Behavioural Brain Research 442 (2023) 114305

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Chronic stress is associated with specific path integration deficits

Osman Akan [a,*], Anne Bierbrauer [b,c], Lukas Kunz [d], Patrick D. Gajewski [e], Stephan Getzmann [e], Jan G. Hengstler [e], Edmund Wascher [e], Nikolai Axmacher [c], Oliver T. Wolf [a]

[a] Department of Cognitive Psychology, Faculty of Psychology, Ruhr University Bochum, Germany
[b] Institute for Systems Neuroscience, Medical Center Hamburg-Eppendorf, Hamburg, Germany
[c] Department of Neuropsychology, Faculty of Psychology, Ruhr University Bochum, Germany
[d] Department of Biomedical Engineering, Columbia University, New York, NY, USA
[e] Leibniz Research Centre for Working Environment and Human Factors (IfADo), Technical University of Dortmund, Germany

ARTICLE INFO

Keywords:
Stress
Cortisol
Navigation
Path integration
Entorhinal cortex
Grid cells

ABSTRACT

Repeated exposure to stress (chronic stress) can cause excess levels of circulating cortisol and has detrimental influences on various cognitive functions including long-term memory and navigation. However, it remains an open question whether chronic stress affects path integration, a navigational strategy that presumably relies on the functioning of grid cells in the medial entorhinal cortex. The entorhinal cortex is a brain region in the medial temporal lobe, which contains multiple cell types involved in spatial navigation (and episodic memory), and a high number of corticosteroid receptors, predisposing it as a potential target of cortisol effects. Here, our goal was to investigate the association between chronic stress and path integration performance. We assessed chronic stress via hair cortisol concentration (physiological measure) and the Perceived Stress Questionnaire (subjective measure) in 52 female participants aged 22–65 years. Path integration was measured using a virtual homing task. Linear mixed models revealed selective impairments associated with chronic stress that depended on error type and environmental features. When focusing on distance estimations in the path integration task, we observed a significant relationship to hair cortisol concentrations indicating impaired path integration particularly during trials with higher difficulty in participants with high hair cortisol concentrations. This relationship especially emerged in the absence of spatial cues (a boundary or a landmark), and particularly in participants who reported high levels of subjectively experienced chronic stress. The findings are in line with the hypothesis that chronic stress compromises path integration, possibly via an effect on the entorhinal grid cell system.

1. Introduction

In response to short-term stressors or daily challenges, the human body responds with the activation of two systems: the rapid sympathetic-adrenal-medullary (SAM) axis leading to a release of catecholamines (adrenaline and noradrenaline) and the slower hypothalamic-pituitary-adrenal (HPA) axis leading to a release of corticosteroids (cortisol in humans; [1]). (Nor)adrenaline and cortisol, among others, function as mediators of the stress response, and they are usually adaptive because they prepare and enable an organism to react fast and cope adequately with environmental demands [2]. The acute response to stress thus typically facilitates adaptation. Because cortisol can pass the blood-brain barrier, HPA axis activity inevitably affects brain structure and function, mainly through effects on corticosteroid receptors. It is thus not surprising that acute stress has been shown to exert a complex variety of both beneficial and detrimental effects on numerous cognitive functions including perception, attention, working memory, declarative memory, and executive functions [3–5]. The specific manifestation of an acute stress effect, i.e., beneficial or detrimental, depends on many factors including stress intensity, type of stressor, timing, context, age, or sex [1,6,7].

In contrast to the adaptive nature of the stress response following an acute stressor, chronic exposure to stress can cause a maladaptive response with dysregulated physiological systems like the HPA axis [8]. One possible outcome of such a dysregulation is hypercortisolemia (excess levels of circulating cortisol), which is a predisposing and precipitating factor for various physiological and mental disorders [9]. A dysregulated HPA axis has primarily detrimental consequences on

* Correspondence to: Department of Cognitive Psychology, Faculty of Psychology, Ruhr University Bochum, Universitätsstr. 150, Room: IB 6/69, D-44780 Bochum, Germany.

E-mail address: osman.akan@rub.de (O. Akan).

https://doi.org/10.1016/j.bbr.2023.114305
Received 12 September 2022; Received in revised form 9 January 2023; Accepted 18 January 2023
Available online 20 January 2023

structural and functional brain integrity [10–12]. Research in rodents showed evidence for dendritic atrophy, impaired synaptic plasticity, and inhibited neurogenesis after repeated exposure to stress, predominantly in hippocampus and prefrontal cortex [13–15]. These changes are accompanied by impairments of cognitive functions including attentional set-shifting or spatial navigation [16,17]. In humans, chronic stress similarly is associated with deficits in episodic and spatial memory [18] and evidence has been accumulated for the wider hypothesis that chronic stress is related to worse general cognitive ability [19–21]. Moreover, chronic stress has been linked to accelerated cognitive decline during aging, particularly comprising deficits in declarative memory and executive function [22,23]. Increased cognitive decline was postulated to relate to hippocampal atrophy as a structural correlate of elevated cortisol levels [18], but some studies were not able to replicate this finding (e.g., [19,24,25]).

The hippocampus is one of the main targets of cortisol because it contains a large number of corticosteroid receptors and is involved in terminating the HPA axis response [2,26]. The sensitivity of hippocampal functioning for stress effects in humans has mainly been shown for memory, but less research has been conducted on spatial navigation, even though spatial navigation constitutes the other most prominent hippocampus-based type of cognition. Furthermore, most of the existing studies in this context focused on acute, and not chronic, effects of stress [27–34]. Studies in rodents, however, have repeatedly shown that chronic stress alters spatial navigation (e.g., [35–40]). In a review of the available literature on this matter, Conrad [41] observed a pattern of results suggesting that chronic stress has impairing effects on spatial memory, but not universally on spatial learning. More specifically, chronic stress appears to impair spatial learning during appetitively motivated tasks but can have no or even beneficial effects under aversive task parameters. Conrad [41] concluded that the effect of chronic stress on hippocampus-based spatial ability depends on whether other brain structures can be engaged, reflecting the idea that when compensatory mechanisms or strategies can be recruited, stress-induced impairments might be diminished.

In general, spatial navigation can rely on various strategies that have been associated with distinct brain regions and neuronal processes [42]. These different strategies include (among others) path integration (PI), map-based navigation and landmark-based navigation, each of them tuned to specific environmental properties and requiring the availability of specific spatial cues [43]. All of these functions rely on networks rather than single regions, but there are specific "core areas" or "hubs" harboring different kinds of spatially selective cells such as place cells or grid cells [44]. In spatially scarce environments with little information and absence of external cues, PI plays a particularly important role [45]. PI involves continuous integration of self-motion cues that are generated during movement, thus enabling calculation of distance and direction traveled from an arbitrary reference point to estimate the current position and orientation. On the neuronal level, PI has been related to grid cell firing in the entorhinal cortex (EC; [46–49]). Grid cells exhibit an arrangement of multiple firing fields organized in a grid-like hexagonal pattern [50,51] and may provide a general spatial metric of distances [44].

Even though PI is based on EC function, which is strongly interconnected to the hippocampus, there are, to our knowledge, no studies that investigated the relationship between PI and chronic stress. The EC itself has also not been focused on in the context of long-term effects of stress [52], although there are several hints signaling its importance. For instance, the EC has been demonstrated to be involved in coping with stress [53], to be associated with stress-induced long-term potentiation in dentate gyrus and amygdala [54,55], and to show increased dopaminergic cell loss and α-synuclein pathology in the presence of elevated corticosterone [56]. Most strikingly, the EC abundantly contains glucocorticoid receptors (GRs; [57]), which – alongside mineralocorticoid receptors (MRs) – constitute the main binding site for cortisol, and thus, it is potentially vulnerable for chronic stress effects.

Spatial navigation in general can serve as a theoretical model system in cognitive neuroscience [58], but current studies suggest that EC functioning in particular may as well be of clinical relevance. This is because spatial disorientation is one of the main and earliest behavioral characteristics of Alzheimer's Disease (AD; [59]) and the EC is among the first regions affected by tau pathology during AD, long before onset of clinical symptoms [60]. EC malfunction could therefore provide an early biomarker for AD. Supporting this idea, we recently demonstrated that PI performance (as a behavioral marker of EC function) of healthy young carriers of the ε4 allele of the apolipoprotein E (APOE) gene, which constitutes the most important genetic risk factor for late-onset AD [61], was worse - compared to *APOE*-ε3 carriers - in environments without spatial cues [62]. When spatial cues (i.e., boundaries or landmarks) were available and provided relevant information, additional brain regions could be recruited, particularly hippocampus [63] and posterior cingulate/retrosplenial cortex [62,64]. Recruiting these brain regions may allow an individual to use boundary and landmark information to stabilize grid cell firing [65] and thereby compensate for PI deficits. Intriguingly, when such spatial cues were available, no difference in performance was found between *APOE* genotypes, potentially reflecting the recruitment of compensatory mechanisms [62,63].

Not only PI, which can potentially serve as an early cognitive biomarker for detecting AD, but also stress plays an important role in AD, underlining the relevance of investigating the relationship between chronic stress and PI. HPA axis dysregulation appears to facilitate the pathogenesis and progression of AD [66,67]. Higher levels of chronic stress are associated with a higher likelihood of dementia [68], patients with amnestic Mild Cognitive Impairment and AD patients exhibit elevated cortisol levels [69], hypercortisolemia is a characteristic feature of early AD [70], and elevated cortisol levels predict lower hippocampal volume and cognitive decline in AD [71].

