life.

169 **3. DATA ANALYSIS**

170 **3.1 The driving simulator session**

171 The task consisted of driving the same 3.1-mile route twice with a rest in between. We
172 analysed data from both drives.

173 **3.2 Accelerator pedal**

174 An analogue sensor in the pedal assembly monitored pedal position (in Volts). This
175 analogue pedal signal was digitized at 200 Hz using a CED 1401 (Cambridge Electronic
176 Design, Cambridge, England) and analysed with Spike 2 Version 5.11 software. The

177 pedal was calibrated to convert from Volts to degrees; the range of pedal position was
178 from 0° (upper limit) to -20° (fully depressed). We performed a frequency distribution
179 analysis of the digitised pedal signal using Spike 2 software to produce a frequency
180 distribution plot with 0.5 degrees bin width for each individual drive. These individual
181 distributions were then exported into excel to produce a group plot (averaged across all
182 drivers in the group). Difference plots were produced by subtracting one group frequency
183 distribution from another and analysed using SPSS. This frequency distribution analysis
184 reveals how much time in a given journey (expressed as a percentage of the journey
185 duration) drivers spend with the accelerator within a specific 0.5 degrees range (e.g.
186 between 4.5 and 5 degrees depressed). The pattern of pedal usage can then be compared
187 in the same subject under different conditions, or between different subjects. This
188 standard signal analysis approach has been used to establish the pedal usage pattern in a
189 number of different conditions and in different populations.

190

191

192 **3.3 Eye-steering coordination**

193 Driving is an everyday example of visually guided behaviour in which the eyes move in
194 coordination with another action (steering) (Chattington et al., 2007). For this reason, we
195 recorded and analysed values that quantify the driver's eye-steering coordination over the
196 drive time: the correlation coefficient and the time lead. The correlation coefficient (r)
197 defines the degree of coordination, and the time lead (Δt) defines the interval by which
198 eye movements lead steering wheel movements across the drive period. Cross-
199 correlograms of horizontal eye vs steering wheel movements were generated using a
200 Spike 2 script. We computed cross-correlograms representing the overall relationship

201 between drivers' horizontal (left–right) eye movements and their turning of the wheel to
202 negotiate bends in the road for each drive. The horizontal component of eye movements
203 (left-right movements) is fundamental for assessing the anticipatory strategy in which eye
204 movements lead steering wheel movements. Left-right eye movements correlate with
205 steering movements when driving because the driver looks across to the inside of the
206 curve of an approaching bend some time before subsequently turning the steering wheel
207 in the same direction. This study used the same analytical techniques as we have
208 previously used in a realistic simulated driving task, and during natural driving on the
209 road (Chattington et al., 2007; Marple-Horvat et al., 2005; Wilson et al., 2007).

210 **3.4 Steering wheel signal**

211 **3.4.1 Familiarization**

212 Driving is a complex task that involves a variety of skills and becomes relatively more
213 automatic with experience because it relies on learned and practised, or routine skills
214 (Freund et al., 2008). For these reasons, we decided to consider separately the initial 3
215 minutes of the steering wheel signal (degrees) of each drive and observed how the wheel
216 movements appeared in this first phase of practice that we called “familiarization”. We
217 chose 3 minutes of driving because drivers reported this to be a time frame long enough
218 to get used to the simulated driving task. Frequency distribution plots of the first 3 minutes
219 of the steering wheel signal were generated for both the Control and DPN group, and then
220 difference plots between the two groups were produced as previously described.

221 **3.4.2 Loss of control events**

222 Visual inspection of the steering wheel signal for a complete drive revealed occasional
223 “loss of control events” that stood out from the rest of the drive as portions where the
224 steering wheel signal had specific different characteristics in terms of amplitude and

225 frequency. Loss of control events consisted of extreme and inappropriate use of the
226 steering wheel, i.e. large and rapid movements that reached the full range of motion of
227 the steering wheel and/or maintained a repetitive frequency (large swings back and forth)
228 for a period of time. Detection of loss of control events from steering wheel movements
229 took place within the context of looking at all signals (wheel, pedal and eye movements)
230 to understand what was going on. We also looked at a section of driving before and after
231 the loss of control event to identify and analyse the characteristics (frequency and
232 amplitude) of steering wheel movement during a time frame that we considered “normal
233 driving”. The two criteria that had to be fulfilled to be a loss of control event were: 1)
234 steering wheel oscillations with a minimum peak to peak value of 150 degrees; 2) at least
235 3 cycles of oscillations. We used these criteria in the steering wheel signal to identify loss
236 of control events. Our observation was that such large swings of the steering wheel were
237 always accompanied by excursion out of lane (either off the road or onto the wrong side
238 of the road) which the driver attempted but failed to prevent. In real driving on the road,
239 this would represent loss of control of the vehicle, rather than adequate control of the
240 vehicle. For each driver experiencing a loss of control, we produced a steering wheel
241 frequency distribution plot of each loss of control event. We also produced a plot for the
242 whole drive to represent their “baseline condition”, so that we could compare these two
243 states in that individual. We were then able to statistically identify (see below) any use of
244 the steering wheel (time spent with the wheel at different degrees of rotation) that differed
245 significantly during a loss of control event compared to baseline driving.

246 **4. STATISTICAL ANALYSIS**

247 We used the Kolmogorov-Smirnov two samples test when we compared accelerator pedal
248 usage over the whole drive, and the steering wheel frequency distribution plots of the first
249 three minutes of driving.

