

# Noradrenaline and cortisol exert differential effects on working memory and risk-taking behaviour in military personnel

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## Research Article

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# Abstract

## *Rationale*

Military personnel are exposed to bouts of acute stress during their careers, in which cognitive processes associated with decision-making might simultaneously suffer. Currently, it is still unclear how stress molecules involved in the acute stress response specifically affect these decision-making subprocesses, particularly in the military.

## *Objectives*

We aimed to expose military personnel to pharmacological stress, in which noradrenaline and/or cortisol activity was stimulated. Next, decision-making subprocesses (i.e. working memory, impulse control and risk-taking) were assessed.

## *Methods*

A sample of 100 Dutch military personnel were recruited. Noradrenaline and/or cortisol activity was stimulated through oral administration of yohimbine and hydrocortisone, respectively. Decision-making subprocesses were assessed through computerised tasks.

## *Results*

Induction of stress was confirmed through psychophysiological measures. Working memory seemed subtly affected by stress, as heightened noradrenaline slowed recall while cortisol accelerated it. Inhibition was unaffected by acute stress. Risk-taking was enhanced solely by noradrenaline, contrasting earlier research positing cortisol as a predictor of amplified risk-taking in civilians.

## *Conclusions*

Our findings contribute to the existing literature of the effects of acute stress on cognitive processes associated with decision-making, emphasising intricacies of the effects of specific stress molecules. Future research is needed to further identify these differential intricacies on cognitive processes, keeping potential differences between demographic subgroups in mind.

The study was preregistered on 18<sup>th</sup> of July 2024 in the Clinical Trials Information System (CTIS), part of the World Health Organization (WHO) registry network, according to EU pharmaceutical law in the Clinical Trial Regulation – EU Clinical Trial number: 2023-508731-31-01.

## 1. Introduction

Daily stressors affect us by preparing the body for potential danger, releasing various stress-related hormones throughout the body (Arnsten, 2009a). Certain professions, such as military personnel, are intermittently exposed to high amounts of acute stress in particular, regardless of deployment experience and frequency (Brooks & Greenberg, 2018; Campbell & Nobel, 2009). While military training aims to prepare future personnel for the potential deleterious effects of both acute and chronic stress on body and mind (Adler & Gutierrez, 2022; Doody et al., 2021), research shows that this does not necessarily prevent the effects of stress on cognitive function. Indeed, military personnel more often wrongfully pulled the trigger during a simulated friend or foe decision task when exposed to acute stress (Gamble et al., 2018). Additionally, military personnel undergoing a 1-week operational commando course showed that increased parameters of arousal during training were linked to impairments observed in executive functioning (Trousselard et al., 2025). Similarly, when compared to other uniformed professions, paramedics and police communicators made significantly more errors during medical tasks and during a complex cognitive task, respectively, after a high-stress event (LeBlanc et al., 2012; Regehr et al., 2013; Regehr & LeBlanc, 2017). These results show that although people in specific stressful careers are selected for beneficial traits and are trained in preparation for moments of high stress, the detrimental effects of stress on cognitive functioning persist, with possible devastating short-term consequences. Even so, cognitive failures in military personnel have been linked to combat experience mediated by the severity of subclinical Post-Traumatic Stress Disorder (PTSD) (Price et al., 2024), further warranting a closer inspection of the effects of acute stress in military personnel.

Acute stress is known to affect decision-making in various ways. Through biological cascades known as the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes, neurotransmitters such as noradrenaline (NA), dopamine (DA), corticotropin-releasing factor (CRF) and cortisol seem to affect various subprocesses of decision-making negatively, such as working memory and risk taking (Kluen et al., 2017c; van Herk et al., 2024). Indeed, earlier dual-process theories speculate that higher order cognitive functioning makes way for reflexive autonomous response when the brain is in a heightened aroused state (Evans, 2003, 2008). Even so, in some cases, stress actually improved cognitive performance by for instance enhancing impulse control (van Herk et al., 2024). The contradictory effects of acute stress on cognitive function have been posited to an inverted U-curve, in which either a scarcity or abundance of catecholamine levels lead to suboptimal functioning of the frontal cortex (Arnsten, 2009b, 2015). CRF and cortisol on the other hand, have been reported to impair sensitivity to reward and increase risk taking behaviour by affecting the striatum, among others (Kluen et al., 2017a; van Herk et al., 2024). However, there is no definitive conclusive information how stress hormones specifically affect decision-making capabilities of a subpopulation trained to withstand copious amounts of stress, such as military personnel.

Acute stress can be elicited in an experimental setting through various means. Golden standards include the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) and the Maastricht Acute Stress Test (MAST) (Smeets et al., 2012). However, because military personnel are typically selected for their stress resilience, and undergo several rigorous stress-management training, we aimed to target stress receptors directly through pharmacological manipulation, increasing the chance of successful stress exposure. Additionally, by implementing a design in which SAM and HPA axes are targeted separately or simultaneously, we further gain knowledge how acute stress more precisely affects cognitive behaviour. Thus, healthy military personnel were orally administered yohimbine hydrochloride (YOH) and/or hydrocortisone (CORT) to stimulate NA and glucocorticoid activity, respectively. After the drugs reached peak activity, participants performed several computer tasks in which working memory, impulse control, and risk taking were measured. Simultaneously, markers of stress (e.g. saliva and physiology) were taken. We hypothesised that similarly to civilians, CORT would increase risk taking behaviour and impair working memory. Likewise, we hypothesised that heightened noradrenaline through YOH would impair working memory and impulse control.

## **2. Methods**

### **2.1. Participants**

Healthy military personnel of the Netherlands Armed Forces (NAF) on active duty were recruited. Exclusion criteria included any current cardiovascular or metabolic disease, neurological disorders, current mental disorders, medication intake within four weeks prior to participation, and any contraceptives for women besides a copper intrauterine device (IUD). This study is part of a larger project on stress and decision-making, with a companion manuscript focusing on moral decision-making currently under review. A summarised overview of sample characteristics can be seen in Table 1, with more detailed characteristics provided in the companion manuscript.