The question arises, whether and how chronic stress, PI performance and AD relate to each other. To shed light on part of this triangular relationship, we here investigated the association between chronic stress and PI at the behavioral level. We used the relatively recent approach of analyzing hair cortisol concentration (HCC) as a physiological marker [72] and the German version of the Perceived Stress Questionnaire (PSQ) as a subjective marker of chronic stress [73]. In their meta-analysis of studies using HCC, Stalder et al. [74] reported significant positive associations between HCC and salivary cortisol data as well as between HCC and chronic stress, reflecting the observation that stress-exposed groups exhibited increased HCC compared to control groups. Notably, studies investigating the association between HCC and cognitive function so far have not led to unequivocal results [75–80]. We decided to measure both physiological and subjective markers of chronic stress because they are often not closely related [81] and thus potentially reflect different dimensions of the stress response. To assess PI performance, we employed a desktop-based virtual reality spatial navigation task containing three subtasks with different environments [62]. These environments differed in availability and type of spatial cues, and thus allowed to reveal potential stress-related impairments that may be specific to distinctively recruited brain regions. We hypothesized that chronic stress is associated with reduced PI performance and that this association is more pronounced in the absence of spatial cues.

2. Material and methods

2.1. Participants

A sample of 593 participants were recruited to take part in the Dortmund Vital Study (trial registration number: NCT05155397, see Gajewski et al. [82]) at the Leibniz Research Centre for Working Environment and Human Factors (IfADo), TU Dortmund, Germany. A subgroup of $n = 139$ participants additionally completed a PI task, of which 60 (52 females & 8 males) agreed to provide a hair sample for HCC analysis [72]. Due to the small number of males and reported cortisol-related hormonal sex differences [83], we only considered the 52 females ranging between 22 and 65 years (44.06 ± 13.23 years; mean ± SD) for further analysis. Inclusion criteria were designed to recruit a healthy and representative sample, where no restrictions regarding education or occupation were imposed and where “healthy” was defined in a broad sense and allowed for a history of diseases (but a history of severe diseases led to exclusion; for a complete list of inclusion and exclusion criteria, see Supplementary Text). Participants had normal or corrected-to-normal vision and received a compensation of 10€ per hour (generally 20€ in total). Each participant gave written informed consent prior to testing and all study procedures were in accordance with the Declaration of Helsinki as approved by the ethics committee of the IfADo (approval number: A93–3).

2.2. Experimental task

Participants performed the “Apple Game” paradigm (Unreal Engine 4, Epic Games, version 4.11; Figs. 1 and S1), a virtual PI task described in detail in Bierbrauer et al. [62]. We here conceptualized PI as the general ability to integrate across several paths and to compute home-coming directions and distances based on vision only and independent of other sensory modalities. The task was completed on a laptop computer using a joystick. An endless grassy plain with a blue sky rendered at

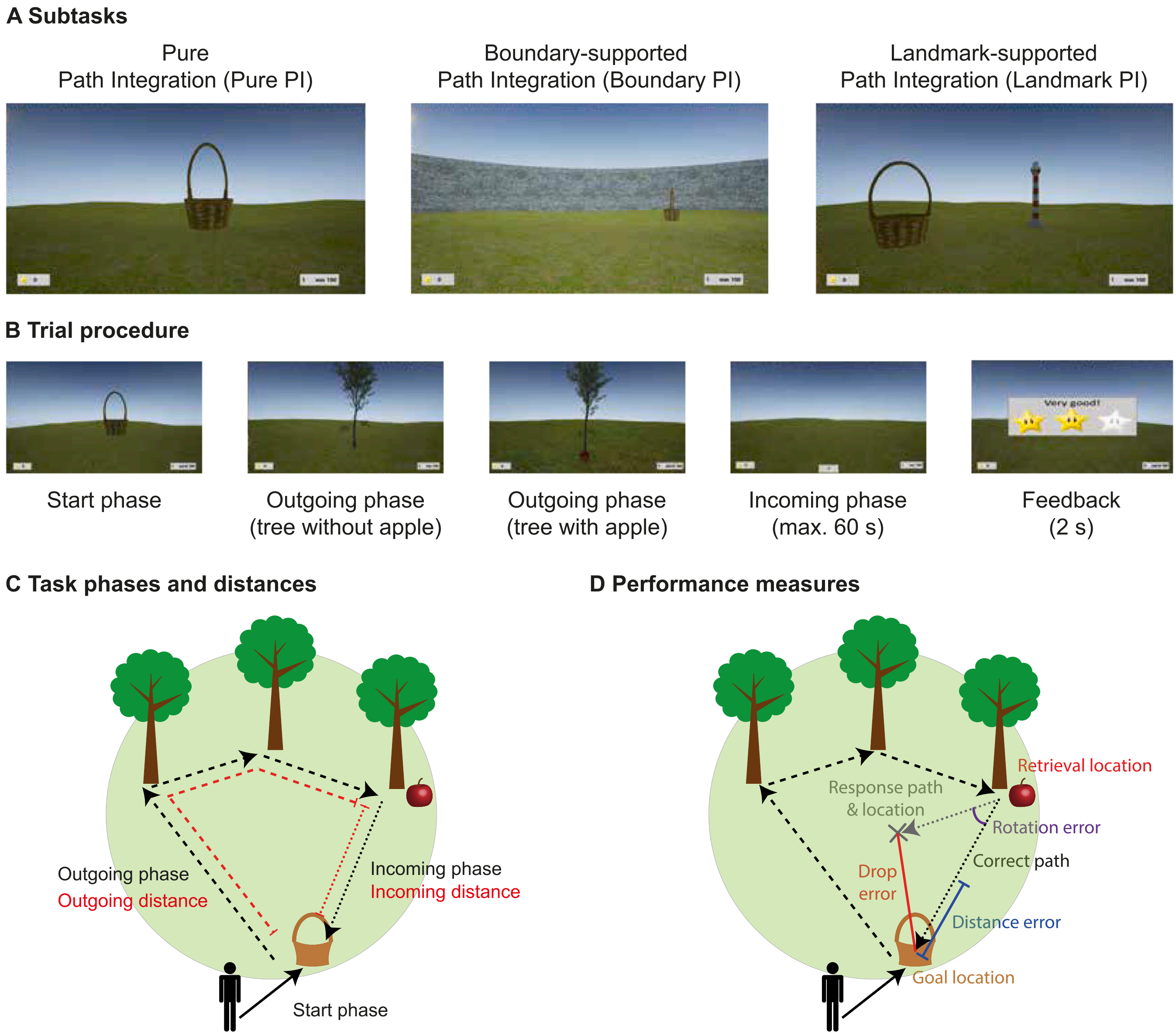

Fig. 1. Experimental path integration task. (A) Three subtasks in different environments: The Pure PI subtask consisted only of a grassy plain, whereas the Boundary PI subtask included a circular stonewall and the Landmark PI subtask included a central lighthouse. (B) During the “start phase”, participants navigated to the basket (goal location) and tried to remember its location. In the following “outgoing phase", they navigated to up to five trees until they reached a tree with an apple (retrieval location). In the final “incoming phase", they were asked to find back to the basket (which was not visible anymore). (C) Outgoing phase (dashed black line) and incoming phase (dotted black line) were quantified regarding their spatial distances. Outgoing distance was the cumulated distance from the goal to the retrieval location (dashed red line), whereas incoming distance described the Euclidian distance between retrieval and goal location (dotted red line). (D) Performance was measured via the drop error, i.e., the distance between goal location and response location (red line). The drop error was further differentiated into distance error, i.e., the difference between retrieval-to-goal distance and retrieval-to-response distance (blue line), and rotation error, i.e., the angular difference between retrieval-to-goal angle and retrieval-to-response angle (purple arc).
Figure adapted from Bierbrauer et al. [62].

infinity formed the environment. The diameter of the circular arena was approximately 13,576 virtual meters (vm). Each trial comprised three phases. Participants first moved to a basket (start phase), the location of which they had to remember (goal location). They then navigated to a variable number of trees (between 1 and 5) appearing successively in different locations (outgoing phase), which allowed to experimentally vary the path distance of the outgoing phase and thus PI difficulty, until the participants arrived at a tree with a red apple (retrieval location). Both basket and trees disappeared as soon as the respective locations were reached. At the retrieval location, participants were instructed to take the shortest path back to the goal location (incoming phase). After reaching the remembered location of the basket (response location), participants pressed a button and received feedback with zero to three stars corresponding to the Euclidian distance between response location and goal location (drop error; three stars for < 1600 vm, two stars for < 3200 vm, one star for < 6400 vm). Locations of basket and trees were equally distributed across an (invisible) grid of 8 × 8 squares such that each participant was forced to visit any square at least once in each environmental condition (Fig. S1). To investigate PI with respect to the availability of different types of spatial cues, the task was divided into three subtasks corresponding to three different environments. The subtask "Pure PI" consisted only of a grassy plain, forcing participants to solely rely on PI based on visual flow, whereas the "boundary-supported PI" (Boundary PI) and the "landmark-supported PI" (Landmark PI) subtasks additionally provided a spatial cue (circular stonewall and central lighthouse, respectively), which was present during the whole trial, and allowed for further orientation unrelated to self-motion cues. The subtasks were designed to distinguish between PI with selective reliance on EC (in Pure PI) and PI with less selective reliance on EC due to the possibility of recruiting other brain regions in the presence of spatial cues (in Boundary PI and Landmark PI). We predicted chronic stress to mainly be associated with PI in the Pure PI subtask and less pronounced or not at all in the Boundary PI or Landmark PI subtasks. Participants completed 16 trials in each of the three subtasks (i.e., 48 trials in total), with the order of subtasks being randomized. The outgoing phase of the 16 trials of each subtask were comprised of three trials with 1, 2, 4 and 5 trees, respectively, and four trials with three trees in randomized order.

