

Background

- Delayed Sleep-Wake Phase Disorder (DSWPD) is one of the most common among circadian sleep-wake disorders, characterized by a 'significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time'¹
- DSWPD patients are reported to have different phenotypes^{2,3}
- Patients with DSWPD commonly report depressive symptoms^{3,4}
- Dim Light Melatonin Onset (DLMO) is a marker of the internal circadian timing commonly used in clinical settings⁵
- For healthy subjects the time between DLMO to bedtime is on average ~2h, ranging from ~4.5h before to 0.5h after sleep onset time⁶

AIM: To compare circadian and sleep behavioral variables in DSWPD patients with and without a diagnosis of depression

Methods

Participants

- 76 DSWPD patients; 26 with a diagnosis of depression (DSWPD-D) and 50 without (DSWPD-ND)
- Age: Mean 37 (16-92 years) (see Table 1)

Methods

- Analysis of the clinical records of DSWPD patients, from a Sleep Medicine Center in Lisbon, Portugal
- In-home salivary DLMO was measured as a marker for circadian phase
- We calculated the phase angle difference between the DLMO to the sleep-wake time variables (Sleep Onset, Mid-sleep and Waketime)
- Mid-sleep on free days corrected (MSF_{sc})⁷ was calculated from the sleep-wake behavior reported in the clinical records as a *proxi* for chronotype

Table 1. Summary of demographic data, sleep, and biological phases of DSWPD patients with and without depression

	Without Depression	Depression	p-value
Sample size	50	26	
Age (years) - median [IQR]	35 [24 – 47]	35 [27 – 41]	0.935
Sex: male n (%)	31 (62)	11 (42)	0.101
Employed: yes n (%)	42 (84)	18 (69)	0.134
Medication			
Melatonin n (%)	27 (54)	13 (50)	0.740
Hypnotics n (%)	18 (36)	7 (26.9)	0.424
Antidepressants n (%)	20 (40)	13 (50)	0.404
Sleep Timings			
Bedtime _w (h) - mean (SD)	2:54 (1:04)	3:12 (1:13)	0.321
Waketime _w (h) - median [IQR]	8:30 [7:20 – 10:38]	10:45 [9:00 – 12:00]	0.006
Mid-sleep _w (h) - median [IQR]	5:30 [4:50 – 7:00]	6:47 [5:50 – 7:46]	0.025
Bedtime _f (h) - mean (SD)	3:57 (1:31)	3:58 (1:15)	0.975
Waketime _f (h) - median [IQR]	12:00 [11:00 – 13:00]	12:00 [11:00 – 13:00]	0.627
Mid-sleep _f (h) - mean (SD)	7:51 (1:34)	8:03 (1:17)	0.623
Sleep Dur _w (h) - mean (SD)	6.15 (1:56)	7.29 (0:96)	0.006
Sleep Dur _f (h) - mean (SD)	7.81 (1:62)	8.16 (1:01)	0.319
Sleep Dur _{week} (h) - mean (SD)	6.74 (1:41)	7.80 (0:99)	0.001
Social Jet Lag (h) - median [IQR]	2.17 [1:25 – 2:90]	0.75 [0:00 – 2:00]	0.002
MSF _{sc} (h) - mean (SD)	7:22 (1:40)	7:57 (1:24)	0.154
Circadian phase			
DLMO (h) - mean (SD)	1:09 (1:35)	1:49 (1:24)	0.079
Relationships between circadian phase and sleep			
DLMO - Bedtime _w mean (SD)	-1.83 (1.35)	-1.66 (1.34)	0.592
DLMO - Waketime _w mean (SD)	-8.23 (2.23)	-9.37 (1.52)	0.022
DLMO - Mid-sleep _w mean (SD)	-5.00 (1.61)	-5.52 (1.17)	0.148
DLMO - MSF _{sc} mean (SD)	-6.25 (1.83)	-6.09 (1.39)	0.715

Mann-Whitney, Student t or Chi-square tests according to data distribution. DSWPD – Delayed Sleep-Wake Phase Disorder; DLMO – Dim Light Melatonin Onset; IQR – interquartile range (reported as Q1 and Q3); MSF_{sc} – mid-point of sleep on free-days sleep corrected; variables reported as _w refer to workdays and variables reported as _f refer to free days. For MSF_{sc} the samples are n = 23 (Depressed) and n = 44 (Non-depressed) due to the use of alarm clock on free days; For SJL the samples are n = 18 (Depressed) and n = 39 (Non-depressed) due to report of having 0 or 7 workdays; All time values presented are given in local time. Statistical differences were set at a p < 0.05.

