S3 Appendix. Table for PLR *AND* Parasympathetic functions

| **Reference** | **Type of parasympat-hetic dysfunction** | **Nature of groups and group comparisons** | **Number of participants** | **Mean age****(yr)****(SD)**  | **Descriptive data for PLR result on patient group and ANOVA/ANCOVA result for PLR in patient group and normal control group (if applicable)** | **Additional measurement of parasympathetic function** | **Assumption** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MCV**$$mm/s$$**(SD)** | **MCA**$$mm/s^{2}$$**(SD)** | **ACA**$$mm$$**(SD)** | **RCA****%****(SD)** | **Latency**$$s$$**(SD)** | **Constrict-ion time****s****(SD)** | **Other PLR parameters** |
| Giza et al. [17] | Parkinson’s disease (PD) (idiopathic) | PD patientnormal controlpatient vs normal | 66 (44 males)44 (20 males) | 64.1 (8.4)age matched | 1.87 (0.46)2.30 (0.43)\* | 16.61 (4.60)21.83 (3.35)\*^ | 0.54 (0.16)0.69 (0.13)\* | N/A | 0.252 (0.016)0.236 (0.018)\* | N/A  | N/A | N/A | + |
| Micieli et al. [28] | Parkinson’s disease (PD) | PD patientnormal controlpatient vs normal | 23 (15 males)26 (20 males) | 58.5 (9.9)54.2 (11.3) | N/A | N/A | 1.35 (0.47)1.53 (0.31)\* | N/A | 0.334 (0.060)0.309(0.026)\*^ | 0.461 (0.107)0.411 (0.056)\* | N/A | N/A | + |
| Tales et al. [30] | Alzheimer’s disease (AD) | AD patientsolder controlyoung controlAD vs older&young control | 12 (4 males)12 (9 males)12 (5 males) | 70 (7)70 (6)29 (5.6) | N/A | N/A | N/A | 0.221 (0.12)0.316 (0.08)0.333 (0.09)\* | 0.663 (0.37)0.485 (0.05)0.455 (0.03)ns | N/A  | N/A  | N/A | +only RCA was significantly different |
| Muppidi et al. [76] | Autonomic dysfunction, defined by CASS score.Part of the high CASS patients were with diabetes, Parkinson | normal CASS scorehigh CASS scorenormal controlhigh CASS vs normal CASS/normal | 282679 | 41.7 (15.3)65.1 (11.4)41.3 (14.8) | 4.62 (0.73)3.44 (1.02) 4.91 (0.73)\*^ | N/A | 1.61 (0.3)1.03 (0.3)1.61 (0.3)\* | 27.8 (5.1)24.7 (6.4)29.4 (4.6)\* | N/A | N/A  | N/A | -QSART (Quantitative Sudomotor Axon Reflex Test)$HR\_{DB}$ range-blood pressure-HR during Valsalva maneuverall of the measurements above contributed to the CASS score | + |
| Zangemeister et al. [39] | Diabetes mellitus (DM)both type 1 and type 2 were included | Patients with two signs of diabetic neuropathy (DNP) as subgroupAll DM patients (including DNP group)Normal controlDNP vs normalall DM vs normal |  2352 (31 males)21 (11 males) | 59.7 (10.1)46.7 46.2 (14.5) | 3.44 (1.28)4.16 (1.22)4.42 (0.93)\*ns | N/A | 1.26 (0.45)1.49 (0.41)1.53 (0.34)\*ns | 30.6 (9.02)31.0 (8.59)29.1 (7.64)nsns | 0.28 (0.04)0.27 (0.09)0.25 (0.03)\*ns | N/A  | N/A | N/A | + |