2.3. Measures of chronic stress

We used two different types of measures for chronic stress. PSQ scores provided a subjective measure and HCCs derived from hair samples served as a physiological measure.

The PSQ, developed by Levenstein et al. [84], is a tool for the subjective assessment of experienced stress. Here, we used the validated German version with 20 instead of the original 30 items [73]. It consists of four subscales (worries, tension, joy, demands) with five items each and one overall score (PSQ total). We used the "recent" version of the questionnaire, which quantifies experienced stress over the period of the last four weeks.

HCC has been suggested a biological marker of chronic stress [72, 85]. The approach takes advantage of the incorporation of lipophilic hormones into the growing hair, thereby delivering a retrospective indicator of the cortisol production over the period of several months (as hair grows at an approximate rate of 1 cm/month). We collected hair samples according to general guidelines from the Society of Hair Testing [86], wrapped in aluminium foil and stored in a dark room until shipment to and analysis at Dresden LabService GmbH, TU Dresden, Germany. HCC was assessed from the first proximal 4 cm-segment using liquid chromatography-mass spectrometry (LC-MS), a standard approach for hair steroid analysis [87]. HCCs are reported in picograms per milligram (pg/mg).

2.4. Data analysis

Behavioral data were extracted from computer-generated log-files using MATLAB (2021a, The MathWorks Inc., Massachusetts) including the Parallel Computing Toolbox (v6.12) and the CircStat Toolbox [88]. Statistical analyses were conducted in R [89] using the lme4 [90], lmerTest [91] and emmeans [92] packages.

The drop error (Euclidean distance between the response location and the goal location; Fig. 1D) as a measure of PI performance has two components: distance error (difference between retrieval-to-goal distance and retrieval-to-response distance; Fig. 1D) and rotation error (angular difference between retrieval-to-goal angle and retrieval-to-response angle; Fig. 1D). Grid cell firing fields are characterized by regular distances and hexadirectional symmetry [51]. Grid cells thus convey detailed information about traveled distances but only limited directional information and have been proposed to be particularly relevant for translational PI [93]. We therefore decided to not only focus on drop error, but to also consider the distance error as measure for PI performance (for analyses considering rotation error, see Fig. S2).

We manipulated number of trees (1−5) to experimentally vary path distance. However, this measure is not well suited as a predictor in a statistical model, because it neither is very accurate (two paths with the same number of trees could differ substantially in length) nor parametrical. Thus, to characterize path distance, and thus PI difficulty, more precisely, two parametrical measures were available: outgoing distance and incoming distance. Outgoing distance corresponds to the cumulated distance from the goal to the retrieval location, whereas incoming distance describes the Euclidian distance between retrieval and goal location (Fig. 1C). Both measures represent different subcomponents of PI: Outgoing distance is relevant for keeping track of the traveled path in relation to the goal location, and incoming distance for computing a direct vector in relation to the goal location. We here focused on incoming distance, because previous studies suggested that it is most closely related to EC activity [94,95].

Before investigating our research question at hand, we conducted a few control analyses only including in-game variables to check whether our task fulfills main characteristics of a PI task. These analyses focused on examining whether we find error accumulation during the outgoing phase, which is a prominent feature of PI [65,96], and were statistically modeled by linear mixed models on the level of single trials using PI performance (drop error, distance error or rotation error) as criterion and outgoing distance as within-subject predictor. "Subject" was added as random factor.

To then analyze PI performance as a function of chronic stress, subtask, and path distance, we conducted a series of linear mixed models on the level of single trials. In all these models, PI performance (drop error or distance error) served as criterion, subtask (Pure PI, Boundary PI and Landmark PI), and path distance (incoming distance or outgoing distance) as within-subject predictors, and chronic stress (HCC and PSQ) as between-subject predictor. "Subject" was added as random factor and age as covariate, because of widely known age-related alterations of navigational abilities [97].

We excluded participants, when they deviated more than three standard deviations (SDs) from the grand mean on any of the between-subject predictors or when they did not provide a hair sample with a minimum length of 4 cm. This led to the exclusion of two participants (one HCC outlier and one hair sample of only 3 cm), leaving a final sample of $n = 50$ participants. For HCC, which typically exhibits a right-skewed distribution, we conducted a natural log (ln) transformation, to obtain normally distributed data. From the PSQ raw data, a PSQ total score was obtained by calculating an average score, which was linearly transformed to a range of 0–100, where 0 reflected a minimal amount and 100 a maximal amount of perceived stress. We then centered within-subject parametric predictors (incoming distance, outgoing distance) to the participant's mean and between-subject parametric predictors or covariates (ln-transformed HCC, PSQ, age) to the grand mean of all participants [98]. For analysis of fixed effects, we always used type III sum of squares. In case of interactions between parametric predictors, we discretized all but one parametric predictor and calculated estimated marginal means (or "adjusted means") or estimated marginal means of linear trends (or "conditional regression equations") based on the minimum, mean and maximum values of these discretized predictors. Post-hoc pairwise comparisons were performed using Tukey-adjusted (or Šídák-adjusted in case of more than one set of means) Fisher's tests correcting for number of subtasks (3), number of HCC levels (3), number of PSQ levels (3), 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. Multicollinearity between predictors was not problematic (all variance inflation factors < 5). All statistical tests were conducted two-tailed at a significance level of $\alpha = 0.05$.

3. Results

3.1. Validity of the PI task

To check whether we were assessing PI even though we used a virtual task that does not provide body-based cues, we inspected relevant outcome measures. Most importantly, outgoing distance had a main effect on drop error ($F_{(1,2346)} = 75.68$, $p < .001$, $\eta p^2 = .031$), distance error ($F_{(1,2346)} = 75.78$, $p < .001$, $\eta p^2 = .031$) and rotation error ($F_{(1,2344)} = 16.52$, $p < .001$, $\eta p^2 = .007$), respectively, indicating error accumulation during the outgoing phase, which is a prominent feature of PI [65,96].

3.2. Measures of chronic stress

HCCs and PSQ scores are depicted in Table 1. To investigate a potential association between these measures of chronic stress, we performed a correlation analysis ($r_{(48)} = .06$, $p = .690$), indicating that both measures were not related to each other.

3.3. Association between chronic stress and PI performance

To assess the association between chronic stress and PI performance, we built two linear mixed models. Both models contained the same between-subject predictors of chronic stress (HCC and PSQ), the same within-subject predictors (subtask and incoming distance), the same covariate (age) and the same random factor (subject). Both models only differed in the performance measure for PI (drop error vs. distance error), which served as criterion. We predicted chronic stress to mainly be associated with PI in the Pure PI subtask and less pronounced or not at all in the Boundary PI or Landmark PI subtasks.

3.3.1. Subjective, but not physiological stress is related to the drop error

Using the model with drop error as measure of PI performance, we replicated findings reported in Bierbrauer et al. [62]: We found a main effect of subtask ($F_{(2,2324)} = 85.48$, $p < .001$, $\eta p^2 = .069$; Fig. 2A, left), and pairwise comparisons showed that the drop error was higher in Pure PI than in Boundary PI and Landmark PI, and higher in Boundary PI than in Landmark PI (all $t \geq 3.80$, all $p_{\text{Tukey}} < .001$, all $d \geq 0.079$). Also, older age ($F_{(1,45)} = 33.90$, $p < .001$, $\eta p^2 = .428$) and higher incoming distances ($F_{(1,2322)} = 497.43$, $p < .001$, $\eta p^2 = .176$) predicted higher drop errors (Fig. 2A, middle and right).

Regarding associations with chronic stress, we found a main effect of PSQ, where higher scores predicted higher drop errors ($F_{(1,46)} = 8.24$, $p = .006$, $\eta p^2 = .151$; Fig. 2B, left), indicating that higher perceived stress relates to worse performance. This effect seemed to be linked to the rotation component of PI, as PSQ did not affect distance error, but rotation error ($F_{(1,46)} = 7.63$, $p = .008$, $\eta p^2 = .143$; Fig. S2). In contrast, we did not observe an effect of HCC on PI performance ($F_{(1,46)} = 2.38$, $p = .130$, $\eta p^2 = .049$; Fig. 2B, right). We found a significant interaction effect between subtask, incoming distance and PSQ ($F_{(2,2341)} = 3.50$, $p = .030$, $\eta p^2 = .003$; Fig. 2C). Post-hoc pairwise comparisons yielded a significant difference between Pure PI and Landmark PI for low PSQ ($t_{(2353)} = 2.99$, $p_{\text{Šídák}} = .025$, $d = 0.062$), indicating a stronger relationship between incoming distance and drop error in Pure PI than in Landmark PI only for participants with low subjective stress levels.