Table 1  
Sample characteristics relevant to cognitive task analyses. Characteristics included the International Standard Classification of Education (ISCED) and Perceived Stress Scale (PSS-14).

| <b>Socio-demographic characteristics</b>         | <b>plac/plac</b> | <b>YOH/plac</b> | <b>CORT/plac</b> | <b>YOH/CORT</b> |                 |
|--------------------------------------------------|------------------|-----------------|------------------|-----------------|-----------------|
|                                                  | <b>n = 24</b>    | <b>n = 25</b>   | <b>n = 26</b>    | <b>n = 25</b>   | <b>p values</b> |
| <b>Age</b> - Mean (SD)                           | 35.42 (8.63)     | 39.16 (11.49)   | 39.77 (11.86)    | 35.28 (9.06)    | 0.417           |
| <b>Education</b> - Frequency (%)                 |                  |                 |                  |                 | 0.607           |
| ISCED 2                                          | 0 (0)            | 0 (0)           | 0 (0)            | 3 (12)          |                 |
| ISCED 3                                          | 10 (41.7)        | 7 (28)          | 7 (26.9)         | 6 (24)          |                 |
| ISCED 4                                          | 7 (29.2)         | 10 (40)         | 6 (23.1)         | 1 (4)           |                 |
| ISCED 5                                          | 0 (0)            | 0 (0)           | 1 (3.8)          | 1 (4)           |                 |
| ISCED 6                                          | 4 (16.7)         | 5 (20)          | 7 (26.9)         | 10 (40)         |                 |
| ISCED 7                                          | 2 (8.3)          | 3 (12)          | 5 (19.2)         | 4 (16)          |                 |
| ISCED 8                                          | 1 (4.2)          | 0 (0)           | 0 (0)            | 0 (0)           |                 |
| <b>Operating branch military</b> - Frequency (%) |                  |                 |                  |                 | 0.435           |
| Army                                             | 11 (45.8)        | 20 (80)         | 14 (53.8)        | 13 (52)         |                 |
| Navy                                             | 6 (25)           | 1 (4)           | 6 (23.1)         | 5 (20)          |                 |
| Air Force                                        | 4 (16.7)         | 3 (12)          | 4 (15.4)         | 5 (20)          |                 |
| Military Police                                  | 3 (12.5)         | 1 (4)           | 2 (7.7)          | 2 (8)           |                 |
| <b>Current rank</b> - Frequency (%)              |                  |                 |                  |                 | 0.478           |
| Enlisted                                         | 3 (12.5)         | 4 (16)          | 1 (3.8)          | 3 (12)          |                 |
| Non-commissioned officer                         | 14 (58.3)        | 10 (40)         | 13 (50)          | 9 (36)          |                 |
| Comissioned officer                              | 7 (29.2)         | 11 (44)         | 12 (46.2)        | 13 (52)         |                 |
| <b># of deployments</b> - Mean (SD)              | 4.25 (8.16)      | 5.16 (5.82)     | 4.12 (3.64)      | 2.96 (2.85)     | 0.355           |
| <b>Years since last deployment</b> - Mean (SD)   | 6.24 (5.73)      | 4.35 (4.26)     | 6.07 (3.19)      | 4.24 (4.05)     | 0.204           |
| <b>PSS-14</b> - Mean (SD)                        | 15.92 (6.47)     | 15.48 (6.84)    | 14.96 (4.92)     | 14.40 (5.82)    | 0.833           |
| *: p-value < .05                                 |                  |                 |                  |                 |                 |
| **: p-value < .01                                |                  |                 |                  |                 |                 |
| ***: p-value < .001                              |                  |                 |                  |                 |                 |

## 2.2. Study Design and Procedure

The study was a double-blind, placebo-controlled, and 2 x 2 factorial design. Participants were randomly distributed to 1 of 4 groups: 1) 30 mg YOH and CORT ( $n = 25$ ), 2) 30 mg YOH and placebo ( $n = 25$ ), 3) 30 mg CORT and placebo ( $n = 26$ ), or 4) double placebo ( $n = 24$ ). Two hours prior to testing, participants were advised to abstain from food and caffeine intake, as well as moderate to high intensity exercise. Repeated measurements were taken to verify the effects of pharmacological stress (baseline measurements before stress, T0 = 0 min; measurements after stress exposure, T1 = + 50 min; T2 = + 65 min; T3 = + 80 min; see Fig. 1). When drugs reached their peak concentration (T1), participants underwent several cognitive behavioural tasks, randomised in order using a Latin square design. In between and after the computer tasks, two more stress verification measurements were taken (T2, T3).

Behavioural tasks were programmed using PsychoPy (version 2024.1.1) (Peirce et al., 2019). All participants were tested at the Central Military Hospital in Utrecht, the Netherlands.

## 2.3. Stress Manipulation and Measurements

To heighten noradrenergic and glucocorticoid signalling, 30 mg of YOH and/or 30 mg of CORT were orally administered. Peak activity of both drugs was expected around T1 and both substances were expected to quickly wash out of the body (D. et al., 1982; Grasing et al., 1996; Le Corre et al., 1999; Patel et al., 1984; Sturgill et al., 1997; Toothaker et al., 1982). At T0, electrodes for an electrocardiogram (ECG) were placed, allowing continuous measurement of heart rate. Second, saliva was collected at each timepoint so that salivary alpha-amylase (sAA) and cortisol could be determined. Third, an eye tracker was utilised to measure pupil size at each timepoint. Lastly, affect grids were implemented to get an indication on an individual's subjective stress experience at each timepoint. During the different repeated stress verification measurements, the following outcomes were taken to verify pharmacological stress manipulation: heart rate variability (HRV), heart rate, pupil size, sAA, salivary cortisol, and subjective stress scores. The full procedures and results of pharmacological stress induction are reported in van Herk et al. (under review).

## 2.4. Cognitive Tasks

The Digit Span Task (DST) is a subtest of the Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV) (Wechsler, 2008) and assesses attention and working memory by requiring participants to remember a sequence of numbers. In this study the sequences were presented via the computer (see Fig. 2A). The DST has been tested previously in healthy military personnel and consisted of three conditions (Gordon et al., 2001; Taverniers et al., 2010). In the forward condition, participants were asked to memorise a sequence of numbers, starting the first trial with three numbers, and correctly repeat the number sequence as it was shown. After one of the first two trials has correctly been guessed, the incremental sequence increased with one additional number for the next two trials. If the participant in this set of two trials again correctly guessed a sequence, the incremental sequence increased with one additional number, up until a maximum of nine numbers. If the participant makes two errors in a trial set, the condition ends and the next condition is initiated. The backward condition required participants to repeat the number sequence in a backwards order, while the final sequential condition required participants to repeat the number sequence in an ascending order. The test first started with four example forward trials, after which the forward, backward, and sequential conditions commenced, respectively. The Reliable Digit Span – Revised (RDS-R) is derived by summing the total number of digits that are reliably repeated in the longest sequence string in all three conditions and served as the main outcome (Wechsler, 2008). Additionally, time taken to answer each digit span trial was also measured.

