

Increased very low frequency pulsations and decreased cardiorespiratory pulsations suggest altered brain clearance in narcolepsy

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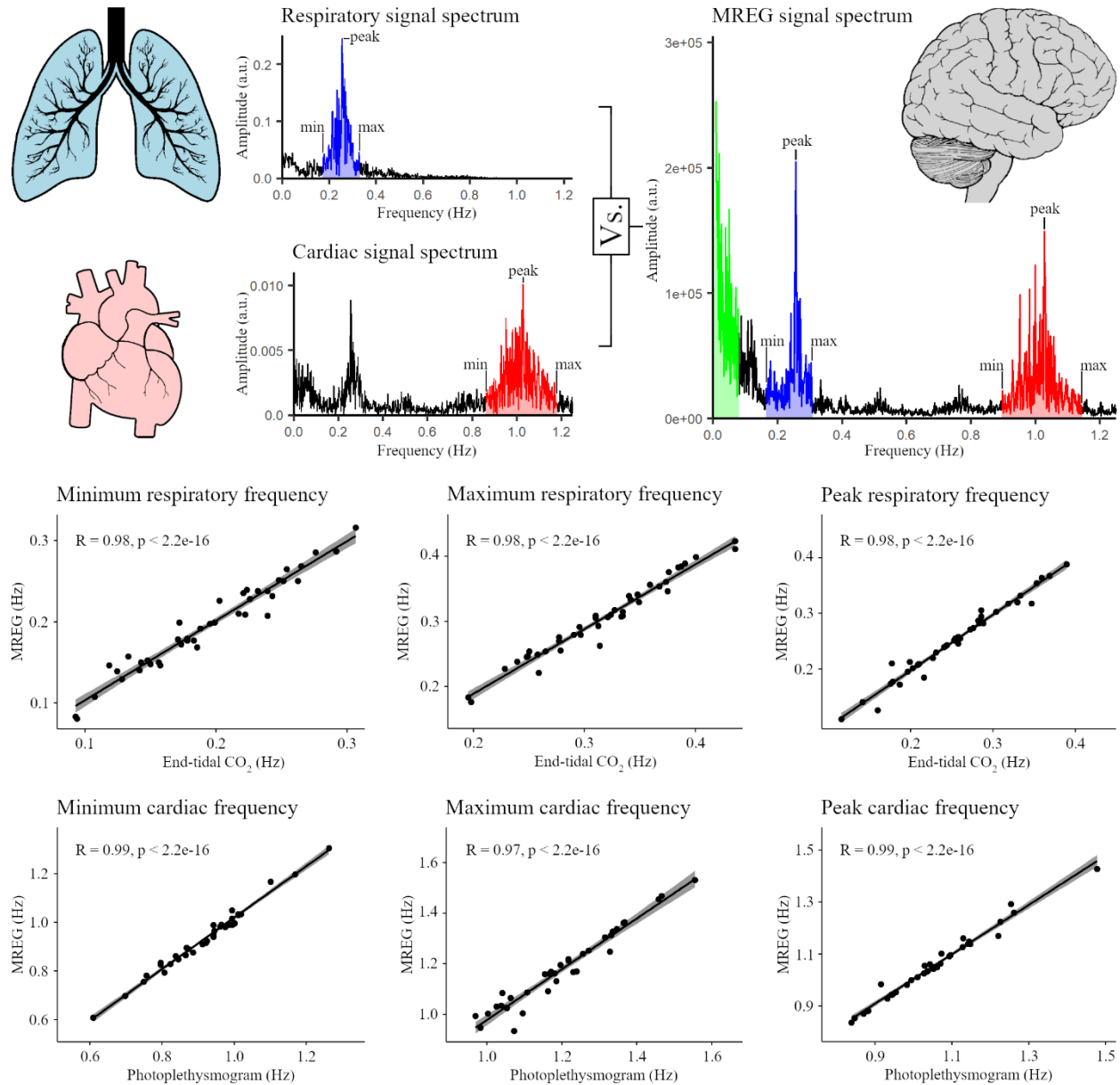
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Supplementary information

Supplementary Figure 1. Cardiorespiratory frequency comparisons between modalities.

Pulsation range estimation verification between MREG and physiological measurements



Individual minimum, maximum, and peak values of respiration (blue signal) and cardiac (red signal) pulse derived from end-tidal CO₂ (n = 41 vs. 41) and photoplethysmogram (n = 35 vs. 35), respectively, correlate extremely well with corresponding values estimated from magnetic resonance encephalography (MREG) data. Min = minimum frequency, max = maximum frequency, peak = peak frequency, green signal indicates very low frequency band, black dots denote individual data points, grey are indicates 95% confidence interval, R = Pearson correlation coefficient, p = p-value.