3.3.2. Absence of stress-related main effects for the distance Error

Regarding the distance error, we observed similar overall effects of task features on PI performance as for the drop error: We found a main effect of subtask ($F_{(2,2323)} = 20.74$, $p < .001$, $\eta p^2 = .018$; Fig. 3A, left), and pairwise comparisons showed that the distance error was higher in Pure PI compared to Boundary PI and Landmark PI (both $t \geq 5.32$, both $p_{\text{Tukey}} < .001$, both $d \geq 0.110$), both of which did not differ from each other ($t_{(2323)} = 0.54$, $p_{\text{Tukey}} = .853$, $d = 0.011$). Older age ($F_{(1,45)} = 22.94$, $p < .001$, $\eta p^2 = .337$) and higher incoming distances ($F_{(1,2322)} = 232.99$, $p < .001$, $\eta p^2 = .091$) predicted higher distance errors (Fig. 3A, middle and right). Neither PSQ ($F_{(1,46)} = 2.45$, $p = .124$, $\eta p^2 = .051$) nor HCC ($F_{(1,46)} = 0.37$, $p = .546$, $\eta p^2 = .008$) predicted the distance error (Fig. 3B). In addition to these main effects, we found a significant interaction between subtask and incoming distance ($F_{(2,2344)} = 3.66$, $p = .026$, $\eta p^2 = .003$; Fig. 3C). Post-hoc tests showed a difference in the effect of incoming distance on distance error between Pure PI and Boundary PI ($t_{(2343)} = -2.68$, $p_{\text{Tukey}} = .020$, $d = -0.055$), indicating a steeper slope in Boundary PI than in Pure PI, presumably reflecting greater difficulty even at lower incoming distances in Pure PI.

3.3.3. Relevance of stress-related interaction effects for the distance error

Although we did not observe stress-related main effects for the distance error, we found several significant interaction effects involving HCC and/or PSQ.

We observed an interaction between HCC and incoming distance ($F_{(1,2322)} = 11.38$, $p < .001$, $\eta p^2 = .005$; Fig. 4A, left), and post-hoc tests revealed that the effect of incoming distance on distance error was stronger for high compared to medium and low HCC, and for medium compared to low HCC (all $t = -3.37$, all $p_{\text{Tukey}} = .002$, all $d = -0.070$). This indicated that higher HCCs potentiated the effect of incoming distance on distance error. The interaction further indicated a particular relevance of difficult trials, as differences in distance error between levels of HCC were not evident for small or medium incoming distances (all $t \leq 2.03$, all $p_{\text{Tukey}} > .05$, all $d \leq 0.143$), but only for larger incoming distances (all $t = -3.15$, all $p_{\text{Tukey}} < .001$, all $d = -0.146$).

This interaction between HCC and incoming distance was further moderated by two other factors, subtask and PSQ, respectively. First, we observed a significant three-way interaction between HCC, incoming distance and subtask ($F_{(2,2342)} = 4.70$, $p = .009$, $\eta p^2 = .004$; Fig. 4B). Follow-up analyses for the individual subtasks showed that the interaction between HCC and incoming distance only emerged in Pure PI (all $t = -4.45$, all $p_{\text{Šídák}} < .001$, all $d = -0.092$), but not in Boundary PI (all $t = -0.66$, all $p_{\text{Šídák}} = .998$, all $d = -0.014$) or in Landmark PI (all $t = -0.72$, all $p_{\text{Šídák}} = .997$, all $d = -0.015$). Thus, high HCC was related to PI performance specifically in difficult trials and in the absence of spatial cues.

Second, we found a significant interaction between HCC, incoming

Table 1
Sample characteristics.

	Min	Max	Median	Mean	SD
$HCC_{pg/mg}$	1.02	31.53	3.51	5.14	4.90
PSQ	0	73.33	30	31.60	18.90
Age_{years}	22	65	46.5	43.60	13.27
$Education_{years}$	8	18	13	14.44	3.56

Abbreviations. HCC: hair cortisol concentration, PSQ: Perceived Stress Questionnaire, Min: minimum, Max: maximum, SD: standard deviation; data presented for final sample of $n = 50$.

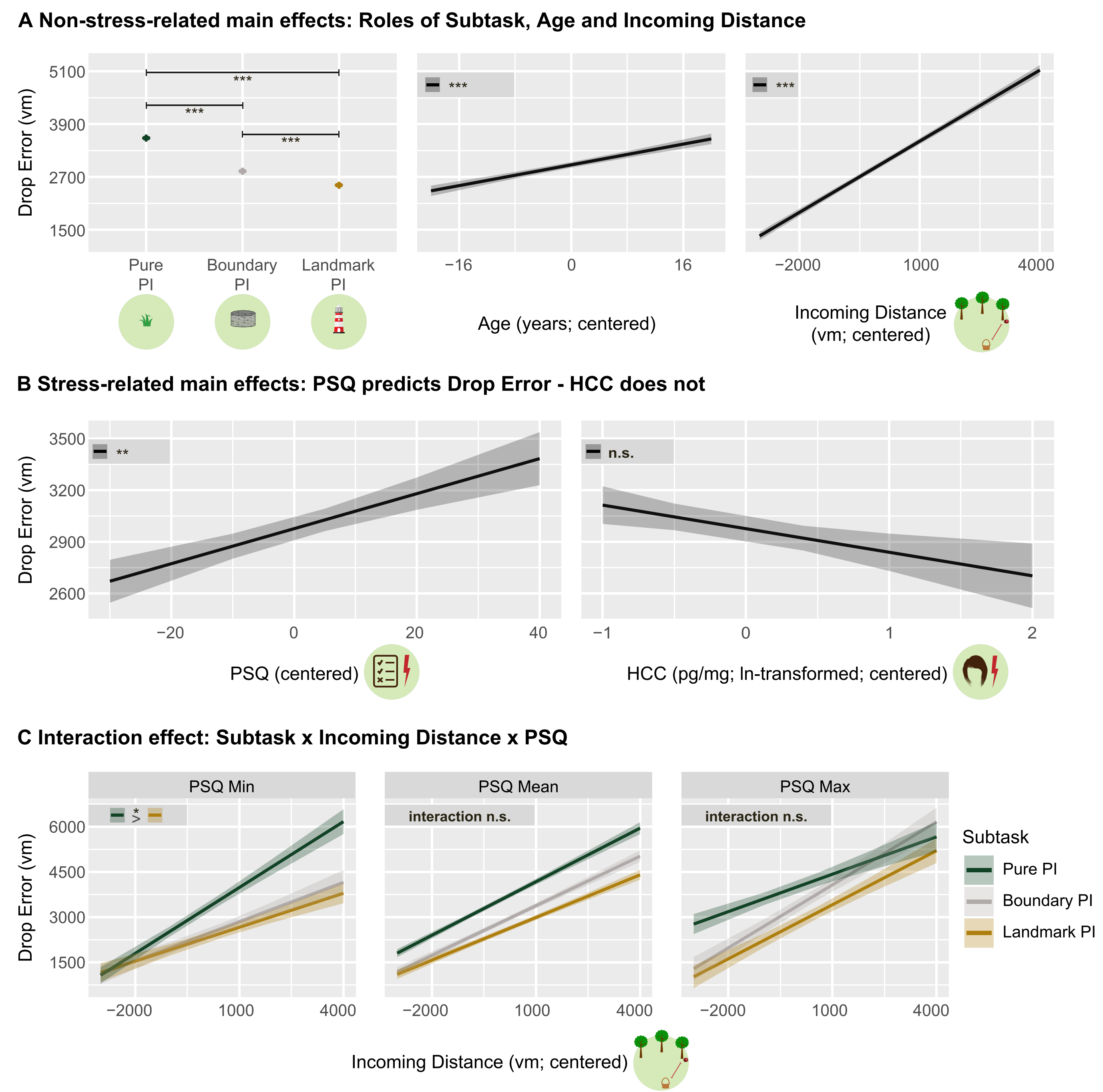

Fig. 2. Predictors of drop error. (A) Drop error was highest when no spatial cues were available and lowest when a landmark was present (Pure PI > Boundary PI > Landmark PI). Older age and higher incoming distances were associated with higher drop errors. (B) Higher PSQ scores were associated with higher drop errors, whereas HCC did not predict the drop error. (C) All slopes differed significantly from zero (all $p < .001$). The interaction effect showed that the relationship between incoming distance and drop error was stronger for Pure PI than Landmark PI only in participants with low PSQ scores (left panel), but not in those with medium or high PSQ scores (middle and right panel). PSQ Min, PSQ Mean, and PSQ Max refer to the minimum, mean and maximum PSQ scores, respectively, and were chosen as bases for estimating adjusted means of linear trends. Error bars and confidence bands represent SEM. HCC: hair cortisol concentration, PSQ: Perceived Stress Questionnaire, Pure PI: pure path integration, Boundary PI: boundary-supported path integration, Landmark PI: landmark-supported path integration, vm: virtual meters, n.s.: not significant, $^{***}p < .001$, $^{**}p < .01$, $^{*}p < .05$.

distance and PSQ ($F_{(1,2323)} = 16.79$, $p < .001$, $\eta p^2 = .007$; Fig. 4C). Post-hoc tests revealed that the interaction between HCC and incoming distance only emerged when PSQ scores were either medium (all $t = -3.37$, all $p_{\text{Šidák}} = .007$, all $d = -0.070$) or high (all $t = -4.86$, all $p_{\text{Šidák}} < .001$, all $d = -0.101$), but not when they were low (all $t = 2.08$, all $p_{\text{Šidák}} = .294$, all $d = 0.043$). When specifically considering participants with high HCC, post-hoc tests revealed that higher PSQ scores predicted a stronger increase of distance error in more difficult trials (all $t = -3.46$, all $p_{\text{Šidák}} = .005$, all $d = -0.072$). Reversely, in participants with low HCC, an increase of PSQ was not related with a stronger, but with a weaker association between incoming distance and distance error (all $t = 4.36$, all $p_{\text{Šidák}} < .001$, all $d = 0.090$).