250 A mixed design factorial ANOVA was used to assess differences between groups
251 (Control, DPN) and drives (Drive 1, Drive 2) concerning eye-steering coordination. Both
252 correlation coefficient (r) values and time lead (Δt) were analysed as dependent variables.

253 Another mixed design factorial ANOVA was performed in each group (DPN, Control) to
254 assess differences between the steering wheel patterns observed during a loss of control
255 event and its baseline condition during the drives (Drive 1, Drive 2). Differences in age,
256 BMI, neuropathy assessment tests (VTP, mNDS), years of driving licence possession and
257 duration of the drives between groups (DPN vs Control) were assessed using an
258 independent samples Student's t-test.

259 All statistical tests were analysed using SPSS statistical package (version 22, Chicago,
260 IL, USA) with significance level set at $p < 0.05$.

261

262 **5. RESULTS**

263 The DPN group presented significantly higher values for both the modified Neuropathy
264 Disability Score (mNDS) and the Vibration Perception Threshold (VPT) compared to the
265 Control group ($p < 0.05$). Considering that mNDS ranges from 0 to 10, with 0 being
266 detection of every sensation applied to the feet and 10 meaning a complete lack of sensory
267 perception in the feet and therefore severe neuropathy, mNDS scores were: (mean \pm SD)
268 8.3 ± 2.0 in the DPN group and 0.5 ± 1.1 in the Control group. Conversely, VPT ranges
269 from 0 to 50 Volts (50 indicating a complete lack of sensory perception in the feet and
270 therefore severe neuropathy) and we found a VPT value of 44 ± 10 Volts in the DPN
271 group and a VPT of 7 ± 3 Volts in the Control group. These values demonstrated that
272 people in the DPN group had severe peripheral neuropathy and confirmed the absence of
273 neuropathy in the Control group. We found a significant difference in the BMI value

274 between groups ($p < 0.05$). There were no significant differences for age and years of
275 driving licence possession between groups ($p > 0.05$).

276 **5.1 The driving simulator session**

277 The duration of the first drive was (mean \pm SD) 12.24 \pm 3.41 minutes in the DPN group
278 and 8.91 \pm 2.45 minutes in the Control group. In the second drive, duration was (mean \pm SD)
279 10.60 \pm 3.3 minutes for the DPN group and 7.96 \pm 1.4 for the Control group. The DPN
280 group drove significantly slower compared to the Control group in both drives ($p < 0.05$).

281 **5.2 Use of accelerator pedal**

282 We found a different pattern in the use of the accelerator pedal between DPN and Control
283 groups ($p < 0.05$). In both the first and second drives, drivers with DPN used the mid-range
284 of the pedal less than healthy controls. This is evident in the frequency distribution plots
285 for the two groups and highlighted in the difference plots (Fig.1). The difference plots
286 have 3 clear regions shown in different colours: a mid-range (-1° to -8°) deficit in use of
287 the pedal by drivers with DPN; a peak or surplus in use of the highest positions (0° to $-$
288 1°); and a second surplus in the low/more extreme positions of the pedal (beyond -8°).
289 The first region (0° to -1° , shown in white) and the third region (beyond -8° , with a black
290 fill) represent the extreme high and low parts of the range of possible pedal positions. The
291 middle region of the frequency distribution, between 1 and 8 degrees (shown in grey), is
292 the mid-range of pedal positions. In the two difference plots on the right-hand side of the
293 figure, bars above the x axis (positive values) show that the DPN group spend more time
294 using the extreme regions/positions (close to zero degrees or beyond 8°) than drivers in
295 the Control group. Bars below the x axis (negative numbers) in the middle of the plots
296 show that the DPN group spend less time using the middle range of the pedal than did the
297 Control group. For clarity, we have superimposed on the frequency distributions the

298 percentage of time that the accelerator pedal was in each of these three regions. In the
299 first drive, significant differences emerged at specific pedal positions in all three regions,
300 high- mid- and low/more extreme (Fig. 1A). Drivers with diabetic peripheral neuropathy
301 used the mid-range of the pedal only 17% of the time, whereas healthy controls used the
302 mid-range of pedal position 50% of the time. A similar deficit in mid-range use of the
303 pedal was seen by drivers with diabetic peripheral neuropathy in drive two (Fig. 1B).
304 Conversely, drivers with neuropathy used the high and low more extreme ranges of pedal
305 position more than healthy controls in both drives.

306

307 Figure 1

308

309

310

311 **5.3 Eye-steering coordination**

312 We obtained good quality eye movement data for all participants in the Control group in
313 both drives. In the DPN group, for technical reasons, (poor quality eye movement signals
314 due to the small size of the pupil or large head movements when driving) we were able
315 to analyse 8 drivers for the first drive, reducing to 5 drivers for the second. We
316 acknowledge the small sample size for this specific variable. The problem was that in this
317 DPN group, whenever drivers were struggling to retain or regain control, they frequently
318 made exaggerated head movements which sometimes resulted in loss of eye tracking. For
319 the second drive, the small sample meant, the statistical power of eye-steering
320 coordination was 0.766, which is below the preferred minimum of 0.8

321 As regards degree of eye-steering coordination, we found a main effect for “group”,
322 drivers in the DPN group had significantly lower eye-steering coordination than Controls
323 ($p < 0.05$). We also observed a main effect for “drives” ($p < 0.05$) but no significant

324 interaction effect “group x drives” ($p>0.05$). The correlation coefficient increased
325 significantly between the first and the second drive in the Control group, but a similar
326 increase in the DPN group failed to reach significance ($p>0.05$) (Fig. 2A).