The Stop Signal Task (SST) tests response inhibition by presenting both 'go' and 'no-go' stimuli (see Fig. 2B) (Logan et al., 1997; Verbruggen & Logan, 2008). About 75% of the trials indicated a visual 'go' stimulus, prompting the participant to press a button. Occasionally in 25% of the trials, the visual signal would very quickly be followed by a 'no-go' auditory stop signal, requiring a participant to inhibit themselves. First, participants were exposed to an example block, which also provided feedback if a response was right or wrong. This feedback was not included in the following experimental block. Stop-signal reaction time (SSRT) on 'no-go' trials, successful stop rate on 'no-go' trials, and go accuracy rate were taken as outcomes.

The Balloon Analogue Risk-taking Task (BART) measures risk-taking and impulsivity, in which a single balloon is presented on a computer screen and participants are instructed to press a button to pump the balloon without exploding it (see Fig. 2C) (Lejuez et al., 2002). The modified task, as implemented previously (Klueen et al., 2017b), consisted of 60 trials with three risk categories: 'low risk', 'moderate risk', or 'high risk' of exploding, with each risk category having 20 trials. Furthermore, risk categories were colour coded and randomly presented among all 60 trials. Low risk trials had 1 to 64 integers, in which the computer randomly selected an integer. When the number '1' was chosen, the balloon exploded. Moderate risk trials had 1 to 32 integers, while high risk trials had 1 to 16 integers. Participants were not informed about these different risk categories. Participants had the choice to continue pumping the balloon or to 'cash-out' the temporary score, and move the score to the permanent bank. When a balloon popped, the temporary score for that trial would not be added to the bank. The total score was not visible to the participants up until the end of the task. The main measurements were the mean number of pumps (button clicks), adjusted for only the unpopped trials and calculated for each risk condition, the total pop rate per risk category, and the total score earned in the task.

## 2.5. Statistical Analyses

We included YOH and CORT as separate factors in a 2 x 2 factorial design, with an interaction term included for all statistical analyses. Additionally, after each main analysis, sensitivity analyses were performed to see if theoretically relevant participant characteristics could explain variance for our main outcomes. To determine potential covariates, we implemented correlation analyses for continuous factors, Kruskal-Wallis tests for ordinal factors, and analyses of variance (ANOVAs) for purely categorical factors (see *Table S1* and *S2*). Consequently, variables showing relevant associations with the outcome were then entered into follow-up analyses of covariance (ANCOVAs) models to test if main findings changed. For the DST, first an ANOVA was run for RDS-R score, followed by an ANCOVA including potential covariates. Assumptions were tested using Shapiro-Wilk tests and Levene's tests for homogeneity of variance. Furthermore, a linear mixed-model (LMM) was run on time spent on digit span trials, with trial type (forward, backward, and sequential) and trial number within trial type included as additional factors. Looking at the SST, stop-rate and go accuracy showed group-independent violations in normality (see *Table S3*). However, since proportional outcomes are inherently sensitive to non-normality and these outcomes proved to be robust against heteroskedasticity, a normal multivariate analysis of variance (MANOVA) was run for SSRT, stop-rate, and go accuracy, with an additional multivariate analysis of covariance (MANCOVA) follow-up. For the BART, mean adjusted pumps violated assumptions of normality in specific groups only, with no problems with heteroskedasticity. Nevertheless, to make sure that results were not influenced by group-dependent skewed distributions, a robust ANOVA was done for mean adjusted pumps, while pop rate was analysed with an ANOVA. As done previously, potential covariates were included in linear models (LMs) with heteroskedasticity-robust standard errors for mean adjusted pumps, while pop rate sensitivity analysis was done with an ANCOVA. Lastly, BART outcomes with pharmacological factors included were corrected with Holm.

## 3. Results

The total sample consisted of 100 participants (male = 92), with no concerning socio-demographic differences between groups. Specific sample characteristics can be observed in *Table 1*. The LMM run for time spent on digit span trials showed model improvement when each participant was allowed a random intercept and slope per trial (see *Table S4*). After adding trial number and span type as fixed effects, the model collapsed due to singularity issues. To improve model stability, we opted to remove the correlations between random intercept and slope, resulting in an uncorrelated random-effects structure. Finally, interactions between trial number, span type and pharmacological manipulations resulted in the model with the best fit.

There were no effects of YOH and CORT on working memory (RDS-R), as all groups showed a total score around 18 (all  $p > .05$ ; see *Tables S3, S5* and *Fig. 3A*). As a follow-up, education emerged as a potential factor for the sensitivity analysis ( $H(6) = 13.24$ ,  $p = .039$ ), however, an ANCOVA with education included did not change the main outcome (all  $p > .05$ ). Additionally, when looking at forward, backward, and sequential spans separately, no differences between stress conditions were observed (all  $p > .05$ ). In contrast, an LMM of time spent during span trials of the DST showed an effect of CORT between forward and backward trials ( $p = .000$ ; see *Table 2* and *Fig. 3B*). Post-hoc comparisons with Tukey correction revealed that the YOH only condition significantly needed more time during backward trials, compared to the CORT only ( $p = .015$ ) and YOH/CORT conditions ( $p = 0.045$ ). Overall, more time was needed during the backward trials, compared to forward and sequential trials.

Table 2

Final full linear mixed model of time spent during span trials of the DST. Estimation was done with REML. Final model included 100 participants.