To clarify whether the interaction between HCC and incoming distance related to a general effect of trial difficulty or was specific to outgoing or incoming distance, respectively, we built a separate, third linear model, where outgoing distance replaced incoming distance. In

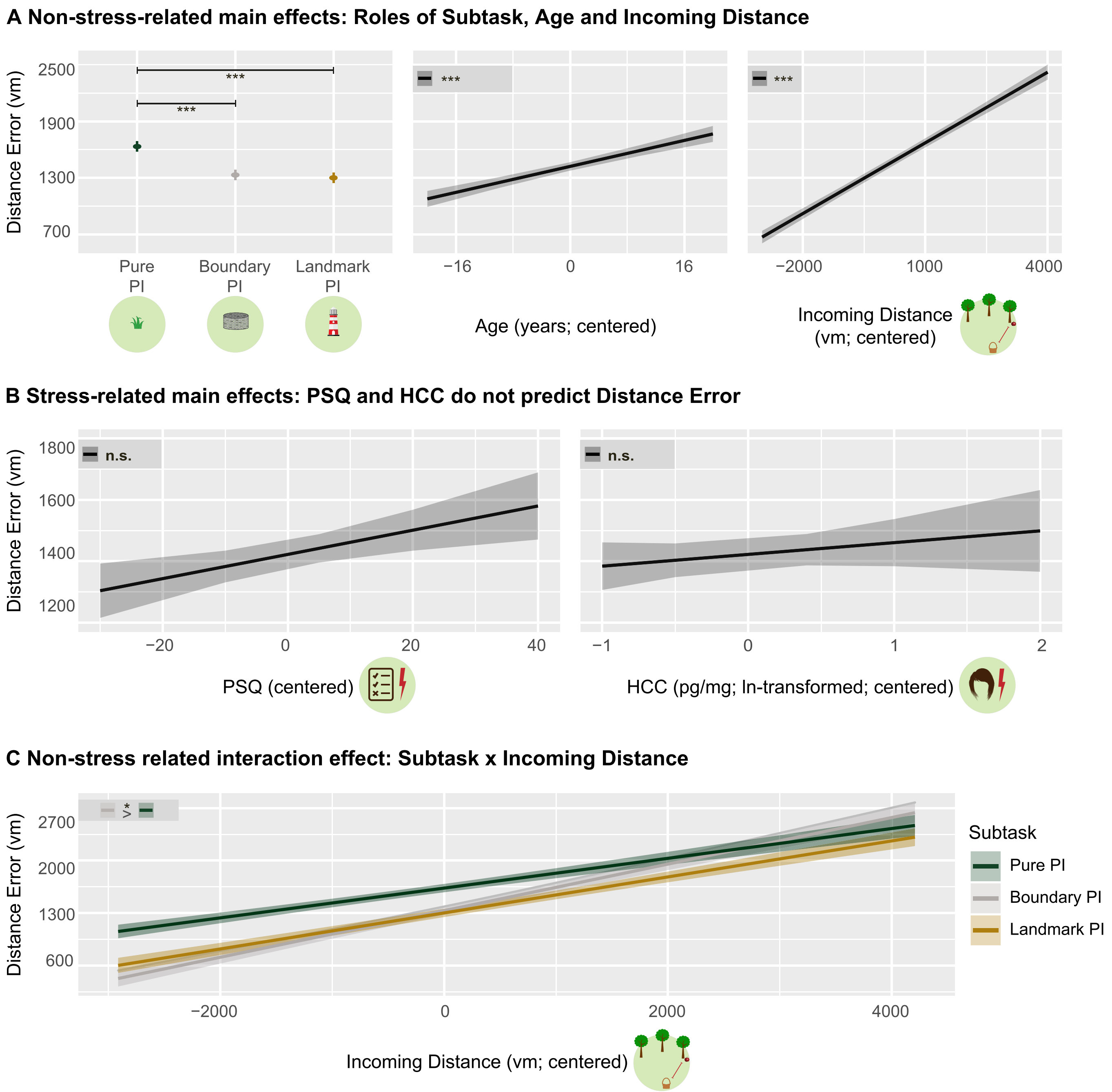

Fig. 3. Predictors of distance error. (A) Distance error was highest when no environmental cues were available (Pure PI). Boundary PI and Landmark PI did not differ from each other. Older age and higher incoming distances were associated with higher distance errors. (B) Neither PSQ nor HCC predicted the distance error. (C) All slopes differed significantly from zero (all $p < .001$). The effect of incoming distance on distance error was more pronounced (steeper slope) in the Boundary PI compared to the Pure PI subtask. Error bars and confidence bands represent SEM. HCC: hair cortisol concentration, PSQ: Perceived Stress Questionnaire, Pure PI: pure path integration, Boundary PI: boundary-supported path integration, Landmark PI: landmark-supported path integration, vm: virtual meters, n.s.: not significant, $^{***}p < .001$, $^{*}p < .05$.

this model, no associations between measures of chronic stress, outgoing distance and PI performance were found (Fig. S3).

3.3.4. Summary and generalization

Altogether, our results showed that incoming distance predicted PI performance especially when chronic stress levels were high (as indicated by higher HCCs and PSQ scores) and when no spatial cues were available. The interaction between HCC, PSQ and incoming distance further indicated differential contributions of physiological and subjective stress on PI, manifesting particularly in difficult trials and when both types of stress mediators exhibited high loads. Based on our findings, we developed a working model about chronic stress effects on PI performance (Fig. 5). We postulate that PI performance of an individual is disturbed under conditions of high levels of subjective and physiological stress when two things come together, namely high levels of difficulty and scarce environments with little spatial information. We propose that the assumed disruption of PI performance under these circumstances is mainly caused by impairments in distance estimation.