Supplementary Table 1. Brainstem AAN nuclei-wise p-values and statistical information for mean variance.

	MREG _{vlf}	MREG _{resp}	MREG _{card}
DR	p = 0.37; NT1: M = 3377 [Q1: 2371, Q3: 13515]; HC: M = 4367 [Q1: 1238, Q3: 5810]; W = 281; 95% CI [-1636, 3531]	p = 0.35; NT1: M = 5842 [Q1: 2726, Q3: 9489]; HC: M = 7489 [Q1: 4222, Q3: 11564]; W = 201; 95% CI [-4773, 1551]	p = 0.027; NT1: M = 7778 [Q1: 6512, Q3: 13269]; HC: M = 12718 [Q1: 7986, Q3: 30572]; W = 148; 95% CI [-16042, -397]
LC	p = 0.17; NT1: M = 3368 [Q1: 2098, Q3: 6652]; HC: M = 2920 [Q1: 998, Q3: 4103]; W = 301; 95% CI [-551, 2592]	p = 0.68; NT1: M = 5073 [Q1: 2363, Q3: 11717]; HC: M = 5489 [Q1: 3714, Q3: 12880]; W = 224; 95% CI [-3796, 2457]	p = 0.35; NT1: M = 8903 [Q1: 4377, Q3: 11259]; HC: M = 9103 [Q1: 6551, Q3: 21534]; W = 201; 95% CI [-6186, 1907]
MR	p = 0.30; NT1: M = 3755 [Q1: 1917, Q3: 8222]; HC: M = 3091 [Q1: 1288, Q3: 5897]; W = 287; 95% CI [-1027, 2849]	p = 0.99; NT1: M = 4340 [Q1: 2407, Q3: 15805]; HC: M = 6313 [Q1: 2290, Q3: 11598]; W = 241; 95% CI [-3603, 3433]	p = 0.080; NT1: M = 4637 [Q1: 3514, Q3: 7400]; HC: M = 8392 [Q1: 3962, Q3: 17034]; W = 167; 95% CI [-9041, 254]
MRF	p = 0.29; NT1: M = 3648 [Q1: 2366, Q3: 12578]; HC: M = 3086 [Q1: 1428, Q3: 7252]; W = 288; 95% CI [-949, 3835]	p = 0.22; NT1: M = 3481 [Q1: 2056, Q3: 9367]; HC: M = 5911 [Q1: 3576, Q3: 10919]; W = 189; 95% CI [-4068, 944]	p = 0.0031*; r = 0.44; NT1: M = 6563 [Q1: 3348, Q3: 10376]; HC: M = 12823 [Q1: 7830, Q3: 26854]; W = 118; 95% CI [-12950, -2017]
PAG	p = 0.18; NT1: M = 6080 [Q1: 3251, Q3: 13544]; HC: M = 4319 [Q1: 1679, Q3: 9889]; W = 300; 95% CI [-1204, 5901]	p = 0.58; NT1: M = 5805 [Q1: 2870, Q3: 10299]; HC: M = 7585 [Q1: 4455, Q3: 12851]; W = 218; 95% CI [-4825, 2408]	p = 0.062; NT1: M = 16018 [Q1: 7867, Q3: 23583]; HC: M = 22116 [Q1: 13035, Q3: 53286]; W = 162; 95% CI [-25053, 551]
PBC	p = 0.13; NT1: M = 3323 [Q1: 2232, Q3: 6146]; HC: M = 2514 [Q1: 1044, Q3: 3950]; W = 307; 95% CI [-344, 2555]	p = 0.86; NT1: M = 4159 [Q1: 2800, Q3: 8087]; HC: M = 4348 [Q1: 2293, Q3: 10477]; W = 250; 95% CI [-2503, 2537]	p = 0.17; NT1: M = 4332 [Q1: 2941, Q3: 5959]; HC: M = 5551 [Q1: 3614, Q3: 12125]; W = 183; 95% CI [-4117, 511]
PO	p = 0.26; NT1: M = 3708 [Q1: 2124, Q3: 7265]; HC: M = 3052 [Q1: 1275, Q3: 5895]; W = 291; 95% CI [-794, 2856]	p = 0.95; NT1: M = 4423 [Q1: 2348, Q3: 14195]; HC: M = 5640 [Q1: 2213, Q3: 10654]; W = 245; 95% CI [-3551, 3462]	p = 0.076; NT1: M = 4177 [Q1: 2852, Q3: 7793]; HC: M = 7695 [Q1: 4136, Q3: 16301]; W = 166; 95% CI [-8850, 253]
PPN	p = 0.48; NT1: M = 2533 [Q1: 1915, Q3: 10433]; HC: M = 2729 [Q1: 973, Q3: 4756]; W = 273; 95% CI [-912, 2002]	p = 0.84; NT1: M = 4143 [Q1: 1759, Q3: 9989]; HC: M = 4723 [Q1: 2216, Q3: 9631]; W = 233; 95% CI [-2602, 2874]	p = 0.039; NT1: M = 2688 [Q1: 1766, Q3: 4022]; HC: M = 3947 [Q1: 2365, Q3: 5928]; W = 154; 95% CI [-2824, -88]
VTa	p = 0.48; NT1: M = 2013 [Q1: 1155, Q3: 6201]; HC: M = 2099 [Q1: 786, Q3: 4041]; W = 273; 95% CI [-981, 1715]	p = 0.81; NT1: M = 5190 [Q1: 1970, Q3: 12736]; HC: M = 3550 [Q1: 2281, Q3: 8281]; W = 253; 95% CI [-1884, 4100]	p = 0.031; NT1: M = 2531 [Q1: 1848, Q3: 4806]; HC: M = 4453 [Q1: 3384, Q3: 7527]; W = 150; 95% CI [-3161, -149]