327 Analysis of time lead values did not show any main effect or interaction effect. In both
328 drives, there were no significant differences in the time lead values between groups
329 ($p>0.05$) or any significant improvement between drives 1 and 2 ($p>0.05$). In the first
330 drive, we observed a longer time lead in the Control group (mean \pm SD: $\Delta t -0.71 \pm 0.32$)
331 compared to the DPN group ($\Delta t -0.44 \pm 0.70$). During the second drive the DPN group
332 increased their time lead ($\Delta t -0.85 \pm 0.59$) while the Control group stayed the same ($\Delta t -$
333 0.73 ± 0.56) (Fig. 2B).

334 Figure 2

335 **5.4 Steering wheel signal**

336 **5.4.1 Familiarization**

337 In the first three minutes of the first drive, the DPN group steering wheel frequency
338 distribution plots differed from the steering pattern of the Control group at -65° , -55° and
339 -30° ($p<0.05$) (Fig. 3A). These particular differences reflect the general difference that
340 drivers in the DPN group drove for more of the time with the steering wheel turned by
341 larger amounts, and for less time with the wheel turned by smaller amounts. In the second
342 drive, there were no significant differences between the two groups of drivers ($p>0.05$)
343 (Fig. 3B).

344

345 Figure 3

346

347 **5.4.2 Loss of control events**

348 During the first drive, we observed a total of 25 loss of control events: 5 in the Control
349 group and 20 in the DPN group. During the second drive the Control group exhibited no
350 loss of control event, while there were 10 events in the DPN group. Only 27% of the
351 healthy Control group experienced at least one loss of control event during the first drive,
352 compared to 73% of the DPN group.

353

354

Group	Total	Drive 1	Drive 2	First 3 minutes	Sharp bend	Other	% participants
Control	5	5	0	2	1	2	27%
DPN	30	20	10	10	9	11	73%

355

356 Table 1: Number of loss of control events: total; in a specific drive (Drive1 or Drive2); or in a
357 particular part of the route (first 3 minutes, sharp bend or other).

358

359 When considering where these loss of control events happened along the route, we saw
360 that the likelihood these events occurred during the familiarization period (first 3 minutes)
361 or in other unspecified portions of the road was the same in the control group, 40%. As
362 regards the DPN group, the likelihood that a loss of control event occurred during the first
363 3 minutes was 33% and slightly higher 37% when we considered other road sections.
364 Considering a particularly challenging situation of a sharp (hairpin) bend, the percentage
365 of loss of control events were 20% for Controls and 30% for drivers in the DPN group
366 (Table 1). For drivers in the DPN group, we found a main effect for “drive state” (loss of
367 control, baseline) in both drives ($p < 0.05$). In the first drive their pattern of steering (% of
368 time spent with the steering wheel turned by different amounts) during loss of control
369 events differed significantly from the baseline condition (Fig. 4A). The same was true of

370 the second drive but the two patterns of steering were significantly different over a smaller
371 range of steering wheel positions.

372 For drivers in the Control group, we could only look for significant differences during
373 loss of control in the first drive, as none occurred during the second drive. During the first
374 drive, we again found significant differences in steering between loss of control and
375 baseline conditions ($p < 0.05$) (Fig. 4B).

376

377 Figure 4

378

379 **6. DISCUSSION**

380 We show here, for the first time, differences in driving characteristics in people with
381 diabetic peripheral neuropathy compared to controls without diabetes in terms of
382 accelerator pedal use, steering, and eye-steering coordination; and in loss of control
383 events that indicate impaired driving performance with implications for safety. From a
384 positive perspective, we also show a rapid learning/familiarisation effect in people with
385 diabetic peripheral neuropathy, demonstrating the potential for interventions to improve
386 these driving characteristics.

387 The first main finding of this study is that drivers with DPN exhibit a significantly
388 different pattern of control of the accelerator pedal than healthy age-matched controls.
389 Drivers with DPN tended to use the middle range of the pedal less, while the Control
390 group exhibited a more graded use of the accelerator pedal over the mid-range of its
391 travel, and less use of the pedal near the extremes of its range. Drivers with DPN switch
392 between extreme high and low positions of the pedal, an approach that seems to suggest

393 and confirm the physiological evidence for reduced fine motor control and proprioceptive
394 function of the lower limb in this population (Forbes and Cooper, 2013).

395 Our second main finding concerns eye-steering coordination. We found a significantly
396 lower correlation between eye and steering wheel movements in people with DPN
397 compared to the Control group. There are reports in the literature that people with diabetes
398 may have nystagmus and reduced slower smooth pursuit eye movements (Darlington et
399 al., 2000). These clinical manifestations associated with diabetes could have a role in
400 disrupting oculomotor coordination and consequently the specific eye-steering
401 coordination normally seen and required during driving. Another explanation for the low
402 eye-steering coordination could be the loss of control events experienced by drivers with
403 diabetic neuropathy. During these events, exaggerated steering wheel movements
404 produced large swings in heading to left and right, and so large swings in the view ahead
405 seen by the driver. Such large swings in the visual world are an effective optokinetic
406 stimulus, which reflexly produce compensatory eye movements. Thus, during a large,
407 rapid steering wheel movement to the left, the visual world swings to the right, producing
408 an optokinetic nystagmus with rightwards slow phase – opposite to the direction of
409 steering wheel movement. This is the inverse of the usual eye-steering coordination when
410 eye movements lead and are in the same direction as steering. Therefore, across the whole
411 drive, there are two distinct and opposite modes of coordination at different times, which
412 when put together would reduce the overall coordination usually seen when fully in
413 control of the vehicle.

