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Acute stress impairs visual path integration

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ABSTRACT

Acute stress exerts substantial effects on episodic memory, which are often mediated by glucocorticoids, the end-product of the hypothalamic-pituitary-adrenal axis. Surprisingly little is known, however, about the influence of acute stress on human spatial navigation. One specific navigational strategy is path integration, which is linked to the medial entorhinal cortex, a region harboring glucocorticoid receptors and thus susceptible for stress effects. Here, we investigated effects of acute stress on path integration performance using a virtual homing task. We divided a sample of healthy young male participants into a stress group (n_{stress} = 32) and a control group ($n_{control}$ = 34). The stress group underwent the socially evaluated cold-pressor test, while the control group underwent a non-stressful control procedure. Stress induction was confirmed via physiological and subjective markers, including an increase of salivary cortisol concentrations. We applied linear mixed models to investigate the effect of acute stress on path integration depending on task difficulty and the presence or absence of spatial cues. These analyses revealed that stress impaired path integration especially in trials with high difficulty and led to greater decline of performance upon removal of spatial cues. Stress-induced deficits were strongly related to impaired distance estimation, and to a lesser extent to compromised rotation estimation. These behavioral findings are in accordance with the hypothesis that acute stress impairs path integration processes, potentially by affecting the entorhinal grid cell system. More generally, the current data suggests acute stress to impair cognitive functions mediated by medial temporal lobe regions outside the hippocampus.

1. Introduction

Acute exposure to stress activates two major neuronal circuits: the rapid sympathetic-adrenal-medullary axis (SAM), leading to a release of catecholamines (mainly noradrenaline and adrenaline), and the slow hypothalamic-pituitary-adrenal axis (HPA), leading to a release of glucocorticoids (cortisol in humans, corticosterone in most rodents; Joëls and Baram, 2009). Glucocorticoids affect structural and functional brain integrity mainly by binding on two types of corticosteroids receptors: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs; Herbert et al., 2006). MRs possess a higher affinity to glucocorticoids and are mainly located at limbic structures, while GRs possess a lower affinity to glucocorticoids and are expressed more evenly across the brain. One brain region abundantly containing MRs and GRs, with the highest density of MRs in the whole brain, is the hippocampus (Herbert et al., 2006; McEwen et al., 1968; Reul and de Kloet, 1985), making it highly sensitive to stress effects. Hippocampal dependent cognitive functions are thus often influenced by acute stress (Kim et al., 2015), a relationship that has been repeatedly shown for spatial memory in rodents (Cazakoff et al., 2010; de Quervain et al., 1998), or episodic memory in humans (Shields et al., 2017; Wolf, 2009, 2017). However, acute effects of stress on human spatial navigation have not been thoroughly examined, and findings of existing studies are conflicting, as they comprise enhanced spatial navigation (Duncko et al., 2007), impaired cognitive map-based spatial navigation only in females (Thomas et al., 2010), no effects on spatial navigation (e.g., Guenzel et al., 2014; Klopp et al., 2012; Richardson & VanderKaay Tomasulo, 2022), or a change of navigational strategies (Brown et al., 2020; Cao et al., 2017; van Gerven et al., 2016).

One specific navigational strategy that has not yet been investigated under acute stress is path integration (PI), which involves integration of self-referential information to estimate the current position and orientation (in relation to an arbitrary reference point). PI is mainly used in the absence of external spatial cues (e.g., landmarks) and at short trajectories (Wang, 2016), because error accumulation makes it less suitable for the correct estimation of longer trajectories. PI has been linked

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to head-direction cells in the subicular complex (Valerio and Taube, 2012) and to grid cell firing in the entorhinal cortex (EC), providing critical input for hippocampal place cells (Banino et al., 2018; Gil et al., 2018; McNaughton et al., 2006; Stangl et al., 2018). While head-direction cells support the rotational component of PI as angular integrator (Valerio and Taube, 2012), grid cells are relevant for the translational component of PI (Evans et al., 2016), because the characteristic arrangement of multiple firing fields organized in a grid-like hexagonal pattern (Fyhn et al., 2004; Hafting et al., 2005) presumably provides a general spatial metric of distances (Moser et al., 2017). When external spatial cues are available, additional neural systems can be recruited that are tuned to the specific type of cue (e.g., boundary or landmark), including hippocampus (Kunz et al., 2015) and posterior cingulate/retrosplenial cortex (Bierbrauer et al., 2020), which could either stabilize grid cell firing (Hardcastle et al., 2015) or support complementary navigational strategies. One other brain region contributing to navigation particularly in the presence of landmarks is the striatum (Doeller et al., 2008). Because striatal processing appears to be enhanced under acute stress (Schwabe and Wolf, 2013), the presence of spatial cues may be an important moderator of potential stress effects on either performance or strategy use during navigational processes.

As part of the parahippocampal gyrus, the EC is strongly connected to the hippocampus and plays an important role in mediating the stress response, e.g., by modulating coping processes (Umegaki et al., 2003), promoting stress-induced long-term potentiation in dentate gyrus and amygdala (Vouimba et al., 2004; Yaniv et al., 2003), and showing dopaminergic cell loss in presence of elevated glucocorticoid levels (Burtscher et al., 2019). More strikingly, the EC harbors abundant GRs and is therefore a likely target of glucocorticoid-mediated stress effects on PI (Sarrieau et al., 1988). We have recently shown that chronic stress in healthy humans is associated with selective PI deficits (Akan et al., 2023), which were unmasked in scarce environments without spatial cues and in trials with high difficulty. Importantly, acute and chronic stress can act differentially on cognitive processing. Whereas acute stress enhances or impairs cognitive processes (Wolf, 2009), chronic stress has predominantly detrimental consequences (Marin et al., 2011). The main goal of this study was thus to investigate whether acute stress affects PI, and, to compare the findings with the results of our previous study. Because working memory is also a component of PI abilities (Arnold et al., 2014) and typically impaired by stress, especially in cases of high cognitive load (Shields et al., 2016), we also examined stress effects on working memory performance to evaluate the specificity of potential stress effects on PI. We hypothesized acute stress i.) to impair PI predominantly in an environment with no spatial cues and less pronounced when a landmark is available, and ii.) to impair working memory, especially as the task becomes more challenging.

2. Material and methods

2.1. Participants

Sample size was determined via G*Power 3.1 (Faul et al., 2009) with the goal to obtain sufficient power (1-β = 0.8) assuming a medium effect size ($f^2 = 0.15$) in a linear multiple regression fixed model with 3 predictors at the standard alpha error level (α = 0.05). The power analysis yielded a requirement of at least 55 participants. In anticipation of potential drop-out effects and stress non-responders, we recruited 67 healthy male participants, one of which aborted the testing session due to malaise, leaving a final sample size of $n = 66$, aged between 18 and 35 years (24.39 ± 3.95 years; mean ± SD) and with a Body Mass Index between 18 and 30 (23.36 ± 2.18; mean ± SD). Participants were acquired through online advertisements in social media networks, mailing lists and in university classes at Ruhr University Bochum. Exclusion criteria comprised an acute or history of disease (i.e., neurological, psychiatric, cardiovascular, immunologic), current or history of medical or psychological treatment, drug use, female sex, or previous experience with the utilized stress protocol (see 2.2) or with the PI paradigm (see 2.3). Females were excluded due to the known influence of gonadal hormones on the secretion of stress hormones (Kirschbaum et al., 1999) and their associated changes in CNS functioning (Goldfarb et al., 2019). All participants had normal or corrected-to-normal vision and received a compensation of 10€/hour (20–25€ in total) or course credits. Prior to testing, written informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki as approved by the psychological ethics committee of Ruhr University Bochum (approval number: 612).