DR = dorsal raphe, LC = locus caeruleus, MR = median raphe, MRF = midbrain reticular formation, PAG = periaqueductal gray, PBC = parabrachial complex, PO = pontis oralis, PPN = pedunculopontine nucleus, VTA = ventral tegmental area, * = corrected significant p-value ($p < 0.016$), n = 22 vs. 22, M = median, Q1 = 1st quartile, Q3 = 3rd quartile, 95% CI = 95% confidence interval, W = Wilcoxon test statistic, r = Wilcoxon effect size, MREG_{vlf} = very low frequency filtered magnetic resonance encephalography data, MREG_{resp} = respiratory frequency filtered MREG data, MREG_{card} = cardiac frequency filtered MREG data. All p-values displayed with means were calculated with Student's t-test and all p-values displayed with medians were calculated with Wilcoxon rank sum test.

Supplementary Table 2. Brainstem AAN nuclei-wise p-values and statistical information for mean fractional variance.

	MREG _{vlf}	MREG _{resp}	MREG _{card}
DR	p = 0.0050*; r = 0.42; NT1: M = 0.11 [Q1: 0.062, Q3: 0.19]; HC: M = 0.057 [Q1: 0.043, Q3: 0.092]; W = 360; 95% CI [0.013, 0.095]	p = 0.60; NT1: M = 0.11 [Q1: 0.074, Q3: 0.15]; HC: M = 0.098 [Q1: 0.056, Q3: 0.16]; W = 265; 95% CI [-0.031, 0.050]	p = 0.017*; d = 0.75; NT1: $\mu = 0.18 \pm 0.084$ SD; HC: $\mu = 0.24 \pm 0.090$ SD; 42 df; T = -2.4859; 95% CI [-0.12, -0.012]
LC	p = 0.0017**; r = 0.46; NT1: M = 0.091 [Q1: 0.069, Q3: 0.13]; HC: M = 0.055 [Q1: 0.030, Q3: 0.076], W = 373; 95% CI [0.013, 0.069]	p = 0.84; NT1: M = 0.1074 [Q1: 0.075, Q3: 0.15]; HC: M = 0.12 [Q1: 0.057, Q3: 0.17], W = 251; 95% CI [-0.048, 0.040]	p = 0.24; NT1: $\mu = 0.18 \pm 0.082$ SD; HC: $\mu = 0.21 \pm 0.082$ SD; 42 df; T = -1.1923; 95% CI [-0.079, 0.020]
MR	p = 0.0050*; r = 0.42; NT1: M = 0.12 [Q1: 0.088, Q3: 0.19]; HC: M = 0.062 [Q1: 0.043, Q3: 0.098], W = 360; 95% CI [0.017, 0.093]	p = 0.58; NT1: M = 0.14 [Q1: 0.11, Q3: 0.19]; HC: M = 0.13 [Q1: 0.066, Q3: 0.22], W = 266; 95% CI [-0.046, 0.069]	p = 0.12; NT1: $\mu = 0.16 \pm 0.088$ SD; HC: $\mu = 0.21 \pm 0.12$ SD; 42 df; T = -1.5685; 95% CI [-0.11, 0.014]
MRF	p = 0.00017*; d = 1.3; NT1: $\mu = 0.17 \pm 0.089$ SD; HC: $\mu = 0.083 \pm 0.037$ SD; 27.836 df; T = 4.3398; 95% CI [0.047, 0.13]	p = 0.77; NT1: M = 0.13 [Q1: 0.090, Q3: 0.17]; HC: M = 0.11 [Q1: 0.077, Q3: 0.17], W = 255; 95% CI [-0.041, 0.044]	p = 0.012*; d = 0.79; NT1: $\mu = 0.19 \pm 0.10$ SD; HC: $\mu = 0.27 \pm 0.099$ SD; 42 df; T = -2.6168; 95% CI [-0.14, -0.018]