414 Driving requires perception and control of self-motion at great speed (Kemeny and
415 Panerai, 2003). In particular, it is necessary to look where you need to steer next (the next
416 bend) early enough in time, and with sufficient distance, to have enough time to prepare
417 steering. For drivers who might be challenged by this, one potential strategy to allow

418 adequate time between looking ahead at the upcoming bend, and subsequently turning
419 the steering wheel, is to reduce driving speed to have a longer interval of time between
420 the eye and steering wheel movements. The slower overall driving speed of drivers with
421 diabetic peripheral neuropathy might therefore be a compensatory mechanism to help
422 mitigate any consequences of the difficulty they experience in the control of the vehicle
423 (Perazzolo et al., 2019). Such an interpretation is supported by the observation that
424 healthy drivers (Controls) showed a time-lead of eye movements over steering of around
425 0.70 seconds in both drives. Similar values have previously been obtained in the identical
426 driving simulation in a younger cohort of healthy drivers who had received the same
427 instruction as in the current study to drive safely as if in a real car on the road (Marple-
428 Horvat et al., 2008). In actual driving on the road, the time lead is even longer, 0.90
429 seconds (Chattington et al., 2007). These observations identify that safe driving in this
430 simulation involves an overall time lead of eye movements over steering of around 0.70
431 seconds, not less.

432 These time leads contrast markedly with the value of 0.44 seconds seen for drivers with
433 DPN in the first drive. It is perhaps not surprising, therefore, that in their first drive,
434 drivers with DPN, exhibiting an unusually low time lead in eye movements relative to
435 steering, experienced loss of control events. It should also be noted, that this short time
436 lead was observed despite people with DPN driving more slowly than controls. It is
437 noteworthy and encouraging that during the second drive, presumably in response to the
438 difficulties experienced in the first drive, drivers with DPN almost doubled their time lead
439 value, and in fact exceeded that seen for the Control group. This might suggest a rapid
440 learning effect after the first drive in people with DPN.

441 When combined with the observation that loss of control events greatly reduced in the
442 second drive, it seems clear that a certain minimum time lead is required to safely

443 complete the driving task. The DPN group's time lead was inversely related to the number
444 of loss of control events: in the first drive a shorter (too short) time lead value of 0.44
445 seconds was accompanied by a higher number of loss of control events. In the second
446 drive DPN's improvement in the time lead value, roughly doubling it to 0.85 seconds,
447 allowed them to greatly reduce, in fact halve, the number of these events. Therefore, as
448 eye-steering coordination changed to more resemble the values seen in healthy
449 individuals, loss of control reduced. For these reasons, we consider time lead values a
450 powerful instrument to assess driving fitness.

451 During the first 3 minutes of the first drive, while familiarizing with the driving simulator,
452 use of the steering wheel showed important, even critical differences, between the two
453 groups of drivers. During this relatively short time frame of driving, we observed a total
454 of 10 loss of control events in the DPN group but just 2 in the Control group, results that
455 suggest that the DPN patients start off worse or take more time to get used to the new
456 'vehicle'. Conversely, use of the steering wheel in the first 3 minutes of the second drive
457 did not show any difference between the two groups, demonstrating that DPN patients
458 can and did improve with practice. Since 30% of the loss of control events occurred at
459 the most difficult corner on the route, and there were roughly 50 bends along the whole
460 route, clearly there was a greater tendency to lose control in the challenging situation, but
461 there was no hard and fast rule that loss of control would happen just at this location.

462 Three quarters of the participants with DPN (73%) but only a quarter (27%) of Controls
463 experienced this 'uncontrolled' pattern of steering wheel movement. We have identified
464 its characteristics – large rapid turns of the wheel back and forth for a number of
465 oscillations. This characteristic pattern is completely different from steering wheel
466 movements seen at other times, during controlled driving which is a quite different
467 'baseline' condition. The differences we have identified provide for discrimination

468 between normal, safe driving and a different state that represents an increased risk for
469 driving safety.

470 **Limitations**

471 We acknowledge that the present sample size is relatively small, and these results are best
472 considered as preliminary evidence of the several consequences of DPN on driving. Some
473 differences between the groups directly relevant to their clinical conditions do represent
474 residual confounding variables that we have not been able to control for; any effect of
475 these other variables on their driving remains unknown and could be the focus of further
476 studies. Considering the scope and limitations of the test methods used, which are in some
477 ways non-standard (driving) methodology (for instance, we do not present analysis of
478 glances to different areas of the scene), the findings of this study may perhaps be regarded
479 as an initial standard characterization of a new approach to testing driving fitness. This is
480 a characterisation based on standard signals analysis, of the drivers gaze and signals from
481 the car's controls which reflect how the driver is attempting to solve the control problem
482 of driving successfully and safely. These signal processing techniques are capable of
483 identifying impaired driving in quite small groups of individuals. What is more, the group
484 size in the current study (n=11) is comparable with a previous study in the identical
485 simulator and with the same analytical techniques which successfully identified
486 significantly impaired driving due to, in that case, alcohol intoxication; and a study of
487 driving on the road using the same techniques (n=10). Additional signals could also be
488 included in future, in particular to monitor use of the brake (and clutch pedal in a
489 simulated manual gearchange vehicle) and ideally in a variety of driving conditions as
490 would be encountered in a real car on the road. We can say at this stage that the current
491 findings contribute to the emerging global picture of the consequences of DPN on driving

492 and form the basis for future studies with a wider scope that will further deepen our
493 understanding.