2.2. Stress induction and assessment

Participants were randomly assigned to either a stressful experimental group ($n_{stress} = 32$) or to a non-stressful control group ($n_{control} = 34$). Participants in the experimental group underwent the socially evaluated cold-pressor test (SECPT), a standardized stress protocol reliably inducing psychological (feeling of distress) and physiological stress (SAM and HPA axis activation; Schwabe et al., 2008). Briefly, participants had to immerse their hand into ice-cold water (0–2 °C) for a period of maximum 3 min, while they were videotaped and observed by a neutral, and distanced, experimenter. In the control group, participants underwent a control procedure of the SECPT. Here, participants were neither videotaped nor observed by an additional experimenter, and immersed their hand into warm water ranging from 35 to 37 °C.

To evaluate the success of the experimental manipulation, we assessed both subjective and physiological markers of stress. For subjective stress, we used four questions examining the adversity of the situation. Participants were asked to judge the difficulty, unpleasantness, stressfulness, and painfulness of the procedure on a scale ranging from 0 ("not at all") to 100 ("very"). The physiological stress response was measured via cortisol assessed out of salivary samples using Salivettes (Sarstedt, Nümbrecht, Germany) and cardiovascular measurements (blood pressure, middle arterial pressure, and heart rate) assessed using a Dinamap Vital Signs Monitor (Critikon, Tampa, FL, USA), collected at several time-points (see Fig. 2). Saliva samples were stored at −20 °C until assay. Salivary cortisol concentrations were extracted from the samples using a time-resolved fluorescence immunoassay (IBL, Hamburg, Germany) at the Genetic Psychology Lab of Ruhr University Bochum and are reported in nanomole per liter (nmol/l). Intra- and inter-assay coefficients of variations were below 6.7%.

2.3. Experimental PI task

We used an adapted version of the "Apple Game" paradigm (Unreal Engine 4, Epic Games, version 4.11; see Fig. 1), a virtual PI task completed on a desktop computer using a joystick and described comprehensively in Bierbrauer et al. (2020). PI is here conceptualized as the ability to integrate across several paths and to calculate home-coming vectors based only on visual cues. The environment in the task was created as a circular arena with a diameter of 13,576 virtual meters (vm) and was formed by an endless grassy plain with a blue sky rendered at infinity. In short, each trial had three phases. Participants first moved to a basket (start phase) and had to memorize its location (goal location). They then navigated to a variable number of trees (1–5), which appeared consecutively in different locations (outgoing phase), thereby manipulating the path distance of the outgoing phase and thus difficulty, until a tree containing a red apple (retrieval location) was reached. Basket and trees disappeared upon arrival at the respective locations. From the retrieval location, participants were asked to take the shortest path back to the goal location (incoming phase). When arriving at the presumed location (response location), participants pressed a button and received visual feedback via zero to three stars depending on the Euclidean distance between response location and goal location (drop error; three stars for <1600 vm, two stars for <3200 vm, one star for <6400 vm). To investigate the effect of spatial cues on PI, the original version of the task was divided into three subtasks, of which we used two

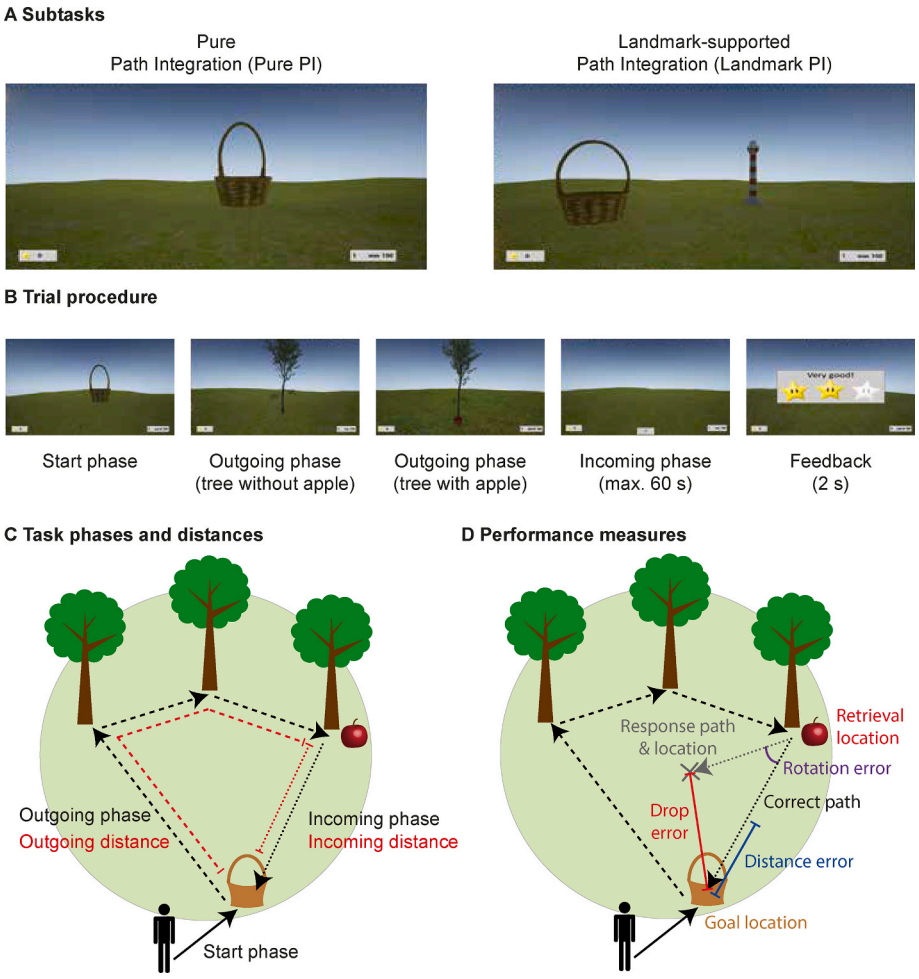

Fig. 1. Experimental path integration task. (A) The Pure PI subtask was formed only by a grassy plain, while the Landmark PI subtask contained a central lighthouse as spatial cue. (B) During the initial "start phase", participants navigated to the basket (goal location), the location of which they should remember. The "outgoing phase" followed, in which they navigated to a variable number of trees (1–5) until reaching a tree with an apple (retrieval location). During the "incoming phase", participants tried to get back to the goal location. Finally, feedback was given via zero to three stars according to response accuracy. Basket and trees disappeared as soon as they were reached. (C) Outgoing phase (dashed black line) and incoming phase (dotted black line) were quantified to obtain measures of path distance: outgoing distance referred to the cumulated distance from goal to retrieval location (dashed red line), and incoming distance to the Euclidean distance between retrieval and goal location (dotted red line). (D) PI performance was assessed by the drop error, which represented the distance between goal location and response location (solid red line). The drop error can be differentiated into distance error, describing the difference between retrieval-to-goal distance and retrieval-to-response distance (blue line), and rotation error, portraying the angle between the retrieval-to-goal path and the retrieval-to-response path (purple arc). Figure adapted from Bierbrauer et al. (2020).