PAG	p = 0.0036*; r = 0.43; NT1: M = 0.12 [Q1: 0.063, Q3: 0.24]; HC: M = 0.062 [Q1: 0.033, Q3: 0.090], W = 364; 95% CI [0.015, 0.11]	p = 0.27; NT1: M = 0.089 [Q1: 0.066, Q3: 0.11]; HC: M = 0.062 [Q1: 0.042, Q3: 0.12], W = 290; 95% CI [-0.016, 0.047]	p = 0.031*; d = 0.67; NT1: $\mu = 0.20 \pm 0.096$ SD; HC: $\mu = 0.27 \pm 0.11$ SD; 42 df; T = -2.2344; 95% CI [-0.13, -0.0068]
PBC	p = 0.0033*; r = 0.44; NT1: M = 0.12 [Q1: 0.095, Q3: 0.18]; HC: M = 0.077 [Q1: 0.044, Q3: 0.10], W = 365; 95% CI [0.015, 0.087]	p = 0.88; NT1: M = 0.14 [Q1: 0.10, Q3: 0.16]; HC: M = 0.13 [Q1: 0.075, Q3: 0.22], W = 249; 95% CI [-0.048, 0.045]	p = 0.092; NT1: $\mu = 0.15 \pm 0.077$ SD; HC: $\mu = 0.19 \pm 0.082$ SD; 42 df; T = -1.7222; 95% CI [-0.090, 0.0071]
PO	p = 0.0068*; r = 0.40; NT1: M = 0.12 [Q1: 0.086, Q3: 0.19]; HC: M = 0.065 [Q1: 0.041, Q3: 0.10], W = 356; 95% CI [0.015, 0.093]	p = 0.67; NT1: M = 0.13 [Q1: 0.11, Q3: 0.18]; HC: M = 0.13 [Q1: 0.073, Q3: 0.22], W = 261; 95% CI [-0.044, 0.064]	p = 0.11; NT1: $\mu = 0.16 \pm 0.088$ SD; HC: $\mu = 0.21 \pm 0.12$ SD; 42 df; T = -1.6196; 95% CI [-0.12, 0.013]
PPN	p = 0.0054*; r = 0.41; NT1: M = 0.15 [Q1: 0.12, Q3: 0.26]; HC: M = 0.11 [Q1: 0.065, Q3: 0.14], W = 359; 95% CI [0.016, 0.11]	p = 0.99; NT1: $\mu = 0.20 \pm 0.10$ SD; HC: $\mu = 0.20 \pm 0.10$ SD; 42 df; T = 0.0026758; 95% CI [-0.062, 0.063]	p = 0.041; NT1: M = 0.12 [Q1: 0.080, Q3: 0.22]; HC: M = 0.17 [Q1: 0.14, Q3: 0.21], W = 155; 95% CI [-0.092, -0.0059]
VTa	p = 0.098; NT1: M = 0.12 [Q1: 0.080, Q3: 0.23]; HC: M = 0.010 [Q1: 0.068, Q3: 0.13], W = 313; 95% CI [-0.0052, 0.083]	p = 0.79; NT1: M = 0.18 [Q1: 0.14, Q3: 0.28]; HC: M = 0.20 [Q1: 0.15, Q3: 0.28], W = 254; 95% CI [-0.055, 0.070]	p = 0.033; NT1: M = 0.11 [Q1: 0.069, Q3: 0.26]; HC: M = 0.20 [Q1: 0.17, Q3: 0.34], W = 151; 95% CI [-0.13, -0.011]

DR = dorsal raphe, LC = locus caeruleus, MR = median raphe, MRF = midbrain reticular formation, PAG = periaqueductal gray, PBC = parabrachial complex, PO = pontis oralis, PPN = pedunculopontine nucleus, VTA = ventral tegmental area, * = corrected significant p-value ($p < 0.033$), ** = corrected significant p-value ($p < 0.016$), n = 22 vs. 22, μ = mean, M = median, Q1 = 1st quartile, Q3 = 3rd quartile, 95% CI = 95% confidence interval, W = Wilcoxon test statistic, r = Wilcoxon effect size, T = t-test statistic, d = Cohen's d effect size. MREG_{vlf} = very low frequency filtered magnetic resonance encephalography data, MREG_{resp} = respiratory frequency filtered MREG data, MREG_{card} = cardiac frequency filtered MREG data. All p-values displayed with means were calculated with Student's t-test and all p-values displayed with medians were calculated with Wilcoxon rank sum test.