494

495 **7. CONCLUSION**

496 We have identified, in several fundamental aspects of driving; use of the pedals, the
497 steering wheel, and eye-steering coordination, differences in the driving of individuals
498 who have peripheral neuropathy as a complication of diabetes, compared to healthy age-
499 matched controls. Together, these differences amount to a unique pattern that
500 characterises driving with DPN. These findings shed light on possible driving impairment
501 due to DPN and offer a general method for evaluating it. This set of measurements might
502 be useful for assessing fitness to drive, and an integrated method, including all of these
503 factors, seems the best way of identifying and quantifying changes in driving as a
504 consequence of diabetic peripheral neuropathy, with the possibility to then implement a
505 person-specific behavioural intervention to help drivers to drive more safely for longer.
506 A final goal would be to use these insights to create an algorithm implemented in an
507 automated driver assistance system that could intervene in subtle ways and at crucial
508 times to reduce the risk of serious accidents and help support drivers in real life situations.

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514 **Keywords:** Diabetic peripheral neuropathy, driving simulator, accelerator pedal, eye-
515 steering coordination.

516 **References**

- 517 American Diabetes Association, 2013. Diabetes and Driving. *Diabetes Care* 36:S80-S85.
518
- 519 Andreassen, C.S., Jakobsen, J., Ringgaard, S., Ejksjaer, N., Andersen, H., 2009. Accelerated atrophy of lower
520 leg and foot muscles—a follow-up study of long-term diabetic polyneuropathy using magnetic resonance
521 imaging (MRI). *Diabetologia* 52:1182-91.
522
- 523 Anstey, K.J., Wood, J., Lord, S., Walker, J.G., 2005. Cognitive, sensory and physical factors enabling driving
524 safety in older adults. *Clinical Psychology Review* 25:45-65.
525
- 526 Boulton, A.J., Malik, R.A., Arezzo, J.C., Sosenko, J.M., 2004. Diabetic somatic neuropathies. *Diabetes Care*
527 27:1458-86.
528
- 529 Chattington, M., Wilson, M., Ashford, D., Marple-Horvat, D., 2007. Eye–steering coordination in natural
530 driving. *Experimental brain research* 180:1-14.
531
- 532 Chiles, N.S., Phillips, C.L., Volpato, S., Bandinelli, S., Ferrucci, L., Guralnik, J.M., Patel, K.V., 2014. Diabetes,
533 peripheral neuropathy, and lower-extremity function. *Journal of diabetes and its complications* 28:91-95.
534
- 535 Cho, N., Shaw, J., Karuranga, S., Huang, Y., da Rocha Fernandes, J., Ohlogge, A., Malanda, B., 2018. IDF
536
- 537 *Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes*
538 *research and clinical practice* 138:271-81.
539
- 540 Cox, D.J., Kovatchev, B., Vandecar, K., Gonder-Frederick, L., Ritterband, L., Clarke, W., 2006. Hypoglycemia
541 preceding fatal car collisions. *Diabetes Care* 29:467-68.
542
- 543 Darlington, C.L., Erasmus, J., Nicholson, M., King, J., Smith, P.F., 2000. Comparison of visual–vestibular
544 interaction in insulin - dependent and non - insulin - dependent diabetes mellitus. *Neuroreport* 11:487-
545 90.
546
- 547 *Diabetes UK Facts and Stats, October 2016.* [https://diabetes-resources-production.s3-eu-west-](https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/DiabetesUK_Facts_Stats_Oct16.pdf)
548 [1.amazonaws.com/diabetes-storage/migration/pdf/DiabetesUK_Facts_Stats_Oct16.pdf](https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/DiabetesUK_Facts_Stats_Oct16.pdf)
549
- 550 *Driver and Vehicle Licencing Agency, 2015. FOI response on driving licence statistics.*
551 <https://www.gov.uk/government/publications/how-many-people-hold-driving-licences-in-the-uk>
552
- 553 Forbes, J.M., Cooper, M.E., 2013. Mechanisms of diabetic complications. *Physiological reviews* 93:137-88.
554
- 555 Freund, B., Colgrove, L.A., Petrakos, D., McLeod, R., 2008. In my car the brake is on the right: Pedal errors
556 among older drivers. *Accident Analysis & Prevention* 40:403-09.
557
- 558 Inkster, B., Frier, B.M., 2013. Diabetes and driving. *Diabetes, Obesity and Metabolism* 15:775-83.
559
- 560 Kemeny, A., Panerai, F., 2003. Evaluating perception in driving simulation experiments. *Trends in cognitive*
561 *sciences* 7:31-37.
562
- 563 King, R., 2001. The role of glycation in the pathogenesis of diabetic polyneuropathy. *Molecular Pathology*
564 54:400.
565

566 Kua, A., Korner-Bitensky, N., Desrosiers, J., Man-Son-Hing, M., Marshall, S., 2007. Older driver retraining: A
567 systematic review of evidence of effectiveness. *Journal of Safety Research* 38:81-90.

568 Land, M.F., Lee, D.N., 1994. Where we look when we steer. *Nature* 369:742-44.

569

570 Marmeleira, J., Godinho, M., Vogelaere, P., 2009. The potential role of physical activity on driving
571 performance and safety among older adults. *European Review of Aging and Physical Activity* 6:29-38.

572

573 Marple-Horvat, D., Chattington, M., Anglesea, M., Ashford, D., Wilson, M., Keil, D., 2005. Prevention of
574 coordinated eye movements and steering impairs driving performance. *Experimental brain research*
575 163:411-20.