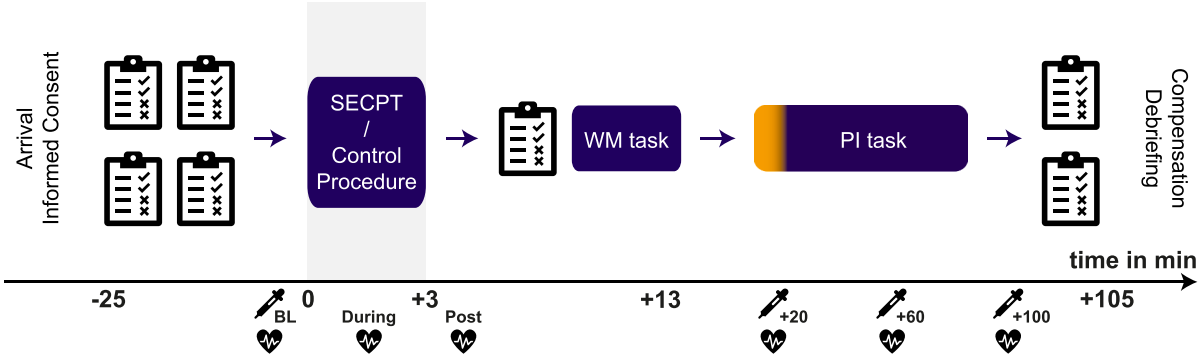

Fig. 2. Experimental procedure. Participants were subdivided into two groups (stress, control). After arrival and signing informed consent, an acclimatization period followed, in which questionnaires were filled out. Then, the SECPT followed in the stress group and the non-stressful control procedure in the control group. Thereafter, subjective stress was assessed using a questionnaire and the working memory (WM) task followed. About 13 min after stressor onset (or control procedure), participants familiarized with the path integration (PI) task by conducting up to eight training trials. The first experimental block started 20 min after stressor onset. Because of its self-paced nature, the duration of the whole task differed between participants, but on average it lasted about 75 min, leading to a finish at about 95 min after stressor onset. Finally, explicit strategies were assessed, and participants were debriefed and compensated. collection of saliva sample; assessment of blood pressure, middle arterial pressure, and heart rate.

in this study. The "Pure PI" subtask consisted only of a grassy plain and forced participants to solely rely on visual flow, whereas the "landmark-supported PI" (Landmark PI) subtask included a central lighthouse as spatial cue. After getting familiar with the task by playing up to eight training trials, a total of 64 experimental trials (32 per subtask) divided into four blocks were presented (16 trials per block). The outgoing phase of the 32 trials of each subtask were composed of six trials with 1, 2, 4 and 5 trees, respectively, and eight trials with three trees in randomized order. The task was completed using a joystick on a 23″ desktop computer with a resolution of 1920 × 1080 pixels and a frame rate of 60 per second. The

joystick was attached to a custom-made frame, which also served as armrest, and the screen was located at approximately 50 cm in front of the participant. Evidence for the validity of the task was presented in our previous work (Akan et al., 2023), where we conducted control analyses of in-game variables showing that error accumulation is found in the task, and that it can be reduced by spatial cues, which are both main features of PI (Hardcastle et al., 2015).

2.4. Working memory task

We used the Digit-Span Forward and Digit-Span Backward from the most recent edition of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008) in its German Version (Petermann, 2012). The tasks essentially consist of verbally presenting numeric sequences, which must be repeated by participants either in the same order (forwards task) or in the inverse order (backwards task) of presentation. During either task, participants go through several stages, and each new stage increases task difficulty as another number is added to the sequence. The first stage begins with a sequence length of three in the forwards task, and two in the backwards task. At any stage, the prevailing sequence length is presented twice (using differing sequences), and the successful repetition of each sequence is worth one point. When participants fail twice at a certain stage, the task ends. Otherwise, the task continues until reaching a maximum sequence length of eight in the forwards task, or seven in the backwards task.

2.5. Experimental procedure

Testing sessions were scheduled between 12.00 p.m. and 6.30 p.m. to control for the circadian rhythm of cortisol secretion (Clow et al., 2004). Upon arrival, participants awaited an acclimation period of 20 min, in which they read study information, gave written informed consent, and answered questionnaires. Then, the stress or control procedure took place (see 2.2), after which subjective stress and working memory were assessed. The working memory task was included to investigate stress effects on working memory for the evaluation of the specificity of potential stress effects, but also served to fill a standardized waiting period between stressor and PI task. Subsequently, the PI task was presented on a laptop computer and participants first played a training block. Then, about 20 min after onset of the stress or control procedure, respectively, the PI task started. Midway through the task, after two of four blocks, a short break was introduced, in which physiological parameters were assessed. After completion of the PI task, participants answered two final questionnaires assessing potential explicit strategies used during the paradigm and, finally, they were debriefed and compensated for participation. The whole procedure is depicted in Fig. 2.

2.6. Experimental design and statistical analyses

Apple Game data were extracted from computer-generated log-files using MATLAB (2021a, The MathWorks Inc., Massachusetts, US), including the Parallel Computing Toolbox (v6.12) and the CircStat Toolbox (Berens, 2009). Statistical analyses were conducted in R (R Core Team, 2021) using the lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017) and emmeans (Lenth, 2022) packages.

During the experimental task, several measures for PI performance and path distance were assessed. General PI performance is reflected by the overall drop error, which is defined as Euclidean distance between the response location and the goal location (Fig. 1D). The drop error can be differentiated into distance error, i.e., the difference between retrieval-to-goal distance and retrieval-to-response distance (Fig. 1D), and rotation error, i.e., the angle between retrieval-to-goal path and retrieval-to-response path (Fig. 1D). As grid cell firing fields are characterized by regular distances and hexadirectional symmetry (Hafting et al., 2005), they convey detailed information about traveled distances but only limited information about direction, and thus have been proposed to be especially important for translational PI and distance estimation (Evans et al., 2016). Therefore, like in our previous study (Akan et al., 2023), we decided to not only focus on drop error, but also consider distance error and rotation error as measures of PI performance. For characterizing path distance, two parametrical measures were assessed. While *outgoing distance* represents the accumulated distance from the goal to the retrieval location, *incoming distance* refers to the Euclidean distance between retrieval and goal location (Fig. 1C). These measures are related to different subcomponents of PI: Outgoing distance is important to keep track of the traveled path in relation to the starting point (i.e., the later goal location), and incoming distance for calculating a direct vector in relation to this goal location. Based on previous studies suggesting that incoming distance is most closely related to EC activity (Epstein et al., 2017; Howard et al., 2014), and the results of our previous work supporting this view (Akan et al., 2023), we again focused on this measure as a proxy of path distance. For additional exploratory analyses focusing on the exact role of the landmark during stress, we assessed two more variables only relevant in Landmark PI. One of these represents the distance between the goal and the spatial cue (goal-to-landmark distance), whereas the other reflects the mean Euclidean distance of the moving participant from the landmark across all time points of the incoming phase (movement-to-landmark distance).