| <b>Fixed effects</b>      | <b>Estimate (SE)</b> | <b>df</b> | <b>t</b> | <b>p</b>        |
|---------------------------|----------------------|-----------|----------|-----------------|
| Intercept                 | 9.236 (0.399)        | 164       | 23.165   | <b>0.000***</b> |
| YOH                       | 0.713 (0.533)        | 137       | 1.339    | 0.183           |
| CORT                      | -1.007 (0.527)       | 137       | -1.911   | 0.058           |
| ΔF-B                      | -4.302 (0.292)       | 1983      | -14.744  | <b>0.000***</b> |
| ΔF-S                      | -2.782 (0.292)       | 2008      | -9.523   | <b>0.000***</b> |
| Trial number              | 1.245 (0.069)        | 427       | 18.000   | <b>0.000***</b> |
| YOH * CORT                | -0.389 (0.680)       | 95        | -0.572   | 0.569           |
| ΔF-B * Trial number       | -0.799 (0.072)       | 2010      | -11.117  | <b>0.000***</b> |
| ΔF-S * Trial number       | -0.537 (0.069)       | 2040      | -7.801   | <b>0.000***</b> |
| YOH * ΔF-B                | -0.371 (0.327)       | 1980      | -1.133   | 0.257           |
| YOH * ΔF-S                | -0.216 (0.327)       | 2008      | -0.659   | 0.510           |
| CORT * ΔF-B               | 1.219 (0.328)        | 1980      | 3.721    | <b>0.000***</b> |
| CORT * ΔF-S               | 0.384 (0.328)        | 2008      | 1.172    | 0.242           |
| <b>Contrasts backward</b> | <b>Estimate (SE)</b> | <b>df</b> | <b>t</b> | <b>p</b>        |
| ΔPLAC-YOH                 | -0.713 (0.533)       | 138       | -1.338   | 0.540           |
| ΔPLAC-CORT                | 1.007 (0.527)        | 137       | 1.910    | 0.229           |
| ΔPLAC-YOH/CORT            | 0.683 (0.574)        | 184       | 1.190    | 0.634           |
| ΔYOH-CORT                 | 1.720 (0.567)        | 191       | 3.032    | <b>0.015**</b>  |
| ΔYOH-YOH/CORT             | 1.396 (0.528)        | 139       | 2.643    | <b>0.045*</b>   |
| ΔCORT-YOH/CORT            | -0.324 (0.522)       | 138       | -0.620   | 0.925           |
| <b>Random effects</b>     | <b>Variance (SD)</b> |           |          |                 |
| Intercept participant     | 2.442 (1.563)        |           |          |                 |
| Slope trial number        | 0.130 (0.360)        |           |          |                 |
| Residual                  | 8.307 (2.882)        |           |          |                 |
| *: p-value < .05          |                      |           |          |                 |
| **: p-value < .01         |                      |           |          |                 |
| ***: p-value < .001       |                      |           |          |                 |

For the SST, examination of the data revealed that several participants did not fully understand the instruction of the task, as nine participants had a successful stop rate of less than 22%, with three of these participants even having a stop rate of 0%. The mean successful stop rate was 0.775, while the median was 0.844. We opted to exclude these participants, since we suspected that they never intentionally inhibited themselves after hearing the 'no-go' signal, resulting in a sample size of 91 for these analyses. Furthermore, these cases were roughly equally distributed among the four groups, confirming that nonadherence of the task was not related to stress manipulation. No effects of YOH and CORT were observed on all outcomes of the SST (all  $p > .05$ ; see *Table S6* and *Figure 4*). Potential covariates on SST outcomes included age, education, years since last deployment, military rank, and branch of the armed forces. Nonetheless, a follow-up MANCOVA with these covariates did not change the effects of YOH and CORT on SST outcomes (all  $p > .05$ ).

Lastly, participants showed regulated risk-taking tendencies based on risk category, in which there was an incremental amount of mean adjusted button presses and pop rate from high- to low-risk category, as expected (both  $p < .000$ ). Next, LMMs revealed no improvement by including an interaction between drug manipulations and risk category, prompting investigation of overall risk-taking, despite of risk categories. Robust ANOVAs corrected for multiple testing with Holm, revealed that YOH increased mean adjusted pump presses ( $p = .034$ ) and increased pop rate of balloons ( $p = .019$ ; see Table 3 and Figure 5). As a follow-up, the Perceived Stress Scale (PSS-14) questionnaire score was revealed to explain variance and thus was added in ANCOVA sensitivity analyses (see Table S2). Nevertheless, both outcomes remained unchanged when PSS-14 score was added as a covariate (both  $p < .05$ ).

**Table 3.** Results of a robust ANOVA and robust ANCOVA on the mean adjusted pumps and pop rate of the BART. PSS-14 score was added as covariate to explain possible variance. Holm correction was applied to pharmacological effects and their interaction. Both tests included 100 participants.

| <i>(Robust) ANOVA</i>  | <i>Mean adjusted pumps</i> |          |                |               | <i>Pop rate</i> |           |          |                |               |
|------------------------|----------------------------|----------|----------------|---------------|-----------------|-----------|----------|----------------|---------------|
| <b>Factor</b>          | <b>df</b>                  | <b>F</b> | <b>p</b>       | <b>Holm p</b> | <b>df</b>       | <b>SS</b> | <b>F</b> | <b>p</b>       | <b>Holm p</b> |
| YOH                    | 1                          | 7.652    | <b>0.007**</b> | <b>0.034*</b> | 1               | 0.151     | 9.180    | <b>0.003**</b> | <b>0.019*</b> |
| CORT                   | 1                          | 0.003    | 0.958          | 1             | 1               | 0.003     | 0.157    | 0.693          | 1             |
| YOH * CORT             | 1                          | 0.251    | 0.618          | 1             | 1               | 0.006     | 0.387    | 0.536          | 1             |
| Residuals              | 96                         |          |                |               | 96              |           |          |                |               |
| <i>(Robust) ANCOVA</i> | <i>Mean adjusted pumps</i> |          |                |               | <i>Pop rate</i> |           |          |                |               |
| <b>Factor</b>          | <b>df</b>                  | <b>F</b> | <b>p</b>       | <b>Holm p</b> | <b>df</b>       | <b>SS</b> | <b>F</b> | <b>p</b>       | <b>Holm p</b> |
| YOH                    | 1                          | 7.376    | <b>0.008**</b> | <b>0.039*</b> | 1               | 0.140     | 9.052    | <b>0.003**</b> | <b>0.020*</b> |
| CORT                   | 1                          | 0.016    | 0.899          | 1             | 1               | 0.001     | 0.033    | 0.857          | 1             |
| PSS-14 score           | 1                          | 3.431    | 0.067          | -             | 1               | 0.108     | 6.982    | <b>0.010**</b> | -             |
| YOH * CORT             | 1                          | 0.267    | 0.607          | 1             | 1               | 0.007     | 0.429    | 0.514          | 1             |
| Residuals              | 95                         |          |                |               | 95              |           |          |                |               |
| *: p-value <.05        |                            |          |                |               |                 |           |          |                |               |
| **: p-value <.01       |                            |          |                |               |                 |           |          |                |               |
| ***: p-value <.001     |                            |          |                |               |                 |           |          |                |               |

## 4. Discussion

Our goal was to differentiate the effects of noradrenaline and/or cortisol stimulation on several cognitive processes involved in decision-making in military personnel of the NAF. We successfully elicited acute stress as reported elsewhere (van Herk et al., under review). We found that working memory seems partially affected by acute stress, not in scores on revised Reliable Digit Span (RDS-R; main outcome of the Digit Span Task), but mainly in time spent per DST span category, which was different for YOH and CORT groups. Surprisingly, impulse control was unaffected by pharmacological stress, as accuracy ratio on 'go', and stop success on 'no-go' of the stop-signal reaction time, was not different between groups. Lastly, risk-taking was enhanced in both groups where YOH was administered, as the mean adjusted pumps and pop rate of balloons was increased, even when correcting for PSS-14 questionnaire scores.