576

577 Marple-Horvat, D.E., Cooper, H.L., Gilbey, S.L., Watson, J.C., Mehta, N., Kaur-Mann, D., Wilson, M., Keil, D.,
578 2008. Alcohol badly affects eye movements linked to steering, providing for automatic in-car detection of
579 drink driving. *Neuropsychopharmacology* 33:849-58.

580

581 McGraw, P., Winn, B., Whitaker, D., 1995. Reliability of the Snellen chart. *BMJ: British Medical Journal*
582 310:1481.

583

584 McGwin Jr, G., Sims, R.V., Pulley, L., Roseman, J.M., 2000. Relations among chronic medical conditions,
585 medications, and automobile crashes in the elderly: a population-based case-control study. *American*
586 *journal of epidemiology* 152:424-31.

587

588 Mendez, J., 2002. Advanced glycosylation end products and chronic complications of diabetes mellitus.
589 *Gaceta medica de Mexico* 139:49-55.

590

591 Meyr, A.J., Spiess, K.E., 2017. Diabetic driving studies—part 1: brake response time in diabetic drivers with
592 lower extremity neuropathy. *The Journal of Foot and Ankle Surgery* 56:568-72.

593

594 Perazzolo, M., Reeves, N., Bowling, F., Boulton, A., Raffi, M., Marple - Horvat, D., 2019. Altered accelerator
595 pedal control in a driving simulator in people with diabetic peripheral neuropathy. *Diabetic medicine*.
596 <https://doi.org/10.1111/dme.13957>

597

598 Public Health England press release, September 2016. [https://www.gov.uk/government/news/38-million-](https://www.gov.uk/government/news/38-million-people-in-england-now-have-diabetes)
599 [people-in-england-now-have-diabetes](https://www.gov.uk/government/news/38-million-people-in-england-now-have-diabetes)

600

601 Said, G., 2007. Diabetic neuropathy--a review. *Nature Reviews. Neurology* 3:331.

602

603 Sansosti, L.E., Spiess, K.E., Meyr, A.J., 2017. Diabetic driving studies—part 3: a comparison of mean brake
604 response time between neuropathic diabetic drivers with and without foot pathology. *The Journal of Foot*
605 *and Ankle Surgery* 56:577-80.

606

607 Schaumburg, H.H., Spencer, P.S., 1979. Clinical and experimental studies of distal axonopathy—a frequent
608 form of brain and nerve damage produced by environmental chemical hazards. *Annals of the New York*
609 *Academy of Sciences* 329:14-29.

610

611 Seeger, R., Lehmann, R., 2011. Driving ability and fitness to drive in people with diabetes mellitus.
612 *Therapeutische Umschau* 68:249-52.

613

614 Sénéchal, M., Johannsen, N.M., Swift, D.L., Earnest, C.P., Lavie, C.J., Blair, S.N., Church, T.S., 2015.
615 Association between changes in muscle quality with exercise training and changes in cardiorespiratory
616 fitness measures in individuals with type 2 diabetes mellitus: Results from the HART-D study. *PloS one*
617 10:e0135057.

618 Shun, C.T., Chang, Y.C., Wu, H.P., Hsieh, S.C., Lin, W.M., Lin, Y.H., Tai, T.Y., Hsieh, S.T., 2004. Skin
619 denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. *Brain*
620 127:1593-605.

621

622 Siegler, I., Reymond, G., Kemeny, A., Berthoz, A., 2001. Sensorimotor integration in a driving simulator:
623 contributions of motion cueing in elementary driving tasks, *Proceedings of Driving Simulation Conference*,
624 pp. 21-32.

625

626 Simoneau, G.G., Ulbrecht, J.S., Derr, J.A., Cavanagh, P.R., 1995. Role of somatosensory input in the control
627 of human posture. *Gait & posture* 3:115-22.

628

629 Spiess, K.E., Sansosti, L.E., Meyr, A.J., 2017. Diabetic driving studies—part 2: a comparison of brake
630 response time between drivers with diabetes with and without lower extremity sensorimotor neuropathy.
631 *The Journal of Foot and Ankle Surgery* 56:573-76.

632

633 Vaz, M.M., Costa, G.C., Reis, J.G., Junior, W.M., De Paula, F.J.A., Abreu, D.C., 2013. Postural control and
634 functional strength in patients with type 2 diabetes mellitus with and without peripheral neuropathy.
635 *Archives of Physical Medicine and Rehabilitation* 94:2465-70.

636

637 Wilson, M., Stephenson, S., Chattington, M., Marple-Horvat, D., 2007. Eye movements coordinated with
638 steering benefit performance even when vision is denied. *Experimental brain research* 176:397-412.