Our first statistical analysis examined the success of stress induction by comparing physiological and subjective markers of stress between groups. For cortisol concentrations and cardiovascular measures, repeated analyses of variance (rANOVAs) were conducted with time as within-subject factor and group as between-subject factor. We conducted a natural log (ln) transformation on cortisol concentrations, which typically exhibit a right-skewed distribution, to obtain normally distributed data. In case of violation of the sphericity assumption, we used Greenhouse-Geisser adjustment and rounded the corrected degrees of freedom to the nearest whole number. Post-hoc pairwise comparisons were performed using Bonferroni-corrected *t*-tests (or Welch's *t*-tests in case of unequal variances). For the subjective markers, we used separate *t*-tests (or Welch's *t*-tests in case of unequal variances) for all four measures (difficulty, unpleasantness, stressfulness, painfulness) as dependent variables and group as independent variable.

To test our first hypothesis and evaluate effects of acute stress, subtask, and path distance on PI performance, we then built linear mixed models with PI performance (drop error, distance error, or rotation error) on the level of single trials as criterion, subtask (Pure PI, Landmark PI) and path distance (incoming distance) as within-subject predictors, and group (stress, control) as between-subject predictor. These models thus only differed in the measure of PI performance. For the first exploratory analysis, which aimed at investigating the effect of goal-to-landmark distance on PI performance, and whether stress influences this relationship, we conducted linear mixed models with PI performance (drop error) on the level of single trials as criterion, goal-to-landmark distance (only in Landmark PI) as within-subject predictor, and group (stress, control) as between-subject predictor. For the second exploratory analysis, which evaluated whether stress affected the employment of navigational strategies (irrespective of performance), we conducted one last linear mixed model with movement-to-landmark distance (only in Landmark PI) on the level of single trials as criterion, and group (stress, control) as between-subject predictor. In all linear mixed models, "subject" was added as random factor and age as covariate. To test our second hypothesis and evaluate effects of acute stress on working memory (and thus the specificity of stress effects on PI), we conducted *t*-tests with either the score of the forwards task or the score of the backwards task as dependent variable and group as independent variable.

Due to technical issues, some trials could not be adequately terminated and were excluded. This exclusion affected 2.9% of all trials, preserving an average of 62.1 trials per participant for statistical analyses. We centered within-subject parametric predictors (incoming distance, goal-to-landmark distance) to the participant's mean and age to the grand mean of all participants (Enders and Tofighi, 2007). For

analysis of fixed effects, we always used type III sum of squares. Post-hoc pairwise comparisons were performed using Tukey-adjusted Fisher's tests correcting for number of subtasks (2), number of groups (2), or a combination of those. We used the Kenward-Roger method for an approximation of degrees of freedom, which we rounded to the nearest whole number. As measures of effect size, we used Partial Eta-Squared (η_p^2) for *F*-tests and Cohen's d (*d*) for *t*-tests. Multicollinearity between predictors was not problematic (all variance inflation factors <5). All statistical tests were conducted two-tailed at a significance level of $\alpha = 0.05$. This study was pre-registered on Open Science Framework (https://osf.io/s7d65?view_only=e585f762595940d0ac437e48eebb0ea1).

3. Results

3.1. Increase of physiological and subjective stress markers after stress induction

Physiological stress. For salivary cortisol concentrations, we found significant main effects of group ($F_{(1,64)} = 28.08$, $p < .001$, $\eta_p^2 = .305$, rANOVA) and time ($F_{(2,144)} = 21.10$, $p < .001$, $\eta_p^2 = .248$, rANOVA), and a significant interaction effect between group and time ($F_{(2,144)} = 10.12$, $p < .001$, $\eta_p^2 = .136$, rANOVA; Fig. 3A). Follow-up analyses showed that the stress group did not differ from the control group in cortisol concentration at baseline ($t_{(64)} = -1.82$, $p_{Bonferroni} = .291$, $d = -0.449$, *t*-test), but exhibited higher cortisol concentrations than the control group for all three time-points following stress induction (all $t \leq -4.37$, all $p_{Bonferroni} < .001$, all $d \leq -1.076$, *t*-tests), i.e., for the entire PI task. Furthermore, when considering cardiovascular measures during the experimental manipulation (Fig. 3B), the stress group showed higher systolic and diastolic blood pressure (both $t \leq -4.95$, both $p_{Bonferroni} < .001$, both $d \leq -1.226$, *t*-tests), higher middle arterial pressure ($t_{(55)} = -6.20$, $p_{Bonferroni} < .001$, $d = -1.536$, *t*-test), but no difference in heart rate ($t_{(53)} = -2.36$, $p_{Bonferroni} = .133$, $d = -0.584$, *t*-test), compared to the control group.

Subjective stress. Participants in the stress group judged the experimental procedure as being more difficult, more unpleasant, more stressful, and more painful than the control group (all $t \leq -10.59$, all $p < .001$, all $d \leq -2.646$, *t*-tests, Table 1) and thus, the subjective stress measures complemented the overall picture of a successful stress

Table 1
Group differences in subjective stress following the experimental procedure.

	control group	stress group	*p*
difficulty	1.47 ± 3.59	70.94 ± 23.60	< .001
unpleasantness	2.06 ± 4.79	67.19 ± 24.66	< .001
stressfulness	1.47 ± 3.59	51.56 ± 26.53	< .001
painfulness	0.29 ± 1.71	71.56 ± 23.84	< .001

Note. Values represent mean ± standard deviation, *p*-values extracted from separate *t*-tests between groups; data presented for final sample of $n = 66$.