Table 2. Logistic Regression: variables associated with depression

	Model 1	Model 2
	OR [CI 95 %]	OR [CI 95 %]
Age	0.98 [0.92 - 1.05]	0.98 [0.92 - 1.04]
Sex (male)	0.61 [0.15 - 2.41]	0.62 [0.16 - 2.38]
Sleep Dur _{week} (higher than 6.76h)	11.44 [1.52 - 86.02]	10.15 [1.75 - 58.97]
SJL (lower than 1.12h)	6.48 [1.17 - 35.80]	6.10 [1.46 - 25.53]
Mid-sleep _w	1.06 [0.48 - 2.34]	
DLMO - Waketime _w	1.10 [0.64 - 1.89]	
Nagelkerke R²		
	0.395	0.393
Cox & Snell R²		
	0.282	0.280
-log likelihood		
	52.236	52.358
χ²		
	18.860	18.739
AUC		
	0.843	0.845

Model 1 is composed of variables associated with depression in the univariate analysis (Values adjusted for age and sex); Model 2 is composed of significant variables in Model 1 (Values adjusted for age and sex); Mid-sleep_w – mid-sleep on workdays, Sleep Dur_{week} – weekly sleep duration, DLMO – waketime on workdays – dim light melatonin onset distance to waketime on workdays, OR – odds ratio, CI – confidence interval, AUC – Area Under the Curve; the AUC of the ROC curve calculated from the predicted values of the models. Statistical differences were set at a p < 0.05.

Results

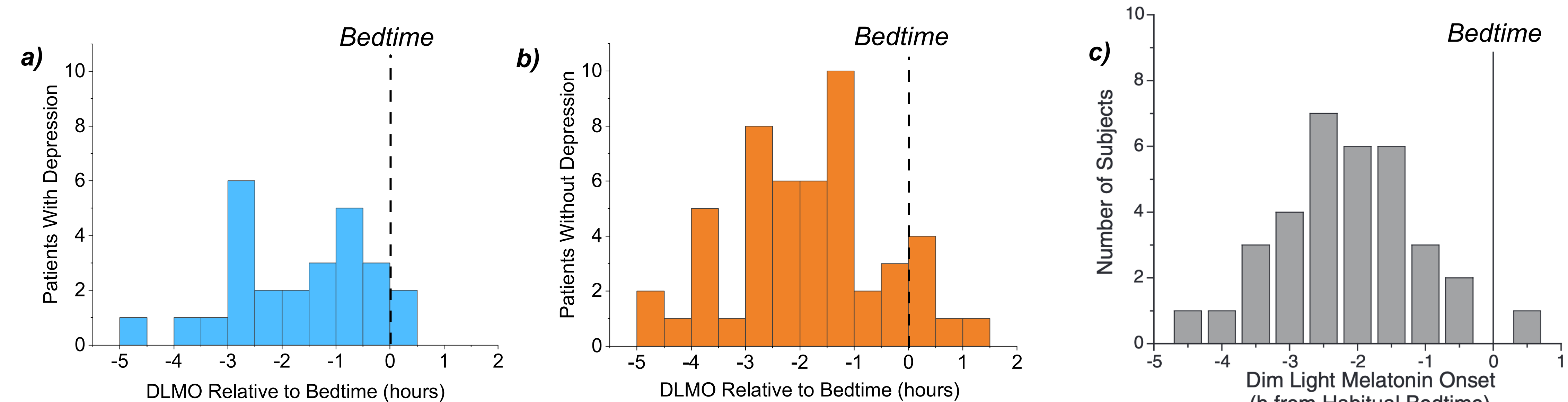


Figure 1. Range of phase relationships between DLMO and bedtime are similar for DSWPD patients, with and without depression, and compared to published ranges in healthy controls. Upper figures – DLMO timing to bedtime distribution. Dash line represents bedtime. **a)** DSWPD patients with comorbid depression; **b)** DSWPD patients without comorbid depression; **c)** Healthy participants from Duffy and Wright, 2005.