Military personnel appear to be affected by acute stress through various mechanisms. We expected working memory to be impaired by heightened noradrenaline as seen in acute stress, but we observed an interesting interaction between two stress molecules. In earlier work, heightened catecholaminergic activity has been linked to diminished working memory capacity reflecting the inverted U-curve relationship (Arnsten, 2009b, 2015). Accordingly, previous simultaneous oral administration of YOH and CORT in civilians resulted in decreased glutamatergic signalling in the dorsolateral prefrontal cortex (dlPFC) and impaired

accuracy in the N-back task (Woodcock et al., 2019). More recent work reported that the immediate and slightly delayed effects of acute stress, through noradrenaline and cortisol respectively, impair working memory performance as measured by using golden standard tasks, such as the Digit Span Task, N-back task, and Item Recognition Task (Geißler et al., 2023; van Herk et al., 2024). Intriguingly, our results suggest that this possible impairment may occur through separate mechanisms. Although we did not find a difference in overall working memory performance contrary to previous findings in military personnel (Taverniers et al., 2010), we did observe differential effects: noradrenaline slowed information processing in the more difficult span category whereas cortisol accelerated it. Indeed, a study implementing a pharmacological blocker of the glucocorticoid receptor (mifepristone) found no overall differences in working memory performance after TSST stress exposure in humans, but did find that the group exposed to mifepristone exhibited longer reaction times (Deuter et al., 2024). This suggests that non-genomic glucocorticoid receptor activation specifically is associated with faster overall cognitive processing, a possible hallmark of the switch of deliberate reasoning to a more reflexive state under acute stress (Henckens et al., 2011). Importantly, participants were not subject to constraints when giving their digit span responses, which might be a possible explanation for the lack of observed differences between groups. If a specific response time interval was given, this might have resulted in overall lower RDS-R score for the slower responders (i.e. YOH administered).

Interestingly, our results indicate no effect of heightened noradrenaline or cortisol on impulse control in military personnel. In contrast, other research investigating aspects of inhibition in military personnel did observe impaired inhibitory control due to acute stress using a shoot/don't shoot paradigm (Gamble et al., 2018). Previous studies in civilians show inconsistent results. A meta-analysis reports that acute stress can enhance response inhibition, however, cognitive inhibition seems to be impaired due to stress (Shields et al., 2016). Indeed, a study implementing brain imaging techniques found that response inhibition accelerated following TSST stress exposure, hallmarked by increased activation in cognitive control networks and decreased activation in default mode networks (Spencer et al., 2024). Moreover, recent studies implementing electroencephalography (EEG) captured specific event-related potentials (ERPs) indicative of slowed cognitive inhibition and accelerated response inhibition following acute stress exposure in Go/No-Go tasks (Dierolf et al., 2017; Kan et al., 2021). It should be noted that the meta-analysis focused on studies that elicited a stress response in an experimental paradigm, but did not distinguish between the differential effects of stress molecules. It could be that effects of pharmacologically induced stress are different from other stress paradigms, as more molecules are actively involved in the natural stress response besides solely noradrenaline and cortisol. Nevertheless, our findings contribute to the growing understanding of the complex nature of inhibitory phenomena.

When looking at risk-taking behaviour in general, we found that noradrenaline in particular increases overall risk, despite of risk category. This contrasts with the findings of a recent civilian study in which a similar pharmacological paradigm of yohimbine hydrochloride (YOH) and hydrocortisone (CORT) was utilised in the BART. More precisely, they report an increase in risk-taking behaviour under the effects of CORT in low and moderate risk conditions in men, while no such effects were observed in women (Kluen et al., 2017a). Considering that our sample primarily consisted of men, we expected similar effects of CORT on risk-taking as reported here. However, we specifically tested military personnel and had a slightly higher dose of both drugs, while testing took place at a somewhat earlier time frame than theirs, which could explain the deviation in results. Nonetheless, the slight increase in dose was justified as military personnel were expected to have higher muscle mass affecting the pharmacodynamics. Additionally, the deviation in timing would actually strengthen the efficacy of cortisol, as cortisol follows a specific diurnal rhythm which is highest in the morning. Looking at acute stress elicited through the TSST, similar increased risk-taking tendencies in the BART in a civilian sample predominantly consisting of young female students was observed (Szaszko et al., 2025). These studies do emphasise that acute stress exposure leads to increased risk-taking behaviour, however, there might be socio-demographic differences between a civilian or military population. Indeed, a study suggests that civilians are more likely to engage in risky behaviours compared to military personnel, while within the military subpopulation deployment experience increases risk tendencies (Thomsen et al., 2011). Additionally, Attention Deficit Hyperactivity Disorder (ADHD) has been associated with increased risk-taking tendencies while similarly being prevalent and underdiagnosed in military personnel (Dekkers et al., 2016; Halbe et al., 2025; Kok et al., 2019). We did measure motivational and inhibitory traits using the Behavioural Approach System and Behavioural Inhibition System Scales (BIS/BAS), however, these were not predictive for risk-taking tendencies and did not deviate from mean reported scores. Nevertheless, it could be that acute stress has specific effects on risk-taking behaviour in people exhibiting ADHD symptomatology, measured with validated ADHD batteries, as stress has been found to worsen specific symptoms in ADHD (Hartman et al., 2019). However, to the best of our knowledge, currently no studies have been reported

investigating the intricacies of the effects of acute stress and ADHD on risk-taking behaviour, even more so in a military population, suggesting a possible avenue for future research.