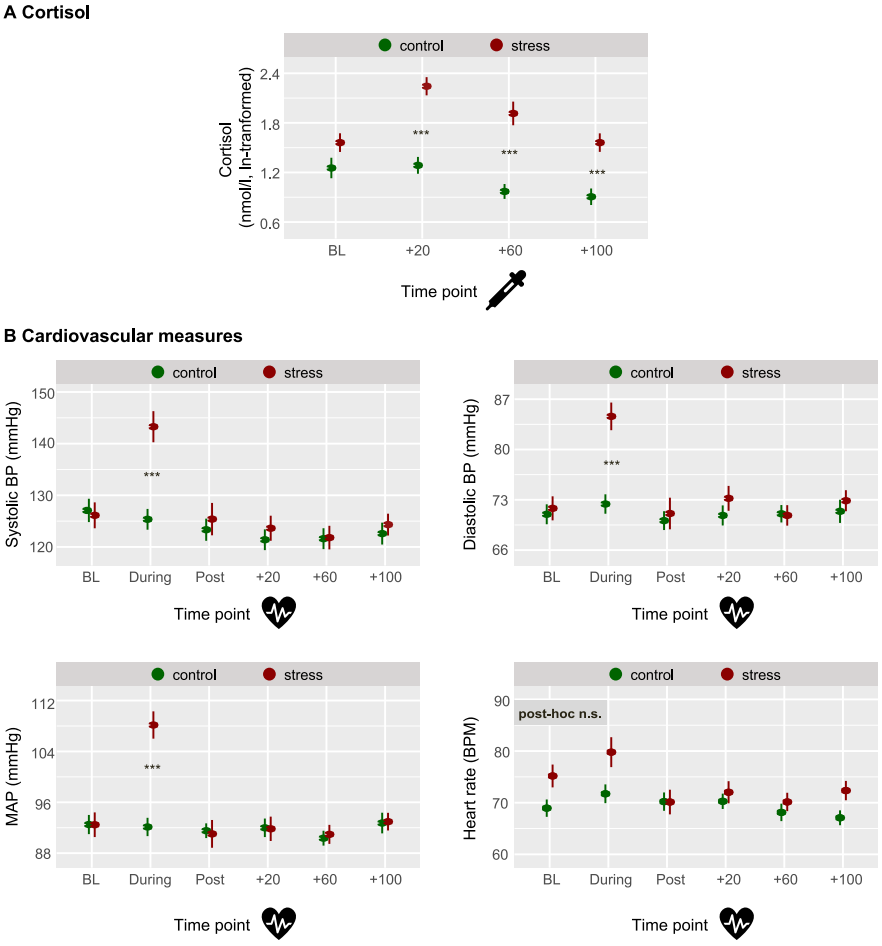

Fig. 3. Time course of stress measures. (A) Stress and control groups did not differ for baseline cortisol concentration, but the stress group exhibited higher values at all timepoints after stress induction. (B) During the stress induction, the stress group showed higher systolic and diastolic blood pressure, and higher MAP, but no difference in heart rate. Error bars represent SEM. BP: blood pressure, MAP: middle arterial pressure, n. s.: not significant, ***$p < .001$.

induction.

3.2. Stress effects on PI

To understand whether and how stress influences PI, we were not only interested in potential main effects of stress, but especially in interaction effects between stress and incoming distance, and stress and subtask, because these interactions represent stress effects at different levels of difficulty and in different environments, respectively. We first examined these effects for prediction of general PI performance, and, in a second step, we examined whether alterations in distance or rotation estimation (or both) led to changes of general PI performance.

3.2.1. Stress induces greater decline in general PI performance with higher incoming distances and upon removal of spatial cues

When considering drop error as measure of general PI performance, we replicated relevant findings of our previous work (Akan et al., 2023; Bierbrauer et al., 2020): We found main effects of subtask ($F_{(1,4025)} = 450.05, p < .001, \eta_p^2 = .101$, LMM; Fig. 4A, left) and of incoming distance ($F_{(1,4025)} = 305.74, p < .001, \eta_p^2 = .071$, LMM; Fig. 4A, middle), indicating higher drop errors in Pure PI than in Landmark PI and for higher incoming distances, respectively. In addition to these main effects, we observed an interaction effect between subtask and incoming distance ($F_{(1,4034)} = 57.54, p < .001, \eta_p^2 = .014$, LMM; Fig. 4A, right). Follow-up analyses indicated a stronger relationship between incoming distance and drop error in Pure PI compared to Landmark PI ($t_{(4034)} = 7.59, p < .001, d = 0.119$, paired t-test).

Regarding associations with acute stress, we did not find a main effect of group ($F_{(1,63)} = 1.43, p = .236, \eta_p^2 = .022$, LMM), indicating no general effect of stress on PI, but we did observe relevant interaction effects. First, we found an interaction effect between group and subtask ($F_{(1,4025)} = 5.75, p = .017, \eta_p^2 = .001$, LMM; Fig. 4B, left). Although pairwise comparisons between groups within subtasks did not reach significance (both $t \geq -1.87$, both $p_{Tukey} \geq .248$, both $d \geq -0.029$, t-tests), the stress group exhibited a greater performance difference between subtasks ($t_{(4025)} = -2.40, p = .017$, d $= -0.037$, t-test; Fig. 4B, right), indicating a greater decline of performance when the landmark is no longer available. Second, we observed an interaction effect between group and incoming distance ($F_{(1,4025)} = 9.04, p = .003, \eta_p^2 = .002$, LMM; Fig. 4C), and post-hoc tests revealed that the effect of incoming distance on drop error was stronger in the stress group as compared to the control group ($t_{(4025)} = -3.01, p = .003, d = -0.047$, t-test).

3.2.2. Stress effects on PI performance are more strongly related to distance estimation than to rotation estimation

We observed that the effects of task features on PI performance were similar for both subcomponents (distance error and rotation error) with main effects of subtask (both $F \geq 126.77$, both $p < .001$, both $\eta_p^2 \geq .031$, LMMs) and incoming distance (both $F \geq 117.10$, both $p < .001$, both $\eta_p^2 \geq .028$, LMMs), and their interaction (both $F \geq 4.44$, both $p \leq .035$, both $\eta_p^2 \geq .001$, LMMs). Notably though, the main effect of incoming distance on rotation error had the opposite direction, such that higher incoming distances led to smaller rotation errors.

Considering the effects of acute stress, we did not find a main effect of group for both error types (distance error: $F_{(1,63)} = 1.65, p = .203, \eta_p^2 = .026$, LMM; rotation error: $F_{(1,63)} = 2.29, p = .135, \eta_p^2 = .035$, LMM),