For further data on phase distance from DLMO to bedtime in healthy participants see poster n° 72.

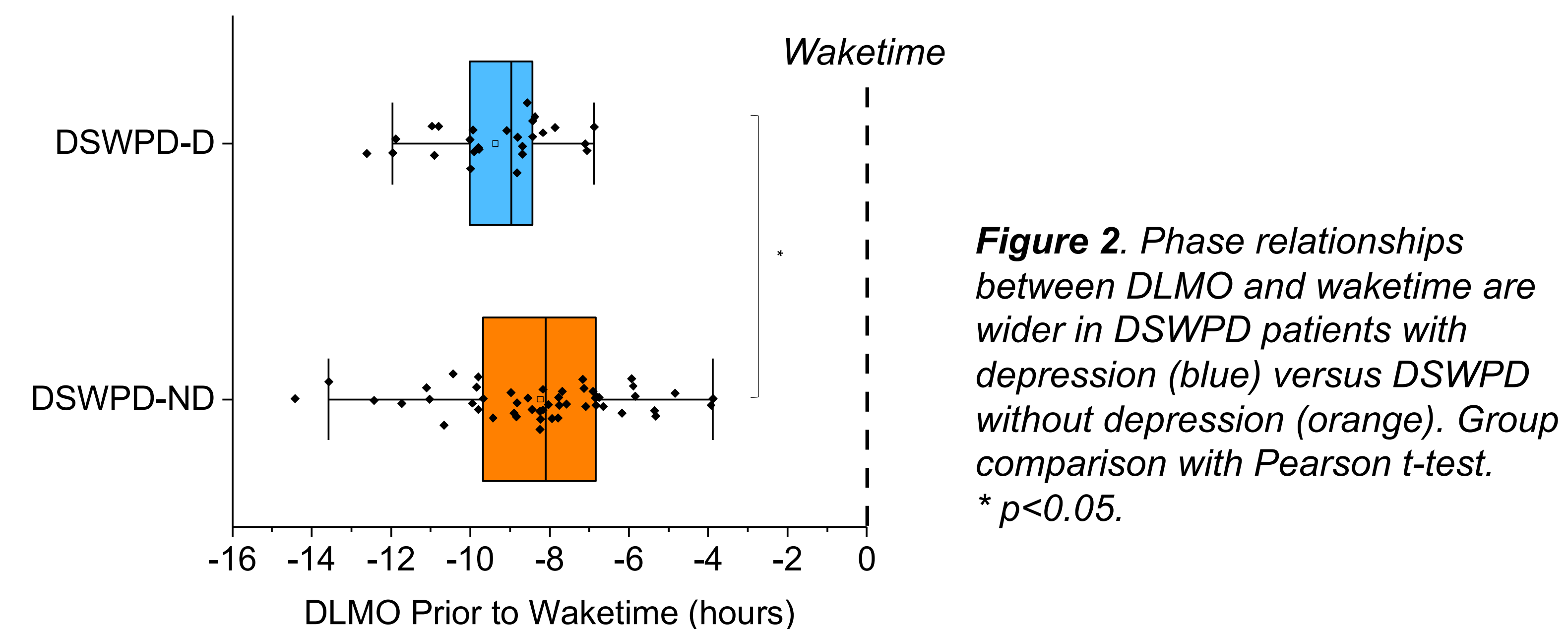


Figure 2. Phase relationships between DLMO and waketime are wider in DSWPD patients with depression (blue) versus DSWPD without depression (orange). Group comparison with Pearson t-test. * p < 0.05.