| Lanting et al. [19] | Diabetes mellitus (DM) | DM patientnormal controlDM vs normal | 29 (14 males)29 (missing gender) | 45.9 range (18-75)40.0 range (18-76) | N/A | N/A | N/A | N/A | 0.236(SEM: 0.006)0.211 (SEM: 0.004)\* | N/A  | N/A | - thermal discrimination threshold-vibratory perception threshold-motor nerve donduction velocity-H-M intervalthermal discrimination threshold showed a positive correlation with the latency | + |
| Bar et al. [20] | Paranoid schizophrenia | patientnormal controlpatient vs normal | 28 (10 males)28 (10 males) | 31 range (18-67)32 range (18-54) | N/A | N/A | N/A | 28.0 (5.2)24.6 (5.2)\* | 0.248 (0.016)0.251 (0.019)ns | N/A  | N/A | -HRV-blood pressure -baroreflex sensitivityall 3 measurements showed a reduced parasympathetic function in line with the PLR result | + |
| Mylius et al. [57] | Migraine headache | patientnormal controlpatient within 48 hours of an attack as subgroupall patient vs normal48 hours vs normal | 42 (10 males)42 (12 males)10 | 27 (5.3) range (20-40)26.4 (3.6) range (21-36)N/A | 4.87 (0.7)4.97 (0.9)4.5 (0.8)ns\* | N/A | 1.84 (0.3)1.89 (0.3)1.74 (0.3)ns\* | N/A | 0.231 (0.02)0.232 (0.02)0.235 (0.02)nsns | N/A  |  | N/A | +a parasympathetic dysfunction reflected by PLR could only valid within 48 hours of an attack |
| Ofte et al. [61] | Episodic Cluster Headache (CH) (during remission) | CH patient:affected sidenon-affected side normal controlpatient vs normalaffected side vs non-affected side | 30 (27 males)30 (gender matched) | 50.2 (13.6)age matched | 4.41 (1.2)4.51 (1.17)5.11 (0.63)\*ns | N/A | (min diameter)4.02 (1.21)4.03 (1.15)3.95 (0.72)nsns | 28.52 (4.17)29.24 (4.13)32.70 (3.75)\*ns | 0.24 (0.02)0.24(0.02)0.22 (0.01)\*ns | N/A  | average constriction velocity\*\* | N/A | + |
| [73]Keivanidou et al., 2010 | Heart failure (HF) patient | HF patientnormal controlpatient vs normal | 1616 | 67.5 (11.2)age matched | 1.83 (0.18)2.40 (0.24)\* | 24.60 (3.36)14. 20 (0.27)\* | N/A | (minimum/baseline)97.49 (1.29)93.96 (4.11)\* | 0.249 (0.021)0.233(0.018)\* | N/A  |  | N/A | + |
| de Vos et al. [45] | Diabetes mellitus (DM) | DM patientsnormal controlpatient vs normal | 1818 | 45 (22-62)39 (18-62) | N/A | N/A | N/A | N/A  | 0.248 (0.025)0.200(0.020)\* | N/A  |  | N/A | + |
| Micieli et al. [58] | Migraine | migraine patient-pain side-pain-free sidenormal controlpatient vs normal | 38 (24 males)22 (gender matched) | 37.3 (11.1)age matched | N/A | N/A | 1.51 (0.4)1.60 (0.4)1.55 (0.3)ns | N/A  | 0.322 (0.029)0.322 (0.066)0.311(0.025)ns | 0.473 (0.097)0.479 (0.079)0.599 (0.048)\* |  | N/A | +weak group differences |
| Perry et al. [65] | Arthritis or chronic myofascial pain | Arthritis patientmyofascial pain groupnormal controlArthritis vs normalMyofascial vs normal | 19 (5 males)17 (0 males)38 (22 males) | 46.5 (3.4)43.8 (3.0)34.1 (1.6) | 36.3 (2.4)$mm^{2}$/s36.1 (2.3)$mm^{2}$/s41.2 (1.3)$mm^{2}$/spupil area per second\*\* | N/A | N/A | 37.8 (1.7)38.6 (2.3)41.2 (1.3)\*\* | N/A | N/A/s/s/s | N/A | -skin conductance-HRV(during mental arithmetic and Valsalva maneuver)the result suggest decreased tonic peripheral parasympathetic tone in both groups and a decreased parasympathetic reaction in arthritis | + |
