**Cortisol awakening response and cognitive performance in hypertensive and normotensive older people.**

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**Supplementary material**

1. **Selection of covariates for regression analyses**

Based on previous studies (e.g., Clow et al., 2010; Cournot et al., 2006; Sindi et al., 2013; Wright and Steptoe, 2005), we selected the following covariates to control for their possible effects on CAR and/or cognitive performance: age, SES, BMI, mean cortisol levels during the session, change in cortisol levels during the session, awakening time, sex, and physical activity. In order to avoid overfitting the regression analyses, we included as covariates only those variables that showed a correlation p<0.010 with the CAR and/or cognitive outcomes. Tables S1 and S2 show the correlation analyses for the complete sample and the 2 Day-CAR subgroup, respectively.

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| Table S1. Correlation analyses for the selected covariates, CAR and cognitive outcomes for the complete sample. |
|  |  | Age | SES | BMI | Mean cortisolsession | Change cortisolsession | Mean sleep time | Awak. time | Sex | Physical activity |
| CAR | *r* | 0.205 | -0.194 | 0.013 | 0.002 | **0.236** | -0.027 | -0.168 | 0.131 | -0.056 |
|  | *p* | 0.137 | 0.161 | 0.924 | 0.988 | **0.085** | 0.844 | 0.224 | 0.344 | 0.686 |
| TMT-A | *r* | **0.331** | **-0.305** | 0.045 | **-0.243** | **0.253** | 0.056 | -0.129 | 0.218 | 0.090 |
|  | *p* | **0.016** | **0.026** | 0.749 | **0.080** | **0.068** | 0.688 | 0.359 | 0.118 | 0.522 |
| TMT-B | *r* | **0.438** | **-0.246** | 0.128 | -0.011 | 0.043 | 0.018 | -0.172 | 0.223 | 0.077 |
|  | *p* | **0.001** | **0.076** | 0.361 | 0.939 | 0.761 | 0.899 | 0.218 | 0.108 | 0.584 |
| W-C naming | *r* | **-0.326** | **0.307** | -0.146 | 0.020 | 0.092 | -0.082 | 0.037 | -0.187 | 0.043 |
|  | *p* | **0.017** | **0.025** | 0.298 | 0.888 | 0.513 | 0.557 | 0.794 | 0.181 | 0.761 |
| Stroop Interf. | *r* | **0.274** | 0.063 | 0.044 | -0.172 | -0.149 | -0.194 | -0.163 | -0.113 | -0.159 |
|  | *p* | **0.047** | 0.652 | 0.754 | 0.219 | 0.288 | 0.165 | 0.243 | 0.421 | 0.254 |
| DS-Forward | *r* | **-0.260** | **0.331** | 0.137 | -0.131 | -0.071 | -0.086 | -0.058 | **-0.551** | -0.065 |
|  | *p* | **0.057** | **0.014** | 0.323 | 0.347 | 0.608 | 0.536 | 0.679 | **<0.001** | 0.641 |
| DS-Backward | *r* | -0.169 | 0.181 | **0.325** | -0.151 | -0.133 | -0.094 | -0.027 | **-0.335** | -0.167 |
|  | *p* | 0.222 | 0.190 | **0.017** | 0.275 | 0.339 | 0.499 | 0.847 | **0.013** | 0.228 |
| RAVLT Learning | *r* | **-0.247** | 0.097 | -0.049 | -0.022 | **-0.231** | -0.078 | 0.173 | 0.133 | **-0.262** |
|  | *p* | **0.071** | 0.485 | 0.726 | 0.874 | **0.093** | 0.577 | 0.210 | 0.338 | **0.056** |
| RAVLT Immed. | *r* | -0.133 | -0.010 | -0.063 | 0.193 | -0.171 | 0.020 | 0.157 | 0.187 | -0.081 |
|  | *p* | 0.338 | 0.942 | 0.653 | 0.162 | 0.215 | 0.885 | 0.256 | 0.175 | 0.562 |