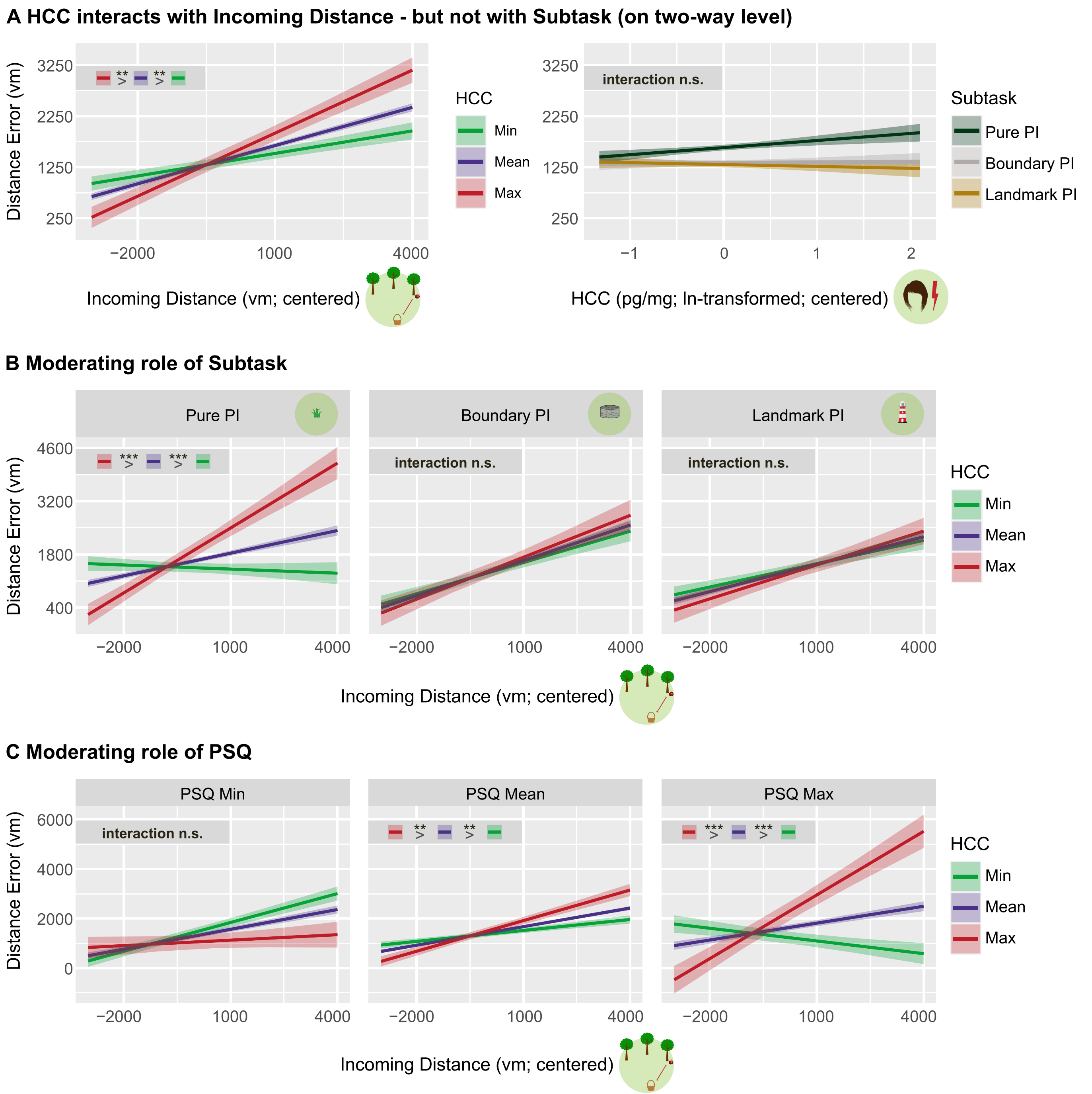

Fig. 4. Stress-related interaction effects for the distance error. (A) All slopes in the left panel differed significantly from zero (all $p < .001$), but no slope in the right panel did (all $p > .05$). The relationship between incoming distance and distance error strengthened when HCC increased (left panel). Effects of HCC and subtask on distance error did not show any general interaction (i.e., independently of incoming distance; right panel). (B) The "Min"-slope in the left panel did not differ significantly from zero ($p > .05$), but all other slopes did (all $p < .01$). The two-way interaction effect between HCC and incoming distance (i.e., trial difficulty) on distance error (top left panel) was only significant in the Pure PI subtask. (C) The "Max"-slope in the left panel and the "Min"-slope in the right panel did not differ significantly from zero (both $p > .05$), but all other slopes did (all $p < .001$). The two-way interaction effect between HCC and incoming distance (i.e., trial difficulty) on distance error (top left panel) was only significant, when subjective stress levels were medium or high (middle and right panel). Further, in participants with high HCC, the effect of incoming distance on distance error was more pronounced when PSQ scores increased (comparison of red lines). PSQ Min, PSQ Mean, and PSQ Max refer to the minimum, mean and maximum PSQ scores, respectively, and HCC Min, HCC Mean, and HCC Max refer to the minimum, mean and maximum HCCs, respectively, and were chosen as bases for estimating adjusted means of linear trends. Confidence bands represent SEM. HCC: hair cortisol concentration, PSQ: Perceived Stress Questionnaire, Pure PI: pure path integration, Boundary PI: boundary-supported path integration, Landmark PI: landmark-supported path integration, vm: virtual meters, n.s.: not significant, $^{***}p < .001$, $^{**}p < .01$.

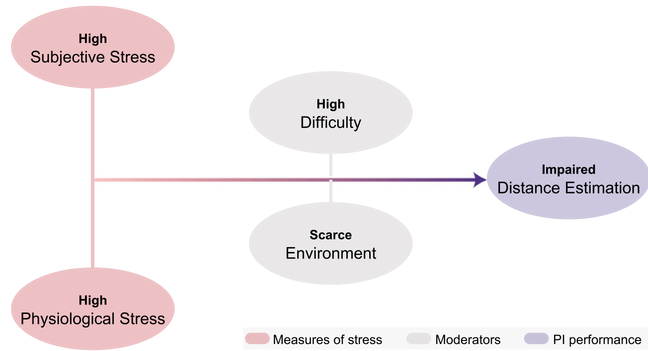

Fig. 5. Working model about the relationship between chronic stress and path integration performance. When high levels of physiological and subjective markers of stress co-occur with high difficulty and scarce environments, impaired PI due to disturbed distance estimation is likely. PI: path integration.

4. Discussion

The goal of this study was to investigate whether chronic stress, assessed through subjective and physiological measures, is associated with PI performance in a sample of healthy young to mid-aged participants. Relevant outcome measures of our task, including the main effect of outgoing distance on all error measures and the observation that spatial cues enhance PI performance, indicated that we were indeed assessing PI. We found a relationship between self-reports of perceived stress, as reflected by the PSQ, and the drop error, but we did not observe such a link between HCC and drop error. Considering the distance error, we found higher HCC to potentiate the relationship between incoming distance and distance error. This was especially the case in environments with no additional spatial information and in participants reporting medium or high subjective stress.

Perceived stress plays an important role for functional and structural alterations in the human brain. For instance, Oumohand et al. [80] reported that perceived chronic stress, but not HCC, was related to poorer performance in several cognitive domains (e.g., executive functioning, processing speed or working memory). Gianaros et al. [99] demonstrated, in a sample of postmenopausal women, that self-reported long-term chronic stress, assessed prospectively over a period of approximately 20 years, was associated with decreased grey matter volume in the hippocampus. The meta-analysis of Stalder et al. [74] suggests that HCC and self-reports of perceived stress are not related, and they were also not associated with each other in our study, supporting the idea that they might reflect different aspects of the stress response. Cortisol is only one, albeit a very important, player in the multitude of physiological alterations caused by stress [1], but subjective ratings may cover a wider range of these alterations. Stalder et al. [74] suggested that the relationship between HCC and perceived stress depends on cortisol levels, such that it is usually non-existent in case of low levels but emerges over a certain threshold. Based on the distributions of PSQ and HCC (Table 1), our sample can be characterized as moderately stressed, and therefore this hypothesis could be an explanation for the difference between the two measures in predicting the drop error.

We furthermore observed an interaction between subtask, incoming distance and PSQ, which indicates a stronger relationship between incoming distance and drop error for Pure PI than Landmark PI in participants with low levels of perceived stress. We previously showed that subtask moderates the effect of incoming distance on drop error such that the difference in performance between Pure PI and the other subtasks increases with higher trial difficulty [62]. Our current finding, however, indicates that the beneficial effect of a landmark as an additional spatial cue is not universally increasing with higher trial difficulty, but does so particularly in subjectively low-stressed participants.

When specifically considering distance estimation (reflected by the distance error) as one relevant subcomponent of PI, we found interaction effects encompassing both measures of chronic stress. The main effect of higher incoming distance leading to higher distance errors was to be expected because trial-difficulty is strongly influenced by incoming distance. We observed that this relationship was strengthened when HCC increased, indicating an association between higher HCC and worse performance especially in more difficult trials. This fits to the idea that subtle changes in cognition induced by stress in healthy participants are especially relevant during tasks with high cognitive load. A meta-analysis reporting this relationship in the context of acute stress and working memory [5] and a study investigating acute high-intensity stress effects on a visuo-spatial path learning task [100] support this hypothesis. Our finding suggests a similar relationship for chronic stress effects on PI.

The two-way interaction between HCC and incoming distance effect was further moderated by subtask and PSQ, respectively. On the one hand, the moderation by subtask indicated that the interaction between HCC and incoming distance only appeared in an environment without spatial cues, which is in accordance with our hypothesis that stress effects become particularly relevant in scarce environments with little or no additional spatial information. In such environments, reliance on EC is greatest and compensatory mechanisms through involvement of other brain regions cannot take place, or at least not to a sufficient extent [62, 63]. The utilization of navigational strategies highly depends on the availability of information, and more information typically leads to more success [43]. The Boundary PI and Landmark PI subtasks both provide additional information and therefore allow for the employment of boundary-based or landmark-based navigational strategies. Consequently, these subtasks are generally less difficult than Pure PI. However, in the additional model, where we replaced incoming distance by outgoing distance (the second most important factor determining trial difficulty), no associations with chronic stress were found, suggesting that chronic stress specifically relates to the effect of incoming distance on PI and hence may reflect impaired EC function. Thus, in addition to the presumed role of stress in more difficult trials, this finding further indicates that certain navigational strategies (Pure PI) are more prone to stress effects than others (Boundary PI or Landmark PI). This is in accordance with a previous study showing intact landmark-based navigation, but impaired map-based navigation in women after acute stress [28]. In Boundary PI and Landmark PI, compensatory mechanisms such as activation of retrosplenial cortex, which is strongly connected to the medial EC [101], might stabilize grid cell activity and mask the deficit [62]. An alternative (not mutually exclusive) explanation is based on differential sensitivity of brain regions to cortisol, leading to a stress-induced shift towards striatal processing [102]. This could also result in behavioral deficits in Pure PI, but preserve performance in Landmark PI, because landmark-based navigation has been associated with striatal processing [103].

We earlier introduced the idea of a triangular relationship between chronic stress, EC functionality, and AD. Similar to what we report here about the association between chronic stress and PI, *APOE*-ε4 carriers also showed specific impairments in Pure PI [62]. In that study, we hypothesized that early AD histopathology in the EC might affect grid cell function, and that this is only unmasked in the condition with highest reliance on EC (Pure PI). How then might chronic stress induce such an effect on the mechanistic level? GRs exhibit a lower affinity to cortisol than MRs and are thus mainly activated in the presence of high circulating cortisol levels [1]. Chronically stressed individuals often experience phases of persisting hyperactivity of HPA axis that might activate GRs of the EC. One way in which excess of cortisol results in functional and structural brain changes, is its influence on synaptic plasticity by targeting glutamatergic transmission, which is strengthened under acute stress, but suppressed under chronic stress [104,105]. Although altered glutamatergic transmission might play a role, we assume that chronic stress rather affects inhibitory transmission in the EC, because administration of stress mediators was shown to have this same effect in layer II of the medial EC, where grid cells are abundantly located [106]. This inhibition in the medial EC has been proposed to follow a gradient along the dorsoventral axis, and this gradient correlates to an increase in spacing of grid cells along the same axis [107]. Thus, chronic stress could elicit disturbances in the nuanced spacing-based allocation of grid cells along the dorsoventral axis of the medial EC, and thereby potentially compromise grid cell function, which may represent the underlying process behind the observed behavioral deficits.

Furthermore, the two-way interaction between HCC and incoming distance was also moderated by PSQ, as it only appeared when PSQ scores were medium or high, but not when they were low. As mentioned earlier, perceived stress may be inherently important in the emergence and maintenance of cognitive alterations [80,99]. In context of the interaction, it appears that HCC only moderates the relationship between incoming distance and distance error when a certain level of stress is perceived. This result shows that chronic stress effects on PI particularly arise, when both physiological and subjective indicators of allostatic load are high, possibly because they together reflect more dimensions of the stress response than either alone.