| Pozzessere et al. [71] | Multiple sclerosis (MS) | all MS patientall controlMS patient baseline pupil ≤ 6mmcontrol baseline pupil ≤ 6mmMS patient 6mm<baseline pupil≤ 6.95mmcontrol 6mm<baseline pupil≤ 6.95mmMS patient baseline pupil> 6.95mmcontrol baseline pupil> 6.95mmall MS vs all normalMS vs normal (baseline pupil ≤6)MS vs normal (6mm<baseline pupil≤6.95mmMS vs normal (baseline pupil>6.95mm | 36 (15 males)36 (15 males)12 (5 males)1214 (6 males)1310 (4 males)11 | 36.5 (6.37)37.1 (7.20)43.1 (3.90)35.9 (7.00)30.4 (5.4) | 2.84 (0.67)3.40 (0.43)2.52 (0.50)3.20 (0.27)2.93 (0.65)3.59 (0.38)3.12 (0.34)3.41 (0.52)\*\*\*ns | N/A | N/A | 23.2 (5.4)29.1 (5.1)23.1 (6.2)30.5 (4.4)23.9 (5.9)30.7 (2.7)23.2 (3.9)27.6 (5.6)\*\*\*ns | 0.276 (0.025)0.269 (0.017)0.2934 (0.0357)0.2714 (0.0108)0.2672 (0.0211)0.2734 (0.0229)0.2739 (0.0172)0.2727 (0.0182)nsnsnsns | N/A | N/A | N/A | + |
| Yuan et al. [44] | Diabetic autonomic neuropathy (DAN)&autonomic dysfunction from other causes (non-DAN) | DANnon-DANDAN vs non-DAN | 40 (21 males)40 (21 males) | 62.4 (28-89)62.5 (26-89) | 2.8 (1.4)3.6 (1.1)\*^ | N/A | 0.9 (0.5)1.2 (0.4)\* | N/A | N/A | N/A | N/A | -QSART -$HR\_{DB}$ range-blood pressure-HR during Valsalva maneuverall of the measurements above contributed to the CASS score | + |
| Fotiou et al. [18] | Alzheimer’s Disease (AD) and Parkinson’s Disease (PD) (with and without cognitive disorder) | AD patientPD patientPDNoCog groupPDCog groupnormal controlAD vs normalPDNoCog vs normalPDCog vs normalPDNoCog vs PDCog | 23 (10 males)22 (10 males)11 (5 males)11 (5 males)23 (10 males) | 72.4 (5.4)72.7 (7.3)72.1 (7.1)73.4 (7.6)71.9 (8.5) | result were showed by AUC value as an index for classification accuracy | T2time for MCV\*nsnsns | T3time for ACA\* |  |  |
| \*\*\*\* | \*\*\*\* | \*ns\*\* | \*N/AN/AN/A | \*ns\*ns |  |
| Hakerem et al. [53] | Acute or chronic schizophrenia | acutechronicnormalnormal vs acutenormal vs chronicacute vs chronic | 37 (16 males)41 (27 males)22 (13 males) | 283022 | nsnsns | N/A | nsnsns | N/A | nsnsns | \*\*ns | Flatn-ess of curvensns ns | N/A | + |
| Dutsch et al. [40] | Type 2 Diabetes mellitus (DM) | DM patientDM patient with PN (peripheral neuropathy) DM patient without PNDM patient with CAN (cardiovascular neuropathy)DM patient without CANnormalall DM vs normalPN vs non PNCAN vs non CAN | 36 (20 males)2016201636 (20 males) | 57.3 (23.5)55.1 (19.7) | 3.90 (1.36)3.76 (0.96)3.79 (0.87)3.67 (0.95)3.88 (0.79)4.49 (0.96)\*nsns | N/A | 1.30 (0.36)1.25 (0.36)1.37 (0.37)1.28 (0.35)1.33 (0.34)1.55 (0.31)\*nsns | N/A | N/A | N/A | N/A | -HRV-blood pressurehelp to identify CAN -nerve conduction-vibratory thresholds-thermal thresholdshelp to identify PN  | + |