| RAVLT Learning | *r* | 0.070 | -0.105 | 0.034 | **-0.535** | 0.096 | **-0.297** | -0.171 | 0.069 | -0.078 |
|  | *p* | 0.614 | 0.448 | 0.809 | **<0.001** | 0.491 | **0.029** | 0.217 | 0.619 | 0.573 |
| **Legend.** Awak. Time: Awakening time; TMT: Trail Making Test; W-C naming: Word and Color task of the Stroop test; Stroop Interf.: Stroop Interference; DS: Digit Span; RAVLT: Rey Auditory Verbal Learning Test. |
| Table S2. Correlation analyses for the selected covariates, CAR, and cognitive outcomes for the 2 Day-CAR subgroup. |
|  |  | Age | SES | BMI | Mean cortisol | Change cortisol | Mean sleep time | Awak. time | Sex | Physical activity |
| CAR | *r* | **0.320** | -0.229 | -0.020 | 0.128 | 0.228 | 0.063 | -0.174 | 0.084 | -0.045 |
|  | *p* | **0.047** | 0.161 | 0.905 | 0.438 | 0.163 | 0.703 | 0.289 | 0.610 | 0.784 |
| TMT-A | *r* | **0.508** | **-0.293** | -0.027 | -0.034 | -0.004 | 0.185 | -0.128 | -0.047 | 0.163 |
|  | *p* | **0.001** | **0.075** | 0.874 | 0.839 | 0.983 | 0.266 | 0.444 | 0.778 | 0.329 |
| TMT-B | *r* | **0.548** | -0.187 | 0.067 | 0.105 | -0.156 | 0.130 | -0.160 | 0.120 | 0.199 |
|  | *p* | **<0.001** | 0.260 | 0.687 | 0.532 | 0.350 | 0.438 | 0.336 | 0.472 | 0.231 |
| W-C naming | *r* | **-0.408** | **0.330** | -0.125 | **-0.296** | **0.283** | -0.101 | -0.004 | -0.087 | -0.063 |
|  | *p* | **0.011** | **0.043** | 0.453 | **0.071** | **0.086** | 0.548 | 0.981 | 0.605 | 0.707 |
| Stroop Interf. | *r* | 0.198 | -0.058 | 0.086 | -0.256 | -0.024 | **-0.290** | -0.258 | 0.039 | -0.160 |
|  | *p* | 0.234 | 0.731 | 0.608 | 0.120 | 0.886 | **0.078** | 0.117 | 0.816 | 0.338 |
| DS-Forward | *r* | -0.266 | **0.317** | 0.224 | -0.005 | 0.114 | -0.024 | 0.047 | **-0.473** | -0.008 |
|  | *p* | 0.101 | **0.049** | 0.170 | 0.974 | 0.489 | 0.884 | 0.777 | **0.002** | 0.960 |
| DS-Backward | *r* | -0.104 | 0.122 | **0.441** | **-0.305** | 0.065 | -0.248 | -0.081 | **-0.284** | **-0.316** |
|  | *p* | 0.528 | 0.459 | **0.005** | **0.059** | 0.692 | 0.128 | 0.623 | **0.080** | **0.050** |
| RAVLT Learning | *r* | **-0.275** | 0.092 | -0.054 | -0.225 | -0.143 | -0.189 | 0.068 | 0.203 | **-0.386** |
|  | *p* | **0.090** | 0.578 | 0.744 | 0.168 | 0.385 | 0.248 | 0.680 | 0.214 | **0.015** |
| RAVLT Immed. | *r* | -0.193 | -0.077 | -0.104 | -0.174 | -0.041 | -0.213 | -0.114 | 0.267 | -0.231 |
|  | *p* | 0.239 | 0.643 | 0.529 | 0.290 | 0.806 | 0.193 | 0.489 | 0.101 | 0.156 |
| RAVLT Learning | *r* | -0.017 | 0.046 | -0.116 | -0.188 | -0.170 | -0.095 | 0.155 | -0.005 | -0.011 |
|  | *p* | 0.919 | 0.779 | 0.483 | 0.253 | 0.301 | 0.567 | 0.347 | 0.974 | 0.949 |
| **Legend.** Awak. Time: Awakening time; TMT: Trail Making Test; W-C naming: Word and Color task of the Stroop test; Stroop Interf.: Stroop Interference; DS: Digit Span; RAVLT: Rey Auditory Verbal Learning Test. |

1. **Differences in cortisol levels across days for the 2 Day-CAR and 1 Day-CAR subgroups**