Our findings support the hypothesis that chronic stress affects PI. Stress-related deficits were predominantly connected to the distance error as measure of PI performance. Because grid cells may provide a general metric of distances, we assume that stress mediators (mainly cortisol) target the (posterior-medial) EC and thereby compromise grid cell activity. The idea that chronic stress can affect navigational circuits is empirically supported by findings of a rodent study, where stress-induced modulation of place cells was found after five days of immobilization stress [108]. Future animal studies should investigate possible effects of stress on grid cells on the level of microcircuits. We further observed an important role of perceived stress, which may either be a relevant independent predictor of cognitive alterations or provide additional predictive value to the information obtained by physiological measures of stress. Based on this, we developed a working model, in which we postulate PI deficits as a consequence of impaired distance estimation to occur when physiological and subjective levels of stress are high and a difficult task is conducted in a scarce environment (Fig. 5).

Our study does not come without limitations. First, results are correlational in nature. Although this is a common limitation in chronic stress research, it impedes causal inferences. Consequently, increased cortisol levels and the observed deficits in PI performance could both be the result of a common cause (genetics, early-life experiences, emerging psychopathology etc.) rather than one causing the other [109]. Animal studies as well as neuroimaging and longitudinal studies in humans are needed, to establish a cause-and-effect relationship. Second, due to the absence of neuroimaging data, we could not test the hypothesized neuronal processes underlying the behavioral effects. However, we were able to rely on the results of our previous study suggesting that the posterior-medial EC (particularly grid-like representations) is especially relevant for the Pure PI subtask, and that the retrosplenial cortex is involved in landmark representations for the Landmark PI subtask [62]. Future research should search for direct relationships between chronic stress, EC functionality and PI performance, and characterize the underlying neural mechanisms to underpin our results. Third, we investigated PI purely based on visual cues. Future studies are needed including both, visual and body-based cues, to get a more comprehensive overall picture. Last, due to sample characteristics, we only considered women, even though sex is known to play a role in stress effects [83] and in spatial navigation [110]. As our results are thus presumably not applicable to males, future research considering both sexes is warranted.

4.1. Conclusion

We provide initial evidence for an association between chronic stress and PI deficits in healthy human participants. PI deficits in physiologically stressed participants selectively emerged in trials with high difficulty in the absence of additional spatial cues, and particularly in those participants also reporting subjective stress.

CRediT authorship contribution statement

Osman Akan: Conceptualization, Formal analysis, Writing – original draft, Visualization. **Anne Bierbrauer:** Conceptualization, Software, Data curation, Writing – review & editing. **Lukas Kunz:** Conceptualization, Software, Writing – review & editing. **Patrick D. Gajewski:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Stephan Getzmann:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Jan G. Hengstler:** Conceptualization, Supervision, Resources. **Edmund Wascher:** Conceptualization, Resources, Project administration. **Nikolai Axmacher:** Conceptualization, Supervision, Writing – review & editing. **Oliver T. Wolf:** Conceptualization, Supervision, Writing – review & editing.

Declaration of interest

None.

Data availability

Data will be made available on request.

Acknowledgments

We are grateful to all participants of the study, and to A. Bäumer, V. Ruzas, R. Schütte, S. Wetter, and the team of the Dortmund Vital Study for data acquisition. Funding: This work (especially the analysis and interpretation of data and writing of the report) was supported by the Deutsche Forschungsgemeinschaft (German Research Foundation, project no. 122679504: SFB 874 “Integration and representation of sensory processes”).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2023.114305.

References

[1] M. Joëls, T.Z. Baram, The neuro-symphony of stress, Nat. Rev. Neurosci. 10 (2009) 459–466, https://doi.org/10.1038/nrn2632.
[2] M. Joëls, Z. Pu, O. Wiegert, M.S. Oitzl, H.J. Krugers, Learning under stress: how does it work? Trends Cogn. Sci. 10 (2006) 152–158, https://doi.org/10.1016/j.tics.2006.02.002.
[3] L. Schwabe, M. Joëls, B. Roozendaal, O.T. Wolf, M.S. Oitzl, Stress effects on memory: an update and integration, Neurosci. Biobehav Rev. 36 (2012) 1740–1749, https://doi.org/10.1016/j.neubiorev.2011.07.002.
[4] O.T. Wolf, Stress and memory in humans: twelve years of progress, Brain Res. 1293 (2009) 142–154, https://doi.org/10.1016/j.brainres.2009.04.013.
[5] G.S. Shields, M.A. Sazma, A.P. Yonelinas, The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol, Neurosci. Biobehav Rev. 68 (2016) 651–668, https://doi.org/10.1016/j.neubiorev.2016.06.038.
[6] R. Hermann, B. Biallas, H.-G. Predel, K. Petrowski, Physical versus psychosocial stress: effects on hormonal, autonomic, and psychological parameters in healthy young men, Stress (Amst., Neth.) 22 (2019) 103–112, https://doi.org/10.1080/10253890.2018.1514384.
[7] M.G. Oyola, R.J. Handa, Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: sex differences in regulation of stress responsivity, Stress (Amst., Neth.) 20 (2017) 476–494, https://doi.org/10.1080/10253890.2017.1369523.
[8] B.S. McEwen, Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders, Ann. N. Y. Acad. Sci. 1032 (2004) 1–7, https://doi.org/10.1196/annals.1314.001.