### *Limitations*

Possible limitations of our study include the fact that we did not recruit a lot of female participants, effectively reducing the generalisability of our findings. In an effort to minimise potential noise caused by contraceptives on cortisol levels, stricter criteria were set for women to participate. However, the majority of military personnel on active duty of the NAF consists of men, with women accounting for 12.9 percent (Ministerie van Defensie, n.d.), suggesting our sample to be fairly representative of military personnel. Even so, these factors combined resulted in a low representation of women in this study, emphasising the need to investigate these phenomena in a larger female sample, as the effects of acute stress on risk-taking for example have been shown to be sex-dependent (Kluen et al., 2017c; Lighthall et al., 2009; Shields et al., 2025). A second limitation is that we chose to have no time constraints during the trials of the DST and BART. Although being able to respond without time pressure is a valid method, additional time constraints would potentially have revealed an additive effect of acute stress on both tasks, as potentially indicated by the effects of YOH on the DST. The absence of a fixed response interval may have allowed compensatory strategies during recall, reducing the sensitivity of the effects of acute stress. Standardised auditory versions of the DST have been executed previously and shown to be influenced by acute stress, although no fixed response windows have been clarified but are implicitly suggested by the experimenter-paced administration (Wechsler, 2008). Nevertheless, our results revealed an intricate interaction between the effects of noradrenaline and cortisol on cognitive processing that might not have been captured if fixed response windows were set.

## Conclusion

Working memory in military personnel seems subtly affected by pharmacological acute stress, as noradrenaline decreases response time during recall, while cortisol increases it. More specifically, noradrenaline might deteriorate prefrontal cortex signalling while cortisol might strengthen overall reflexive autonomous responding. Impulse control remains unaffected by the effects of heightened noradrenaline and cortisol, contributing to the inconsistent results of the effects of acute stress on inhibition. Interestingly, risk-taking tendencies were enhanced by noradrenergic stimulation which contradicts existing literature positing cortisol as a risk enhancing factor. Military personnel might differ from the general population in socio-demographic characteristics, resulting in distinctive effects of acute stress on risk-taking behaviour. Future research is needed to investigate the possible causes of these dissimilar stress effects in a military population.

## Declarations

### **Statement of Author Contributions**

Authors contributed to the study in the following ways, using CRediT taxonomy: Lukas van Herk: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. Antoin D. de Weijer: Conceptualization, Project administration, Resources, Supervision, Writing - review & editing. Bastiaan Bruinsma: Conceptualization, Project administration, Resources, Supervision, Writing - review & editing. Elbert Geuze: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing

**Author contributions** Authors contributed to the study in the following ways, using CRediT taxonomy: Lukas van Herk: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. Antoin D. de Weijer: Conceptualization, Project administration, Resources, Supervision, Writing - review & editing. Bastiaan Bruinsma: Conceptualization, Project administration, Resources, Supervision, Writing - review & editing. Elbert Geuze: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing.

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**Data availability** Anonymised data, analyses scripts, and raw output are made publicly available on The Open Science Framework (OSF, <https://osf.io/rxus6>).

**Ethics statement** The study consisted of human participants and accordingly received ethical approval by the Medical Research Ethics Committee NedMec located in Utrecht, the Netherlands. Additionally, the study is in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki 2024. Informed consent of each participant was taken according to GCP standards.

**Clinical trial number** The study was preregistered on 18<sup>th</sup> of July 2024 in the Clinical Trials Information System (CTIS), part of the World Health Organization (WHO) registry network, according to EU pharmaceutical law in the Clinical Trial Regulation – EU Clinical Trial number: 2023-508731-31-01.

**Competing interests** All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figures

**Figure 1.** Study design and procedures. Participants were randomised in one of four groups: yohimbine and cortisol (YOH/CORT), double placebo (plac/plac), YOH/plac, and CORT/plac. Questionnaires were taken prior to stress measurements. At baseline (T0), +50 min (T1), +65 min (T2), and +80 min (T3), pupil size, saliva and subjective experience of stress was measured. Directly after baseline measurements, CORT or plac was taken, followed by YOH or plac 10 min thereafter. After T1, participants performed two computer tasks, followed by T2, followed by another two tasks and closing with T3. Behavioural tasks were randomised following a Latin square design. All experiments were done in the same lab.

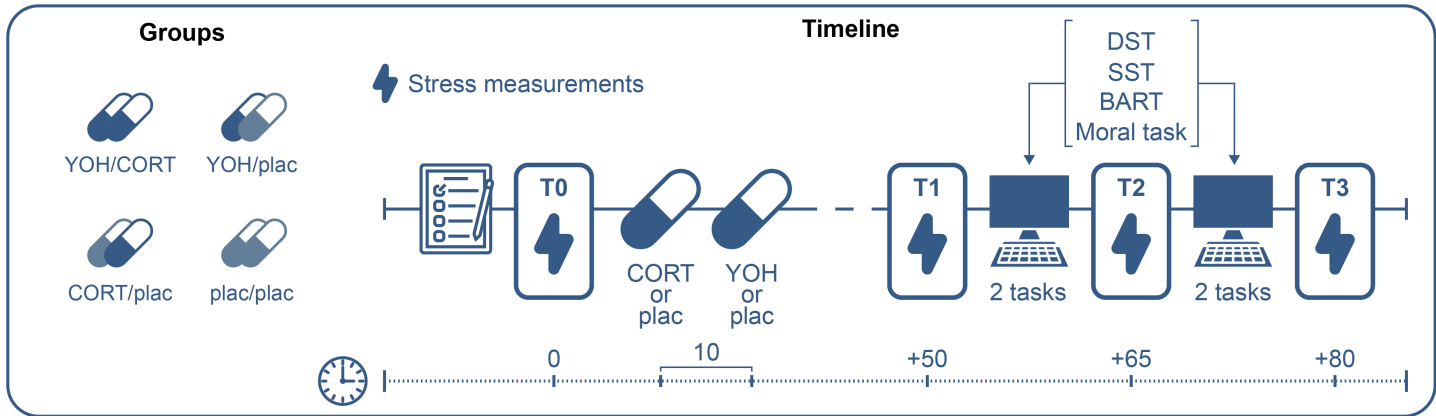


Figure 1

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**Figure 2.** Computerised versions of the cognitive tasks: A) In the Digit Span Task (DST) participants were instructed to memorise a sequence of numbers and then correctly guess the sequence. In the 1<sup>st</sup> block numbers had to be memorised as presented (forward). In the 2<sup>nd</sup> block numbers had to be entered backwards to the presentation order (backward). In the 3<sup>rd</sup> block numbers had to be entered in ascending order from lowest to highest (sequential). One good answer per span length increased the incremental sequence with one additional number. When two wrong answers were given during the same span length, the block ended; B) In the Stop Signal Task (SST) participants had to fixate on the screen and press either the left or right button as quickly as possible when a left or right arrow visual cue was presented, respectively. In 25% of the trials, this arrow was accompanied by an audio cue, letting participants know that they had to abstain from responding; C) In the Balloon Analogue Risk-taking Task (BART) participants were presented with a balloon that they could pump and increase in value by pressing a button. Each press increased the chance that the balloon might pop, in which the value of that balloon was lost. If one chose to bank the balloon's worth before popping, the value was carried over to the total score. Balloons were presented in three colours, representing different risk categories unknown to the participants. All tasks were done on the same computer in the same lab.