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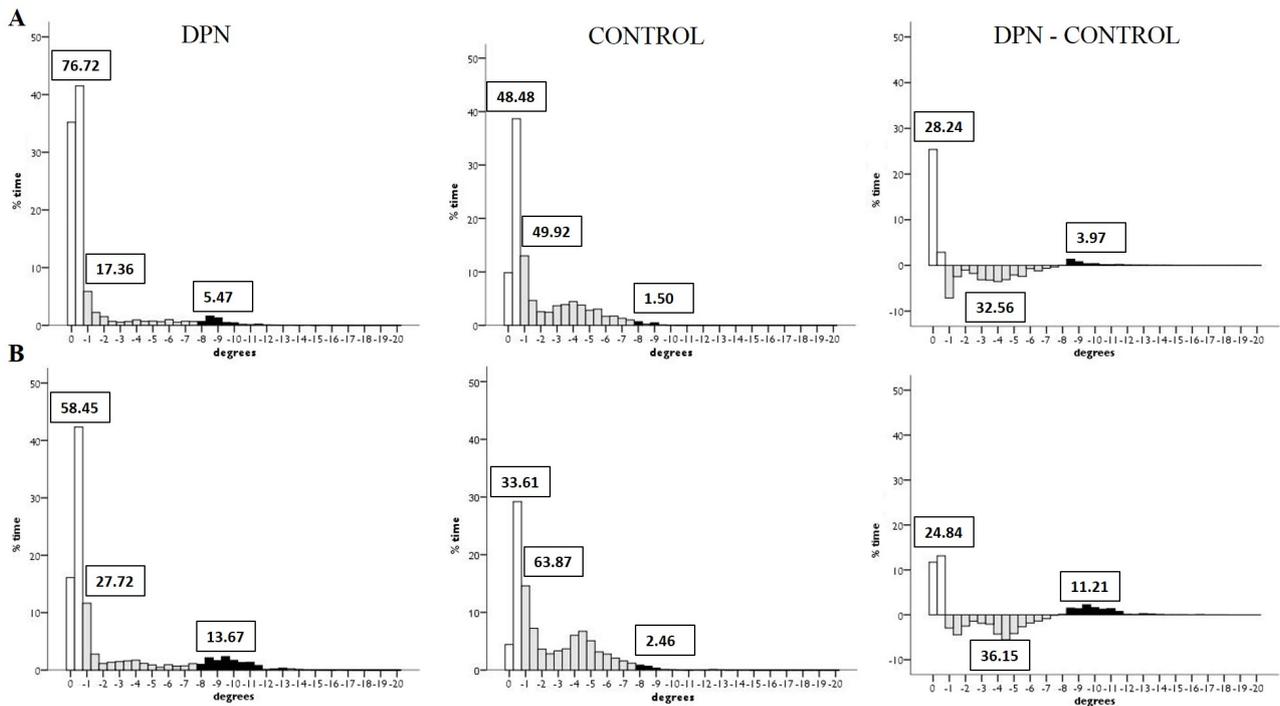
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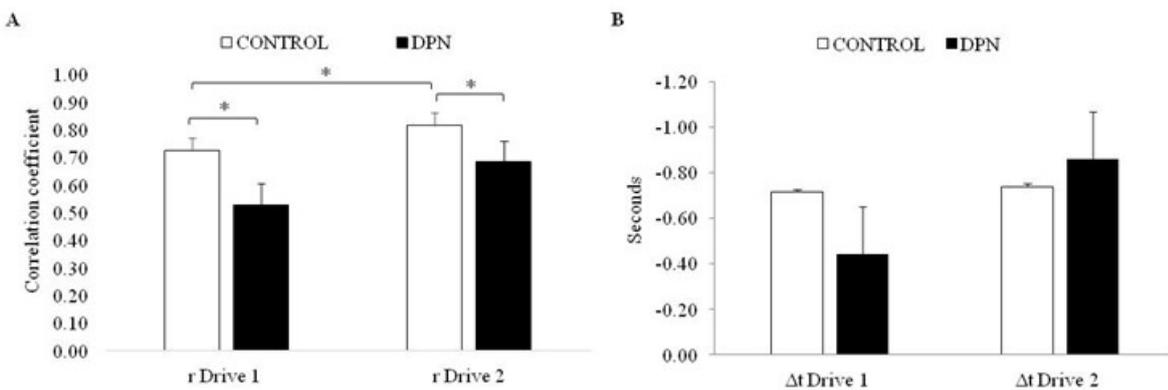
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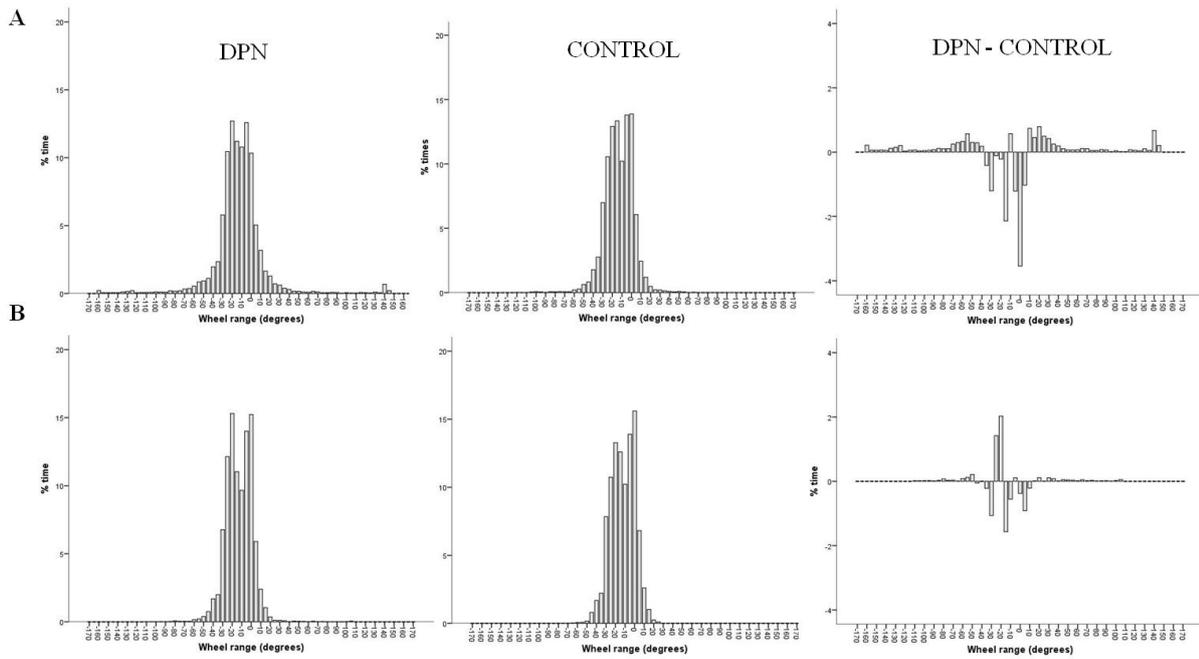
651 **Figure 1:** Accelerator pedal position frequency distribution plots during the first drive (Row A) and the
 652 second drive (Row B). Each bar represents the time (seconds) the accelerator pedal spent in a specific
 653 position, from 0 (no displacement of the pedal) to a maximum of -20° (maximal depression of the pedal)
 654 during driving. The change in the colours highlights the transition between the three pedal regions: high
 655 (white bars), mid (grey bars) and low (black bars) ranges. The numbers inside the boxes represent the
 656 % of time spent in each specific region of the pedal range. Each panel should be read from left to right.
 657 The plots on the left represent the original frequency distribution plot of the patients with diabetic
 658 peripheral neuropathy (DPN), the plots in the middle indicate the original frequency distribution plot of
 659 control subjects (CONTROL) and the plots on the right show the “difference plot” obtained by
 660 subtracting one group plot from another (DPN-CONTROL).