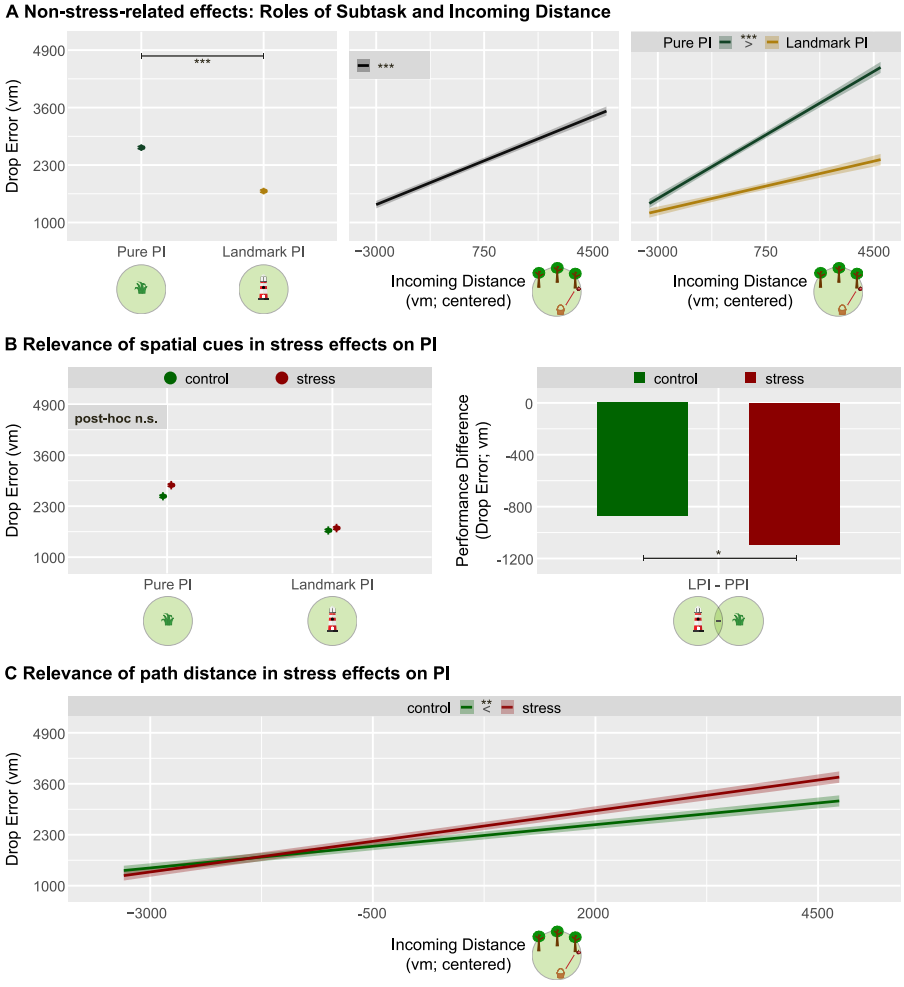

Fig. 4. Effects of stress, subtask, and path distance on general PI performance. (A) Drop error was higher when no spatial cues were available (Pure PI > Landmark PI; left). Higher incoming distances led to higher drop errors (middle) and this effect was stronger in Pure PI than in Landmark PI (right). (B) The effect of stress was more pronounced during Pure PI than Landmark PI (significant interaction), even though post-hoc pairwise comparisons between groups in each condition were not significant (left). The difference in PI performance between both subtasks was larger in the stress group (right). (C) The effect of incoming distance was larger in the stress group. Error bars and confidence bands represent SEM. Pure PI: pure path integration, Landmark PI: landmark-supported path integration, vm: virtual meters, n. s.: not significant, $^{***}p < .001$, $^{**}p < .01$, $^{*}p < .05$.

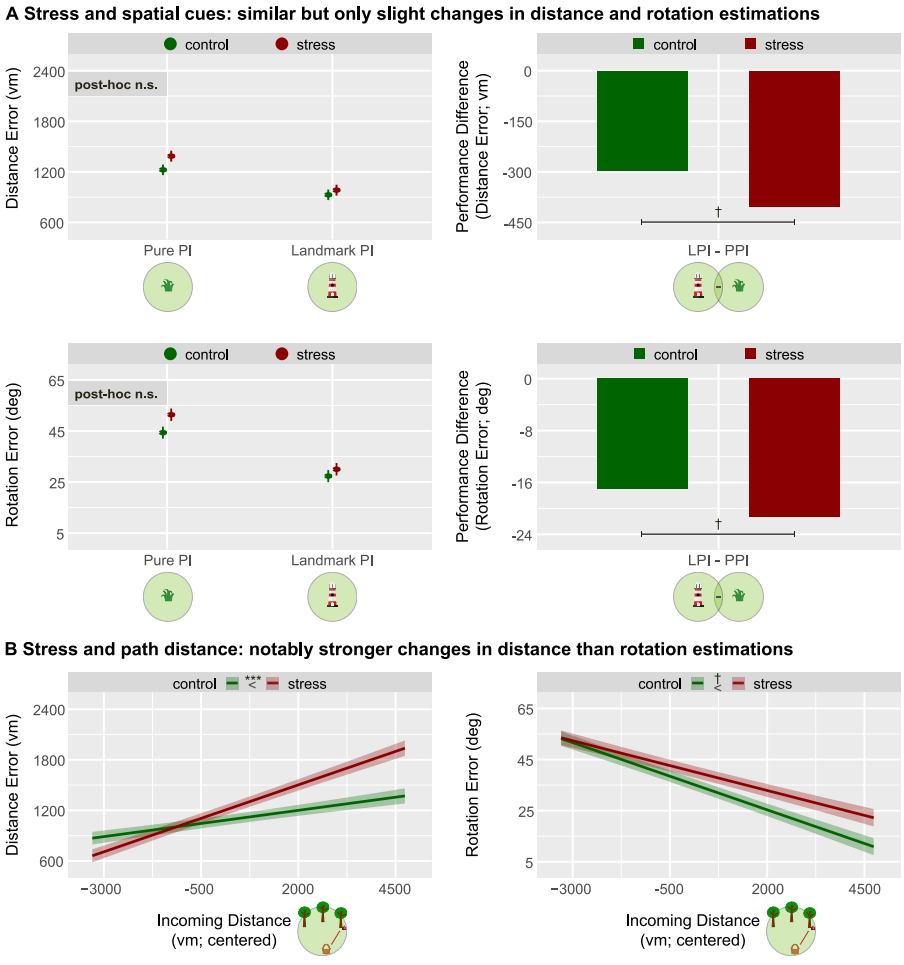

Fig. 5. The role of compromised distance and rotation estimations in stress effects on PI. (A) The interaction between subtask and group showed a trend for distance error (top left) and rotation error (bottom left), but post-hoc pairwise comparisons were each not significant. The difference in PI performance between both subtasks was larger in the stress group on trend-level for both distance error (top right) and rotation error (bottom right). (B) The impairing effect of incoming distance on distance error was larger in the stress group (left), whereas the beneficial effect of incoming distance on rotation error was smaller in the stress group on trend-level (right). Error bars and confidence bands represent SEM. Pure PI: pure path integration, Landmark PI: landmark-supported path integration, vm: virtual meters, n. s.: not significant, ***$p < .001$, $^{\dagger}p < .10$.