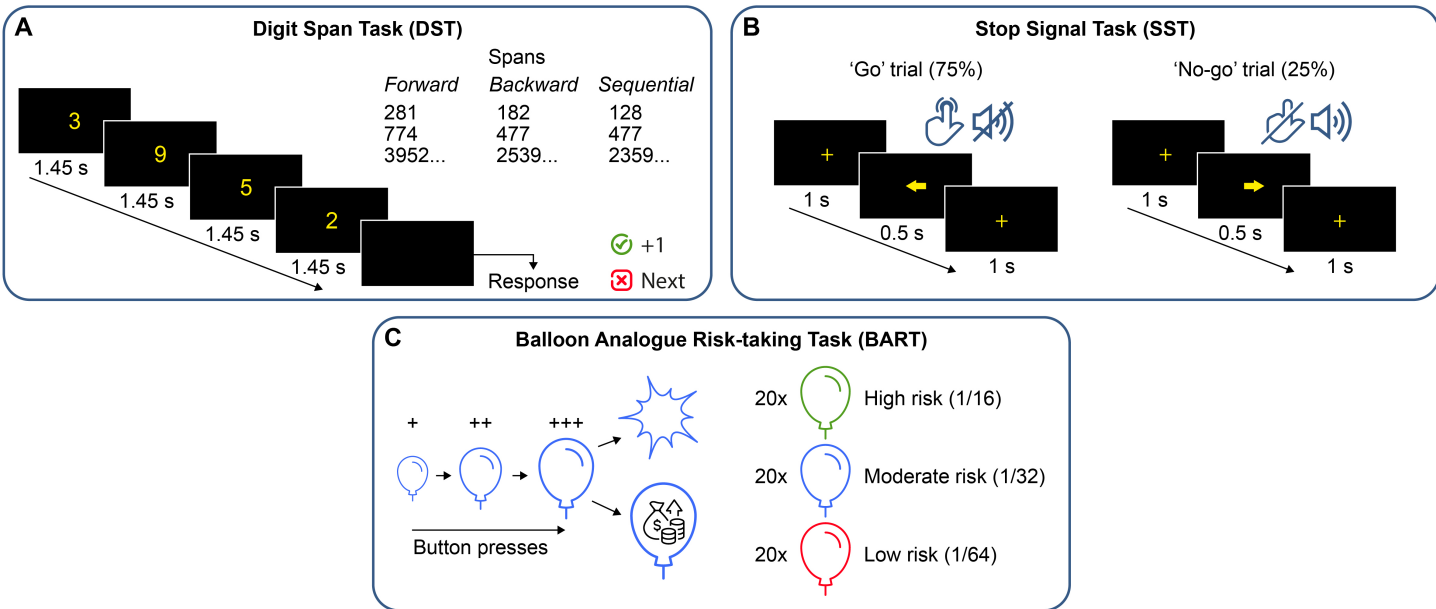


Figure 2

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**Figure 3.** Effects of YOH and CORT on outcomes of the Digit Span Task (DST): A) Reliable digit span score (RDS-R); B) Time spent per separate span category. All outcomes included all 100 participants. Full model specifications are reported in the Supplementary Materials. \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ .

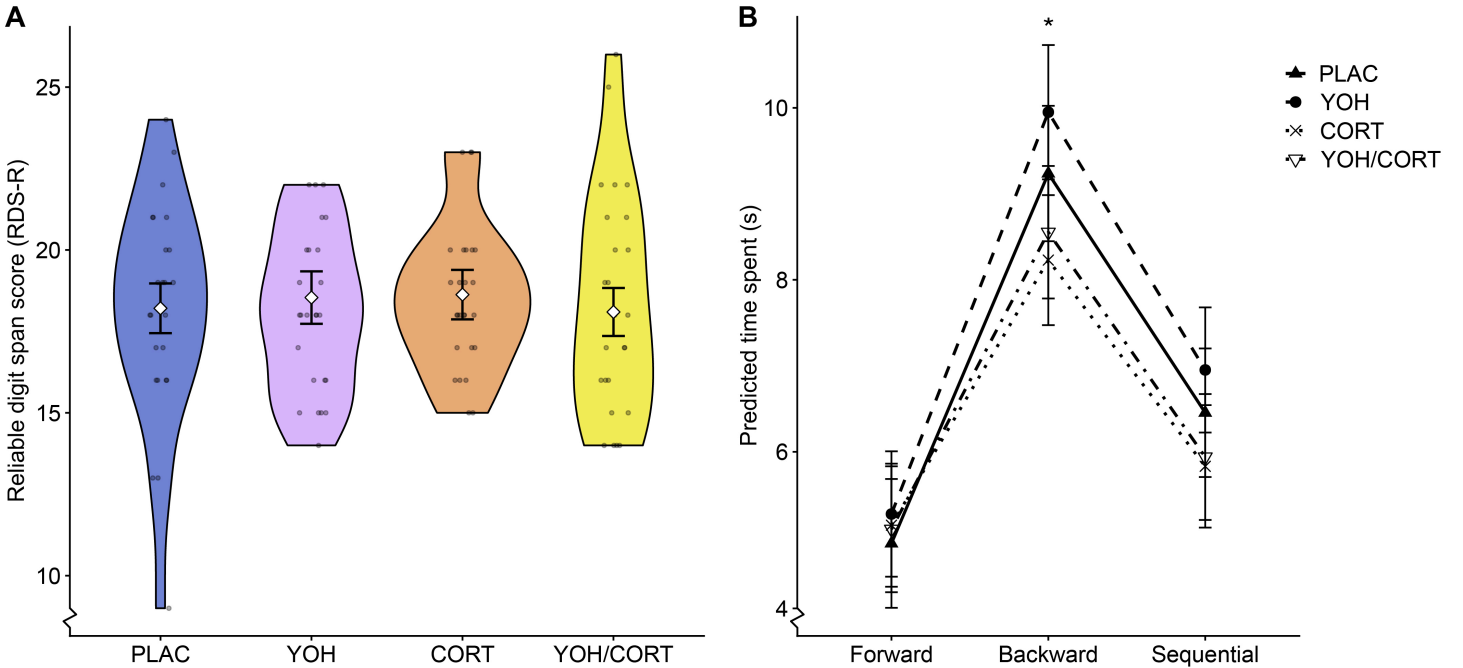


**Figure 3**

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**Figure 4.** Effects of YOH and CORT on outcomes of the Stop Signal Task (SST): A) Stop Signal Reaction Time (SSRT); B) Accuracy ratio on go trials; C) Stop success rate on stop trials. All outcomes included 91 participants.