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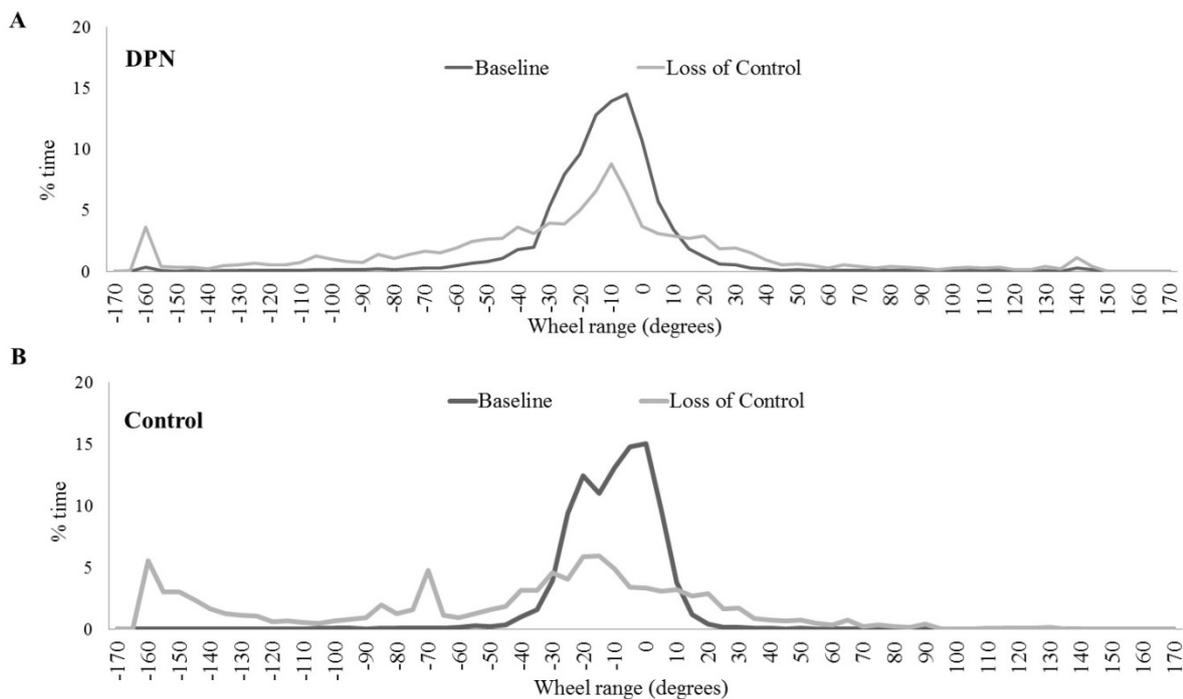
662 **Figure 2:** - A. Eye-steering correlation coefficient “r” during the first drive (r Drive 1) and the second
 663 drive (r Drive 2) in each group: control subjects in white (Control) and patients with diabetic peripheral
 664 neuropathy in black (DPN) B. Time lead values (Δt , seconds) during the first (Δt Drive 1) and second
 665 (Δt Drive 2) drives in each group: control subjects in white (Control) and patients with diabetic
 666 peripheral neuropathy in black (DPN). Values are means and SD. *Significantly different ($p < 0.05$).
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668

669 **Figure 3:** Frequency distribution plots of the steering wheel position during the first three minutes
 670 (familiarization) of the first drive (A) and of the second drive (B). Each bar represents the time (seconds)
 671 the steering wheel spent in a specific position. Each panel should be read from left to right. The plots
 672 on the left represent the original frequency distribution plot of the patients with diabetic peripheral
 673 neuropathy (DPN), the plots on the middle indicate the original frequency distribution plot of control
 674 subjects (CONTROL) and the plot on the right show the “difference plot” obtained by subtracting one
 675 group plot from another (DPN-CONTROL).



676

677 **Figure 4:** The two graphs represent the % of time the steering wheel was in a specific position
 678 during a loss of control event (grey lines) or in a baseline condition (black lines) in patients with
 679 diabetic peripheral neuropathy (DPN) (A) and in the control subjects (Control) (B).

680