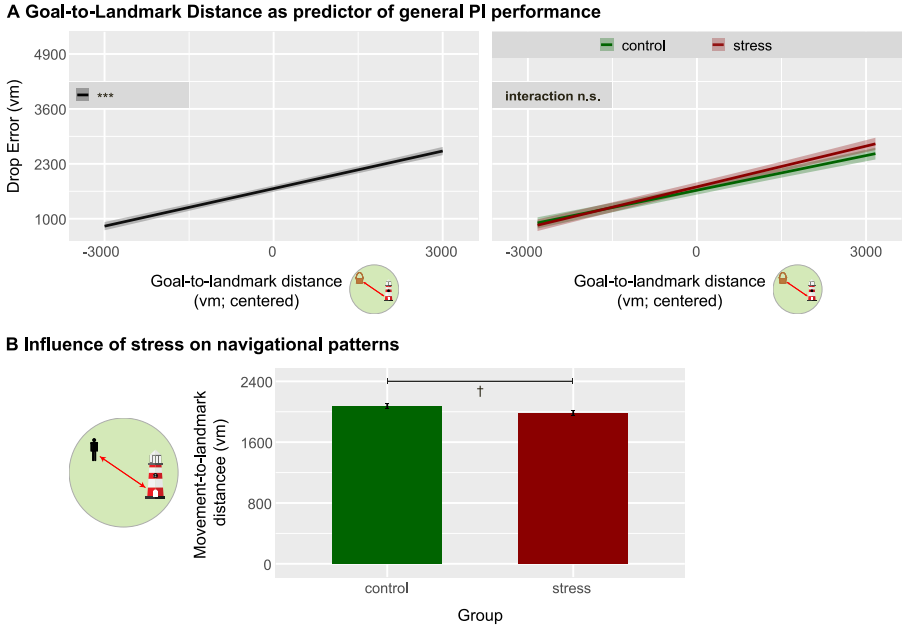

Fig. 6. Strategy use and navigational patterns in Landmark PI. (A) A higher distance between goal location and landmark location predicted higher drop error (left) and this effect did not differ between groups (right). (B) The stress group navigated closer to the landmark (on trend). Error bars and confidence bands represent SEM. vm: virtual meters, n. s.: not significant, ***$p < .001$, $^{\dagger}p < .10$.

indicating no general effect of stress on either subcomponent. However, we observed trends for an interaction between group and subtask (distance error: $F_{(1,4026)} = 2.96$, $p = .085$, $\eta_p^2 < .001$, LMM, Fig. 5A, top panels; rotation error: $F_{(1,4025)} = 3.62$, $p = .057$, $\eta_p^2 < .001$, LMM, Fig. 5A, bottom panels). Pairwise comparisons between groups within subtasks did not reach significance (distance error: both $t \geq -1.80$, both $p_{Tukey} \geq .281$, both $d \geq -0.028$, *t*-tests; rotation error: both $t \geq -2.06$, both $p_{Tukey} \geq .174$, both $d \geq -0.032$, *t*-tests), but the stress group exhibited a greater performance difference between subtasks on trend-level (distance error: $t_{(4026)} = -1.72$, $p = .085$, d = −0.027, *t*-test; rotation error: $t_{(4026)} = -1.90$, $p = .057$, d = −0.030, *t*-test), indicating slightly disturbed distance and rotation estimation when the landmark is not available. Furthermore, we observed an interaction effect between group and incoming distance for distance error ($F_{(1,4025)} = 22.27$, $p < .001$, $\eta_p^2 = .006$, LMM, Fig. 5B, left), and post-hoc analyses revealed that the relationship between incoming distance and distance error was stronger in the stress group as compared to the control group ($t_{(4025)} = -4.72$, $p < .001$, $d = -0.074$, *t*-test). For rotation error, we observed a trend for this interaction ($F_{(1,4025)} = 3.31$, $p = .069$, $\eta_p^2 < .001$, LMM, Fig. 5B, right), and post-hoc analyses showed that the beneficial effect of incoming distance on rotation error was slightly reduced (on trend) in the stress group as compared to the control group ($t_{(4025)} = -1.82$, $p = .069$, $d = -0.028$, *t*-test).

3.2.3. Exploratory analyses: stress induces slight differences in navigational patterns (on trend)

To further investigate group differences regarding strategy use and navigational patterns, we conducted additional analyses only comprising Landmark PI trials. A higher distance between goal location and landmark predicted worse general PI performance ($F_{(1,1983)} = 194.99$, $p < .001$, $\eta_p^2 = .090$, LMM; Fig. 6A), but no stress-related effects emerged. When considering navigational pattern irrespective of PI performance, we found a trend for a main effect of group ($F_{(1,63)} = 3.35$, $p = .072$, $\eta_p^2 = .051$, LMM; Fig. 6B), showing that stressed participants navigated closer to the landmark than controls, presumably suggesting that they used landmark information more than controls.

3.3. Absence of stress effects on working memory

We did not observe any group differences in working memory performance, neither in the forwards task ($t_{(64)} = 0.28$, $p = .784$, $d = 0.069$, *t*-test) nor in the backwards task ($t_{(64)} = 0.08$, $p = .933$, $d = 0.019$, *t*-test).

4. Discussion

The goal of this study was to test whether acute stress affects visual PI performance in healthy young participants. As expected, physiological and subjective markers of stress were significantly enhanced in the stress group. We found acute stress to affect general PI performance in interaction with task-related features, indicating more pronounced stress effects in absence of spatial cues and in trials with higher difficulty. Considering PI subcomponents, the deficits were more strongly associated with impaired distance estimation and only weakly with compromised rotation estimation. In a previous study using the same task, we similarly have found that chronic stress was related to PI performance in conditions of high difficulty and in absence of spatial cues, presumably by affecting distance estimation (Akan et al., 2023). When discussing results of the current study, we will therefore focus on these two factors and further elucidate similarities and differences between the roles of acute and chronic stress in PI. The investigation of acute stress effects on working memory yielded no significant results.

Task difficulty normally affects cognitive performance, and we here observed that higher incoming distance led to worse general PI performance. More strikingly, the interaction between acute stress and incoming distance on predicting PI performance indicated that acute stress does not impair PI universally but enhances the decline in performance that is associated with higher incoming distances. This is in accordance with the observation that effects of acute stress are often unmasked in tasks with high cognitive load (Shields et al., 2016; Taverniers et al., 2011). It also complements our previous finding that chronic stress interacts with incoming distance (Akan et al., 2023), even though in that study we observed such a relationship only for distance error but not for drop error. The drop error represents general PI performance and results from a combination of translational and rotational PI, as represented by distance error and rotation error, respectively. Impairments in one of these processes can thus affect overall performance, but they are not necessarily sufficient in doing so. Depending on how strongly distance or rotation estimations are affected, and on the direction of the respective effects, general PI performance may still be preserved. When comparing the effect sizes of interaction effects in the two studies, we can conclude that distance estimation was similarly affected by acute and chronic stress ($\eta_p^2 = .006$ vs. $\eta_p^2 = .005$). Thus, the finding that acute stress was related to drop error, but chronic stress was not, might be ascribed to unequal effects on rotation error. Even though the interaction between stress and incoming distance was not significant for rotation error in both studies, acute stress seemed to be interfering with rotation error at higher distances on trend-level. Given similar effects of acute and chronic stress on distance estimation, even slight (and insignificant) effects on rotation estimation can contribute to impairments in general PI performance.