| Kuroda et al. [38] | Borderline Diabetes Mellitus (B-DM) and early stage Diabetes Mellitus (E-DM) | B-DM group 1B-DM group 2B-DM group 3E-DM groupcontrolB-DM goup1 vs normalB-DM goup2 vs normalB-DM goup3 vs normalE-DM vs normal | 4 (4 males)6 (6 males)7 (7 males)6 (6 males)9 (9 males) | 48.5 (3.1)48.7 (1.2)48.9 (1.7)46.7 (2.1)50.0 (1.5) | unit for pupil size is $mm^{2}$ instead of mm  | -HRVno differences among groups | + |
| 32.3 (3.0)29.2 (1.8)38.7 (2.1)nsnsns\* | N/A | 10.9 (0.9)15.1 (0.9)nsnsns\* | 40.4 (4.2)39.8 (2.2)45.7 (3.5)59.1 (2.9)54.0 (2.2)\*\*\*ns | 0.2875 (0.0088)0.293 (0.0043)0.2948(0.0071)0.287 (0.0087)0.3009 (0.0059)nsnsnsns | N/A | N/A |
| Harle et al. [59] | Migraine | migraine patienthealthy controlmigraine vs controlinter-eye difference migraine vs normal | 20 (3 males)16 (2 males) | 37.3 range (32-42)36.4range (32-40) | N/A | N/A | nsns | N/A | 0.6380.631ns\* | N/A | anisocoria at baseline and lateraliasation of headache are significantly correlated | N/A | + |
| Kang et al. [29] | Parkinson’s disease (PD) | PD patienthealthy controlPD vs normal | 15 (11 males)18 (9 males) | 65.7 (12.3)60.3 (13.5) | N/A | N/A | N/A | N/A | N/A | N/A | constriction velocity (velocity to minimum diameter)ns | -HRVHF of HRV is significantly lower in PD patient comparing to control group | 0 |
| Dutsch et al. [74] | Familial dysautonomia | FD patienthealthy controlFD vs normal | 14 (8 males)14 (6 males) | 18.7 (8.4)20.4 (6.3) | 3.75 (1.09)5.80 (0.59)\* | N/A | 1.34 (0.21)1.86 (0.14)\* | 22.74 (7.11)30.76 (3.50)\* | N/A | N/A | N/A | N/A | + |
| Fotiou et al. [31] | Alzheimer’s disease (AD) | AD medication freeAD under medicationhealthy controlAD medication free vs normalAD medication free vs AD medicationAD medication vs normal | 555 | The patient group and control group are age and gender matched | N/A | N/A | 0.51 (0.04)0.39 (0.09)0.36 (0.09)nsnsns | N/A | 0.20 (0.03)0.30 (0.05)0.18 (0.07)nsnsns | N/A | latency to maximum constriction\*nsns | N/A | + |
| Inoue and Uemura [68] | Meniere’s disease (MD) | MD in Attack or quasiattack stageMD in interval stagenormal controlMD in Attack or quasiattack stage vs normalMD in interval stage vs normal | 102220 (14 males) | N/A | values shown as differences between the left and right PLR | N/A | +This study only examined the differences between the left and right PLR, which is different than other type of PLR analysis. While MCV was found to be the most sensitive indexes. |
| 0.78 (0.41)0.39 (0.41)0.23 (0.15)\*ns | 0.22 (0.13)0.16 (0.20)0.11 (0.08)nsns | N/A | N/A | 0.013 (0.015)0.013 (0.012)0.007 (0.009)nsns | N/A | N/A |