An ANOVA for repeated measures with Day and Time (cortisol awakening; +30min and +45min) as a within-subject factor was used to investigate differences in cortisol levels across days between the 2 Day-CAR and 1Day-CAR subgroups. Greenhouse-Geisser was used because the requirement of sphericity for the ANOVA for repeated measures was violated (*p*<0.001). These analyses showed that the factor Subgroup (*F*(1,52)=0.220*, p=*0.641, *η2*=0.004) and the interaction between Day and Subgroups (*F*(1,52)=0.181*, p=*0.184, *η2*=0.034) were not significant. The factor Time (*F*(1.67,76.16)=90.58, *p*<0.001, *η2*=0.635) and the interaction between Time, Day and Subgroup were significant (*F*(1.46, 76.16)=16.37, *p*<0.001, *η2*=0.425). *Post Hoc* analyses indicated that the 2 Day-CAR subgroup showed no significant differences in cortisol awakening, +30min and +45min across days (*p*>0.475), and that cortisol levels increase from awakening to +30min on both days (*p*<0.001). For the 1 Day-CAR subgroup, on the day with negative CAR, cortisol levels were higher at awakening than on the day with positive CAR, and lower at +30min and +45min (*p*<0.002). Cortisol levels increase from awakening to +30min on the day with positive CAR (*p*<0.001), but cortisol levels decrease from awakening to +30min and +45min on the day with negative CAR (*p*<0.029).

1. **Results of the analyses repeated for the 2 Day-CAR subgroup.**
	1. ***Subjects’ characteristics and differences in cortisol levels and cognitive performance.***

If the analyses are performed with the 2 Day-CAR subgroup alone, the differences between hypertensives and normotensives on SBP (*t*(37)=4.439, *p*<0.001, *d*=1.433), DBP (*t*(37)=3.006, *p*=0.006, *d*=0.971), time of awakening (*t*(37)=-2.365, *p*=0.023, *d*=0.763), AUCg (*t*(37)=-2.363, *p*=0.023, *d*=0.763) and cortisol awakening (*t*(37)=-2.717, *p*=0.010, *d*=0.877) are still observed.

* 1. ***Relationships among cortisol levels, time of awakening, mean sleep time, and time receiving treatment for hypertension.***

In the hypertensive group, if the analyses are performed with the 2 Day-CAR subgroup alone, associations between night cortisol and less mean sleep time (*r*=-0.51, *p*=0.040), and between cortisol awakening and AUCg (*r*=0.88, *p*<0.002), are still observed. Moreover, the participants taking antihypertensives for a longer time showed a higher CAR (*r*=0.49, *p*=0.051). Although the association between time taking antihypertensives and the CAR was close to being statistically significant (*p*=0.051), it should be noted that the *p* value reported is two-tailed. Given that this analysis is performed to confirm the previous results observed with the complete (and larger) sample, a one-tailed *p* value could also be considered. In this case, the association between time taking antihypertensives and the CAR is statistically significant (*p*=0.026).

In the normotensive group, if the analyses are performed with the 2 Day-CAR subgroup, the association between bedtime and waking time (*r*=0.62, *p*=0.002) and the association between cortisol awakening and AUCg (*r*=0.91, *p*<0.001) remained significant.

* 1. ***Relationship between CAR and cognitive performance.***

We first explored the association between the CAR and cognitive outcomes, controlling the age of the participants. If the analyses are performed with the 2 Day-CAR subgroup alone, a CAR of increased magnitude was still related to better performance on the TMT-B (*p*=0.003) and the Word-Color test (*p*=0.014), but not to performance on the TMT-A (*p*=0.706). As observed for the complete sample, none of the other associations were significant for the 2 Day-CAR subgroup alone (all *p*<0.408).

Finally, we investigated whether the CAR was related to cognitive performance, after controlling for several variables that were related to CAR and/or cognitive performance (see section *1 Selection of covariates for regression analyses*). Additionally, we performed a moderator regression analysis to investigate whether these relationships were different for the hypertensive and normotensive groups.

If the regression analyses are performed with the 2 Day-CAR subgroup alone, the same results are observed as those shown with the complete sample. A CAR of increased magnitude was related to better performance on the TMT-B (β=-0.43, *p*=0.003) and Word-Color naming (β=0.48, *p*=0.004). The interactions between CAR and hypertension were significant for Word-Color naming (p=0.031). The relationship between CAR and Word-Color naming was positive for both groups, but it was significant only for the normotensive group (Normotensive group: β=0.72, *p*=0.001; Hypertensive group: β=0.16, *p*=0.349). As observed for the complete sample, none of the other relationships were statistically significant (all *p*>0.125).

* 1. ***Relationship between time taking antihypertensive medication and cognitive performance.***

When the relationship between time taking antihypertensives and cognitive outcomes was studied in the 2 Day-CAR subgroup, results showed that a longer time taking antihypertensive medication was still related to better performance on the TMT-B (p=0.065). The relationship with processing speed was not significant (p=0.950).

**References**

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