The amount and type of spatial information in an environment is highly relevant for navigation and the employment of different navigational strategies (Jain et al., 2017). As expected, we found a main effect of subtask, showing that general PI performance was decreased in the Pure PI compared to the Landmark PI. Importantly, this effect was moderated by acute stress (for drop error, and by trend for distance error and rotation error), indicating that acute stress led to a greater decline of performance upon removal of the landmark, potentially related to stress-induced disruptions in flexible behavior during prospective navigation (Brown et al., 2020). In general, this in accordance with our hypothesis that acute stress affects PI mainly in environments with little spatial information, where reliance on EC is greatest and the potential of recruiting compensatory mechanisms through other brain regions is minimal (Bierbrauer et al., 2020; Kunz et al., 2015). In our previous study, chronic stress did not interact with subtask for drop error, but a trend was observed for distance error. Thus, acute and chronic stress seem to exert similar modulatory effects on the impact of environmental features on distance estimation. Regarding rotation error, we observed a trend for the interaction between acute stress and subtask, which was not the case for chronic stress. Therefore, the significant interaction effect indicating acute stress to affect general PI performance stronger in Pure PI than in Landmark PI may be driven by subtle effects on both distance and rotation estimation.

The idea that effects of stress are often unmasked in tasks with high cognitive load is well established for working memory (Shields et al., 2016), but we neither found an effect in the forwards task nor in the more difficult backwards task. As Shields et al. (2016) demonstrated in their meta-analysis, acute stress generally impairs working memory, but moderating factors are highly relevant. One of these moderators is stress timing, i.e., the delay between stressor onset and working memory assessment. In this regard, our study differed from previous investigations that found stress effects on working memory (Oei et al., 2006; Rüttgens and Wolf, 2022; Schoofs et al., 2009), even though the timing in our study appeared to be in a window where effects can be expected (Geißler et al., 2023). This, together with the finding that acute stress leads to a stronger decline of PI performance when spatial cues are removed (thus relying on pure PI processes), strengthens the interpretation that the effects of stress on PI are specifically related to that cognitive process.

In an exploratory analysis, we investigated whether acute stress affected navigational patterns in Landmark PI, during which compensatory mechanisms encompassing the employment of landmark-based

strategies and the activation of retrosplenial cortex to stabilize grid cell firing can be recruited (Hardcastle et al., 2015; Mitchell et al., 2018). In general, and in accordance with our previous findings (Bierbrauer et al., 2020), higher distances to the landmark predicted worse PI performance. More interestingly, we observed a trend for an effect of acute stress on the navigational pattern, suggesting stressed participants to navigate closer to the landmark than controls, which may reflect enhanced use of landmark information (Brown et al., 2020), a stronger recruitment of the retrosplenial cortex (Bierbrauer et al., 2020), or a shift towards striatal processing (Schwabe and Wolf, 2013) under stress. Because striatal processing is associated with habitual stimulus-response learning (Poldrack et al., 2001), and landmark-based navigation obeys associative reinforcement (Doeller et al., 2008), acute stress may promote the employment of landmark-based strategies. The same pattern of navigating closer to the landmark has been found for healthy carriers of the ε4 allele of the apolipoprotein E gene (Bierbrauer et al., 2020), the most important genetic risk factor for late-onset Alzheimer's Disease (Corder et al., 1993), supporting the idea of a triangular relationship between stress, EC functionality, and Alzheimer's Disease (Akan et al., 2023). In more detail, the EC is among the first structures to be affected by Alzheimer's Disease neuropathology (Braak et al., 2011) and deficits in risk-carriers are likely related to EC dysfunction, forcing them to rely on compensatory mechanisms more strongly. Likewise, we propose acute stress to both disturb EC function and promote the employment of compensatory mechanisms, leading to behavioral similarities between risk carriers of Alzheimer's Disease and stressed participants during PI.

Our findings demonstrate that acute stress influences PI and thereby support the hypothesis that stress affects the EC, which is assumed to underlie the observed effects. Mechanistically, administration of glucocorticoids has been shown to affect inhibitory transmission in layer II of the EC, which in turn could compromise the spacing-based allocation of grid-cells along the dorsoventral axis of the medial EC (Hartner and Schrader, 2018). This would presumably become most relevant when the potential of error accumulation increases, which is in line with the finding that acute stress particularly disturbed PI during trials with higher incoming distances. However, with our behavioral stress study we can of course not rule out that other neurobiological processes than EC malfunction initiated by cortisol were involved in the observed effects. Future pharmacological fMRI studies are needed to test the causal role of cortisol and to characterize the underlying neural correlates of the behavioral findings.

Our findings are also generally in accordance with our previous study (Akan et al., 2023) because difficulty and environment again played a substantial role in moderating stress effects. However, one difference emerged: Whereas effects of both acute and chronic stress were strongly related to impaired distance estimation, only acute stress seemed to exert subtle effects on rotation estimation, leading to impairments in general PI performance as represented by drop error. This difference in findings could be a representation of differences between acute and chronic stress (McEwen, 2004). Moreover, it is relevant to recognize that samples in both studies differed, consisting only of females within a broader age range (22–65 years) in our previous study as compared to only males within a more narrow and younger age range (18–35 years) in the current study. Sex and age are moderators of both the stress response and navigational ability (Goldfarb et al., 2019; Lester et al., 2017; Lupien et al., 2005; Sneider et al., 2015) and thus possibly explain differences between the findings.

Finally, some limitations of our study need to be acknowledged. First, during real-world navigation PI relies on both body-based and visual cues. Even though visual cues have been shown to sufficiently activate PI processes and grid-cell like representations (Bierbrauer et al., 2020; Stangl et al., 2018), future studies investigating PI based on both types of cues are warranted. Second, our sample consisted only of males, and gonadal hormones play a substantial role in moderating stress effects (Jentsch et al., 2022). However, in our previous study investigating chronic stress instead of acute stress, we could show that a relationship between stress and PI also exists for females (Akan et al., 2023). Third, even though we have reason to assume that the cognitive process of PI is specifically targeted by acute stress, we cannot rule out a generic role of difficulty with the task used, and future research addressing this is warranted (e.g., by conducting pharmacological fMRI studies). Last, the hypothesized neuronal processes underlying the effects were not assessed here. Even though we can partially rely on our previous work that assessed and reported imaging data (Bierbrauer et al., 2020), future neuroimaging studies are needed.

5. Conclusion

We report that acute stress exerts detrimental effects on visual PI in healthy human participants, while working memory was not affected. Importantly, acute stress did not universally impair PI, but particularly in cases of high difficulty, and it further led to a stronger decline of performance when a landmark (serving as spatial cue) was removed. PI deficits were more strongly related to impairments in distance estimation than to impairments in rotation estimation. Regarding strategy use, acute stress appeared to change navigational patterns in the presence of spatial cues, leading to closer navigation to landmarks.

CRediT authorship contribution statement

Osman Akan: Conceptualization, Investigation, Formal analysis, Writing – original draft, Visualization. **Anne Bierbrauer:** Conceptualization, Software, Data curation, Writing – review & editing. **Nikolai Axmacher:** Conceptualization, Supervision, Writing – review & editing. **Oliver T. Wolf:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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