| Pozzessere et al. [37] | Aging | Group 1 (age 15-29)Group 2 (age 30-44)Group 3 (age 45-59)Group 4 (age 60-75)Group 1 vs Group 4Group 2 vs Group 4Group 3 vs Group 4 | 18 (9 males)12 (6 males)12 (6 males)10 (5 males) | 24.8 (3.3)36.9 (5.5)49.4 (4.4)66.0 (5.4) | 3.554 (0.365)3.416 (0.732)3.412 (0.307)2.852 (0.812)\*nsns | N/A | 1.85 (0.27)1.77 (0.35)1.81 (0.27)1.49 (0.25)\*\*\* | 29.604 (5.590)28.177 (5.157)30.906 (4.354)23.765 (4.053)\*\*\* | 0.2733 (0.0179)0.2763 (0.0226)0.2683 (0.0164)0.2855 (0.0169)nsnsns | 0.523 (0.070)0.522 (0.052)0.536 (0.056)0.557 (0.149)nsnsns | N/A | N/A | + |
| Micieli et al. [34] | Multiple system atrophy (MSA): striatonigral degeneration (SND)orolivopontoce-rebellar (OPCA) | MSAParkinson’s Diseasenormal controlMSA vs normalMSA vs PDPD vs normal | 14 (11 males)23 (15 males)26 (20 males) | 59.1 (7.6)58.5 (9.9)54.2 (11.3) | N/A | N/A | \*\*\* | N/A | \*\*\* | \*\*\* | N/A | N/A | + |
| Ferrari et al. [41] | Diabetes Mellitus (DM) with or without cardiovascular autonomic neuropathy (CAN) | DM patient without CANDM patient with CANnormal controlDM without CAN vs normalDM with CAN vs normalDM with CAN vs DM without CAN | 16 (9 type 1, 7 type 2; 15 males)8 (3 type 1, 5 type 2; 7 males)16 (9 males) | 50 (11)51 (5)44 (13) | unit in pixel/s10.28 (3.49)7.87 (3.48)14.57 (5.32)\*\*ns | N/A | unit in pixel7.40 (1.90)5.35 (2.14)9.62 (1.99)\*\*ns | N/A | 0.26 (0.070)0.29 (0.100)0.20 (0.078)ns\*ns | nsnsns | N/A | -HRV-blood pressureto classify patient group with CAN or without CANSystolic blood pressure result showed significant differences between normal control and patients. Diastolic blood pressure was larger in diabetes with CAN in comparison with controls | + |
| Bitsios et al. [22] | Aging | young groupold groupyoung vs old | 12 (8 males)14 (6 males) | 19.5 range (19-26)69 range (61-79) | \* | N/A | \* | N/A | \*only in high intensity | N/A | N/A | N/A | + |
| Bittner et al. [32] | AD | AD patientsmild cognitive impairment (MCI)normal controlAD vs normalMCI vs normalAD vs MCI | 664244 | 74.4 (7.5)69.8 (8.4)66.4 (8.3) | N/A | N/A | 0.93 (0.31)0.94 (0.32)1.04 (0.28)nsnsns | 0.197 (0.070)0.178 (0.069)0.186 (0.060)nsnsns | 0.282 (0.031)0.285 (0.029)0.275 (0.022)nsnsns | N/A | N/A | N/A | 0 |
| Pfeifer et al. [42] | Diabetes Mellitus (DM) | DM patientsnormal control DM vs normal | 2524 | 47 (3) range: 21-6442 (4) range: 22-79 | 0.30 (0.02)0.35 (0.02)ns |  | 2.19 (0.13)2.67 (0.14)\* | N/A | 0.418 (0.005)0.355 (0.004)\* | N/A | N/A | N/A | + |
| Levy et al. [43] | Diabetes Mellitus (DM) | DM patient(half type1 and half type 2)normal controlDM vs normal | 85 (53 males)67 (32 males) | 44 (15)range: 18-6642 (12)range: 19-67 | 3.82 (1.12)5.68 (1.55)ns | N/A | 1.59 (0.51)1.49 (0.47)ns | 32.91 (9.92)33.02 (8.41)ns | 0.25 (0.06)0.23 (0.05)\* | 0.79range (0.67-0.79)0.78range (0.62-1.04)ns | N/A | -Marstock thermal thresholds-Vibration perception thresholds-HRV-blood pressure-sweat testsACA and MCV correlated with R-R interval, postural systolic and diastolic changes in blood pressure | +only latency was significantly different between DM patients and normal controls |