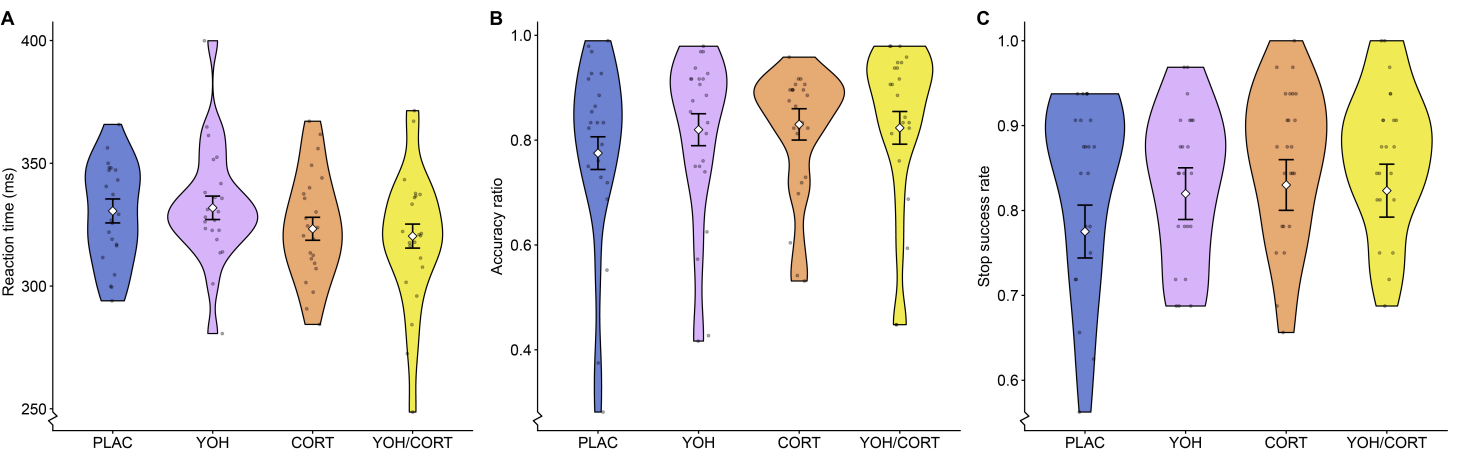


**Figure 4**

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**Figure 5.** Effects of YOH and CORT on outcomes of the Balloon Analogue Risk-taking Task (BART): A) Mean adjusted pumps (button presses); B) Balloon pop rate. All outcomes included all 100 participants. \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ .

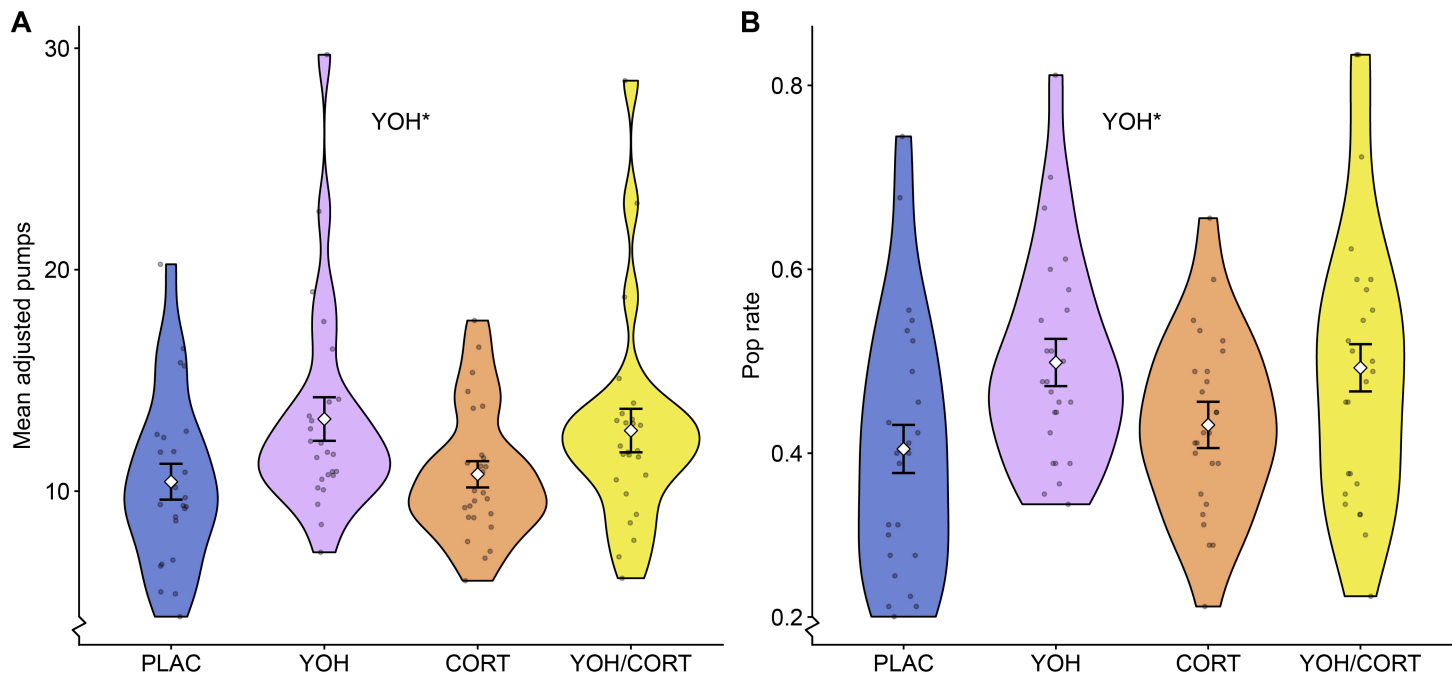


**Figure 5**

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## Supplementary Files

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