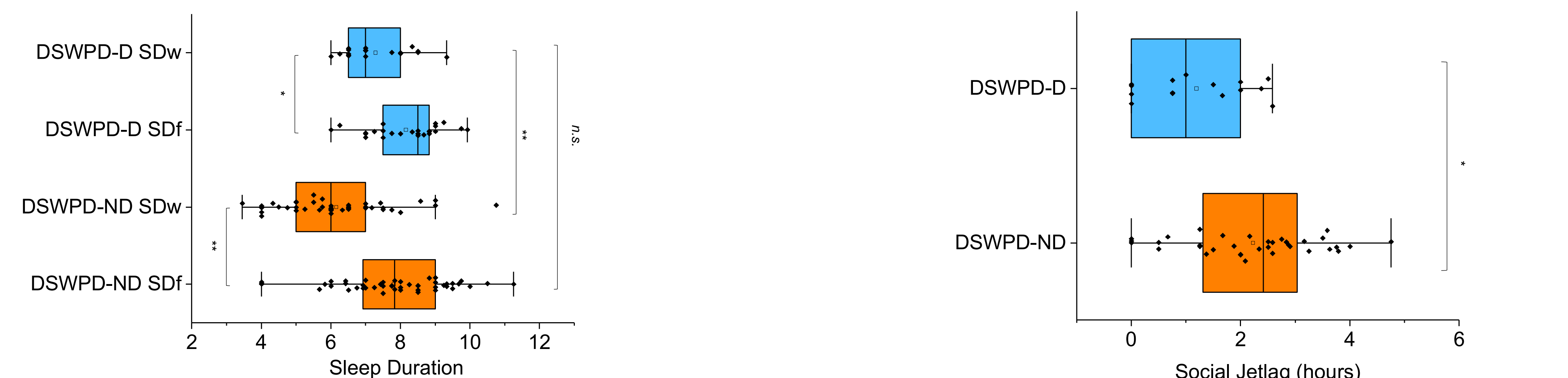


Figure 3. Sleep Duration was shorter for work versus free days and was shorter for patients without depression (DSWPD-ND) versus those with (DSWPD-D) on workdays only. Pearson t-test for group comparisons and paired samples t-test for comparisons between work and free days *p < 0.05, **p < 0.01; n.s. – non-significant.

Figure 4. Social Jet Lag was greater for patients without depression (DSWPD-ND) versus patients with depression (DSWPD-D). Mann-Whitney test. *p < 0.05

Summary and Conclusions

DSWPD patients with and without depression showed a similar range in the time between DLMO and bedtime and are like that reported for healthy subjects⁶.

DSWPD patients with depression showed a wider phase relation between DLMO and waketime versus DSWPD patients without depression. DSWPD patients without depression slept less on workdays, but not free days, and had more social jetlag than DSWPD patients with depression. Future research is needed to replicate findings in larger samples and evaluate the phase relationship between DLMO_{off} and waketime. It is also important to determine the stability of these phenotypic differences and how they may contribute to the etiology and effective treatment of DSWPD.

References

ICSD3 - International Classification of Sleep Disorders, AASM 2014 - McQuibban, E.M., Buys, A.C., Murray, J.M., et al. The phenotype of the disorder distinguishes between circadian and non-circadian delayed sleep phase disorder (DSPD) phenotypes in young adults. *PLoS One*. 2016; 11(1):e0146182. doi:10.1371/journal.pone.0146182. Mahoney, J., Shetter, T., McClure, M., et al. Prevalence of Circadian Misalignment and Its Association with Depressive Symptoms in Delayed Sleep Phase Disorder. *Sleep*. 2017; 40(12):E11. doi:10.1093/sleep/zwx002. Atlas, T., Curtis, M.C. Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorder. *Sleep Med Rev*. 2013; 18(1):1-7. doi:10.1016/j.smrv.2013.12.001. Duffy, J.F., Wright, K.P. Entrainment of the human circadian system by light. *J Biol Rhythms*. 2005; 20(2):226-238. doi:10.1177/0748730405277965. Figueiro, C., Melamed, S.G., Logan, L., et al. Paiva, T., Reinherz, T. Validation of the Portuguese Version of the Munich Chronotype Questionnaire (MCTQ). *Front Physiol*. 2020; 11. doi:10.3389/fphys.2020.00795

Funding

Travel and registration PDE/BDE/114584/2016

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