| Barendregt et al. [66] | rheumatoid arthritis (RH) with ocular dryness | Group 1 (RH patient with ocular dryness)Group 2 (RH patient without ocular dryness)Group 3 (normal control)Group 1 vs Group 2Group 1 vs Group 3 | 18 (0 male)18 (0 male)33 (0 male) | 62range: 32-8255range: 24-7557range: 26-82 | N/A | N/A | N/A | N/A | 0.2600.2450.250\*\* | 0.3500.3200.325\*\* | N/A | N/A | + |
| Pfeifer et al. [46] | non-insulin-dependent diabetes (NIDD) | untreated NIDD patientnormal controlNIDD vs normal | 38 (38 males)58 (58 males) | 57 (1)range: 30-6842 (2)range: 21-78 | N/A | N/A | N/A | N/A | \* | N/A | N/A | -R-R variation as an index of cardiac parasympathetic activitysignificantly correlated with Latency in NIDD patient group | + |
| Piha et al. [49] | obesity | (identical twins)obesenon-obeseobese vs non-obese | 1515 | N/A | 7.35 (2.50)7.57 (2.00)ns | N/A | 2.05 (0.57)2.02 (0.38)ns | 41.1 (7.2)40.1 (4.2)ns | N/A | 0.82 (0.08)0.80 (0.09)ns | N/A | -blood pressure responses during the Valsalva manoeuvre-HRV during deep breathing test-active orthostatic test-isometric handgrip test | 0 |
| Baum et al. [50] | childhood obesity | obesenormal weightobese vs normal weight | 90 (45 males)59 (34 males) | male: 12.2 (2.3) range: 7.9-17.9female:11.9 (2.7)range: 7.4-17.5)male: 12.4 (2.6)range: 8.0-17.3)female: 11.5 (2.6)range: 7.4-17.5 | N/A | N/A | ns | N/A | ns | N/A | constriction velocityns |  | 0 |
| Bremner and Smith [75] | generalized autonomic neuropathy which sub-divided into specific diseases | amyloidosismultiple system atrophy (MSA)pure autonomic failure (PAF)diabetesnormal controlMSA vs normalPAF vs normalnormal vs amyloidosisnormal vs diabetes | 21 (14 males)38 (26 males)33 (15 males)29 (16 males)315 (172 males) | median age: 57range:31-70median age: 58range:40-79median age: 60range: 30-80median age: 46range: 19-76median age: 42 (17-82) | result was based on the comparison of percentage of abnormality within different groups % | N/A | + |
| N/A | N/A | 7.99.728.633.32.0nsns\*\* | N/A | N/A | N/A | N/A |

Note:

The assumption is:

Pupil light reflex is an effective method to measure parasympathetic activity. If a disease is related to parasympathetic dysfunction, then the patients with this type of disease should reflect a different (attenuated) PLR than the comparison group.

N/A: not applicable

ns: not significant

\* : significant

^\*: most sensitive parameters as claimed by the author(s) of that study

+: positive relationship to the assumption

-: negative relationship to the assumption

0: no difference between groups

Only the parameters considered to be related to parasympathetic nervous system function were included (PNS only)

For PLR parameters:

MCV: maximum constriction velocity

MCA: maximum constriction acceleration

ACA: absolute constriction amplitude

RCA: relative constriction amplitude