[9] E.R. de Kloet, M. Joëls, F. Holsboer, Stress and the brain: from adaptation to disease, Nat. Rev. Neurosci. 6 (2005) 463–475, https://doi.org/10.1038/nrn1683.
[10] M.-F. Marin, C. Lord, J. Andrews, R.-P. Juster, S. Sindi, G. Arsenault-Lapierre, et al., Chronic stress, cognitive functioning and mental health, Neurobiol. Learn Mem. 96 (2011) 583–595, https://doi.org/10.1016/j.nlm.2011.02.016.
[11] M. Joëls, H. Karst, D. Alfarez, V.M. Heine, Y. Qin, E. van Riel, et al., Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus, Stress (Amst., Neth.) 7 (2004) 221–231, https://doi.org/10.1080/10253890500070005.
[12] R.-P. Juster, B.S. McEwen, S.J. Lupien, Allostatic load biomarkers of chronic stress and impact on health and cognition, Neurosci. Biobehav Rev. 35 (2010) 2–16, https://doi.org/10.1016/j.neubiorev.2009.10.002.
[13] J.J. Radley, J.H. Morrison, Repeated stress and structural plasticity in the brain, Ageing Res. Rev. 4 (2005) 271–287, https://doi.org/10.1016/j.arr.2005.03.004.
[14] C. Mirescu, E. Gould, Stress and adult neurogenesis, Hippocampus 16 (2006) 233–238, https://doi.org/10.1002/hipo.20155.
[15] N. Sousa, N.V. Lukoyanov, M.D. Madeira, O. Almeida, M.M. Paula-Barbosa, Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement, Neuroscience 97 (2000) 253–266, https://doi.org/10.1016/S0306-4522(00)00050-6.
[16] P.S. Moreira, P.R. Almeida, H. Leite-Almeida, N. Sousa, P. Costa, Impact of chronic stress protocols in learning and memory in rodents: systematic review and meta-analysis, PLOS ONE 11 (2016), e0163245, https://doi.org/10.1371/journal.pone.0163245.
[17] C. Liston, M.M. Miller, D.S. Goldwater, J.J. Radley, A.B. Rocher, P.R. Hof, et al., Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting, J. Neurosci. 26 (2006) 7870–7874, https://doi.org/10.1523/JNEUROSCI.1184-06.2006.
[18] S.J. Lupien, M.J. Leon, S. de, Santi, A. de, Convit, C. Tarshish, N.P.V. Nair, et al., Cortisol levels during human aging predict hippocampal atrophy and memory deficits, Nat. Neurosci. 1 (1998) 69–73, https://doi.org/10.1038/271.
[19] A.M.J. MacLullich, I.J. Deary, J.M. Starr, K.J. Ferguson, J.M. Wardlaw, J.R. Seckl, Plasma cortisol levels, brain volumes and cognition in healthy elderly men, Psychoneuroendocrinology 30 (2005) 505–515, https://doi.org/10.1016/j.psyneuen.2004.12.005.
[20] M.N. Starkman, B. Giordani, S. Berent, M.A. Schork, D.E. Schteingart, Elevated cortisol levels in Cushing's disease are associated with cognitive decrements, Psychosom. Med. 63 (2001) 985–993, https://doi.org/10.1097/00006842-200111000-00018.
[21] D. Arifi, N. Bitterlich, M. Wolff, D. von, Poethig, P. Stute, Impact of chronic stress exposure on cognitive performance incorporating the active and healthy aging (AHA) concept within the cross-sectional Bern Cohort Study 2014 (BeCS-14), Arch. Gynecol. Obstet. 305 (2022) 1021–1032, https://doi.org/10.1007/s00404-021-06289-z.
[22] G. Li, M.M. Cherrier, D.W. Tsuang, E.C. Petrie, E.A. Colasurdo, S. Craft, et al., Salivary cortisol and memory function in human aging, Neurobiol. Aging 27 (2006) 1705–1714, https://doi.org/10.1016/j.neurobiolaging.2005.09.031.
[23] I. Beluche, I. Carrière, K. Ritchie, M.-L. Ancelin, A prospective study of diurnal cortisol and cognitive function in community-dwelling elderly people, Psychol. Med. 40 (2010) 1039–1049, https://doi.org/10.1017/S0033291709991103.
[24] L. Gerritsen, H.C. Comijs, Y. van der Graaf, A.J.G. Knoops, B.W.J.H. Penninx, M.I. Geerlings, Depression, hypothalamic pituitary adrenal axis, and hippocampal and entorhinal cortex volumes—the SMART Medea study, Biol. Psychiatry 70 (2011) 373–380, https://doi.org/10.1016/j.biopsych.2011.01.029.
[25] J.T. O'Brien, A. Lloyd, I. McKeith, A. Gholkar, N. Ferrier, A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects, Am. J. Psychiatry 161 (2004) 2081–2090, https://doi.org/10.1176/appi.ajp.161.11.2081.
[26] B.S. McEwen, R.M. Sapolsky, Stress and cognitive function, Curr. Opin. Neurobiol. 5 (1995) 205–216, https://doi.org/10.1016/0959-4388(95)80028-X.
[27] D.J.H. van Gerven, T. Ferguson, R.W. Skelton, Acute stress switches spatial navigation strategy from egocentric to allocentric in a virtual Morris water maze, Neurobiol. Learn Mem. 132 (2016) 29–39, https://doi.org/10.1016/j.nlm.2016.05.003.
[28] K.G. Thomas, H.E. Laurance, L. Nadel, W.J. Jacobs, Stress-induced impairment of spatial navigation in females, South Afr. J. Psychol. 40 (2010) 32–43, https://doi.org/10.1177/008124631004000104.
[29] F.M. Guenzel, O.T. Wolf, L. Schwabe, Sex differences in stress effects on response and spatial memory formation, Neurobiol. Learn Mem. 109 (2014) 46–55, https://doi.org/10.1016/j.nlm.2013.11.020.
[30] C. Klopp, C. Garcia, A.H. Schulman, C.P. Ward, J.L. Tartar, Acute social stress increases biochemical and self report markers of stress without altering spatial learning in humans, Neuro Endocrinol. Lett. 33 (2012) 425–430.
[31] L. Schwabe, M.S. Oitzl, C. Philippsen, S. Richter, A. Bohringer, W. Wippich, et al., Stress modulates the use of spatial versus stimulus-response learning strategies in humans, Learn. Mem. 14 (2007) 109–116, https://doi.org/10.1101/lm.435807.
[32] Z. Cao, Y. Wang, L. Zhang, Real-time acute stress facilitates allocentric spatial processing in a virtual fire disaster, Sci. Rep. 7 (2017) 189, https://doi.org/10.1038/s41598-017-14910-y.
[33] R. Duncko, B. Cornwell, L. Cui, K.R. Merikangas, C. Grillon, Acute exposure to stress improves performance in trace eyeblink conditioning and spatial learning tasks in healthy men, Learn. Mem. 14 (2007) 329–335, https://doi.org/10.1101/lm.483807.
[34] T.I. Brown, S.A. Gagnon, A.D. Wagner, Stress disrupts human hippocampal-prefrontal function during prospective spatial navigation and hinders flexible behavior, e8, Curr. Biol. 30 (2020) 1821–1833, https://doi.org/10.1016/j.cub.2020.03.006.
[35] R.L. Wright, C.D. Conrad, Chronic stress leaves novelty-seeking behavior intact while impairing spatial recognition memory in the Y-maze, Stress (Amst., Neth.) 8 (2005) 151–154, https://doi.org/10.1080/10253890500156663.
[36] R.L. Wright, E.N. Lightner, J.S. Harman, O.C. Meijer, C.D. Conrad, Attenuating corticosterone levels on the day of memory assessment prevents chronic stress-induced impairments in spatial memory, Eur. J. Neurosci. 24 (2006) 595–605, https://doi.org/10.1111/j.1460-9568.2006.04948.x.
[37] M. Orsetti, L. Colella, A. Dellarole, P.L. Canonico, P. Ghi, Modification of spatial recognition memory and object discrimination after chronic administration of haloperidol, amitriptyline, sodium valproate or olanzapine in normal and anhedonic rats, Int J. Neuropsychopharmacol. 10 (2007) 345–357, https://doi.org/10.1017/S1461145706006705.
[38] R. Bellani, L.J. Luecken, C.D. Conrad, Peripubertal anxiety profile can predict predisposition to spatial memory impairments following chronic stress, Behav. Brain Res 166 (2006) 263–270, https://doi.org/10.1016/j.bbr.2005.08.006.
[39] J.J. Cerqueira, F. Mailliet, O.F.X. Almeida, T.M. Jay, N. Sousa, The prefrontal cortex as a key target of the maladaptive response to stress, J. Neurosci. 27 (2007) 2781–2787, https://doi.org/10.1523/JNEUROSCI.4372-06.2007.
[40] R.N. Sadowski, G.R. Jackson, L. Wieczorek, P.E. Gold, Effects of stress, corticosterone, and epinephrine administration on learning in place and response tasks, Behav. Brain Res 205 (2009) 19–25, https://doi.org/10.1016/j.bbr.2009.06.027.
[41] C.D. Conrad, A critical review of chronic stress effects on spatial learning and memory, Prog. Neuropsychopharmacol. Biol. Psychiatry 34 (2010) 742–755, https://doi.org/10.1016/j.pnpbp.2009.11.003.
[42] A.D. Ekstrom, E.A. Isham, Human spatial navigation: Representations across dimensions and scales, Curr. Opin. Behav. Sci. 17 (2017) 84–89, https://doi.org/10.1016/j.cobeha.2017.06.005.
[43] D. Jain, I.R. Jakhalekar, S.S. Deshmukh, Navigational Strategies and Their Neural Correlates, J. Indian Inst. Sci. 97 (2017) 511–525, https://doi.org/10.1007/s41745-017-0053-1.
[44] E.I. Moser, M.-B. Moser, B.L. McNaughton, Spatial representation in the hippocampal formation: A history, Nat. Neurosci. 20 (2017) 1448–1464, https://doi.org/10.1038/nn.4653.
[45] R.F. Wang, Building a cognitive map by assembling multiple path integration systems, Psychon. Bull. Rev. 23 (2016) 692–702, https://doi.org/10.3758/s13423-015-0952-y.
[46] A. Banino, C. Barry, B. Uria, C. Blundell, T. Lillicrap, P. Mirowski, et al., Vector-based navigation using grid-like representations in artificial agents, Nature 557 (2018) 429, https://doi.org/10.1038/s41586-018-0102-6.
[47] M. Gil, M. Ancau, M.I. Schlesiger, A. Neitz, K. Allen, R.J. de Marco, et al., Impaired path integration in mice with disrupted grid cell firing, Nat. Neurosci. 21 (2018) 81–91, https://doi.org/10.1038/s41593-017-0039-3.
[48] B.L. McNaughton, F.P. Battaglia, O. Jensen, E.I. Moser, M.-B. Moser, Path integration and the neural basis of the 'cognitive map', Nat. Rev. Neurosci. 7 (2006) 663–678, https://doi.org/10.1038/nrn1932.
[49] M. Stangl, J. Achtzehn, K. Huber, C. Dietrich, C. Tempelmann, T. Wolbers, Compromised grid-cell-like representations in old age as a key mechanism to explain age-related navigational deficits, e6, Curr. Biol. 28 (2018) 1108–1115, https://doi.org/10.1016/j.cub.2018.02.038.
[50] M. Fyhn, S. Molden, M.P. Witter, E.I. Moser, M.-B. Moser, Spatial representation in the entorhinal cortex, Sci. (N. Y., N. Y.) 305 (2004) 1258–1264, https://doi.org/10.1126/science.1099901.
[51] T. Hafting, M. Fyhn, S. Molden, M.-B. Moser, E.I. Moser, Microstructure of a spatial map in the entorhinal cortex, Nature 436 (2005) 801–806, https://doi.org/10.1038/nature03721.
[52] A. Avital, E. Ram, R. Maayan, A. Weizman, G. Richter-Levin, Effects of early-life stress on behavior and neurosteroid levels in the rat hypothalamus and entorhinal cortex, Brain Res Bull. 68 (2006) 419–424, https://doi.org/10.1016/j.brainresbull.2005.09.015.
[53] H. Umegaki, W. Zhu, A. Nakamura, Y. Suzuki, M. Takada, H. Endo, et al., Involvement of the entorhinal cortex in the stress response to immobilization, but not to insulin-induced hypoglycaemia, J. Neuroendocrinol. 15 (2003) 237–241, https://doi.org/10.1046/j.1365-2826.2003.00979.x.
[54] R.-M. Vouimba, D. Yaniv, D.M. Diamond, G. Richter-Levin, Effects of inescapable stress on LTP in the amygdala versus the dentate gyrus of freely behaving rats, Eur. J. Neurosci. 19 (2004) 1887–1894, https://doi.org/10.1111/j.1460-9568.2004.03294.x.
[55] D. Yaniv, R. Vouimba, D.M. Diamond, G. Richter-Levin, Simultaneous induction of long-term potentiation in the hippocampus and the amygdala by entorhinal cortex activation: mechanistic and temporal profiles, Neuroscience 120 (2003) 1125–1135, https://doi.org/10.1016/S0306-4522(03)00386-5.
[56] J. Burtscher, J.-C. Copin, J. Rodrigues, S.T. Kumar, A. Chiki, I. Guillot de Suduiraut, et al., Chronic corticosterone aggravates behavioral and neuronal symptomatology in a mouse model of alpha-synuclein pathology, Neurobiol. Aging 83 (2019) 11–20, https://doi.org/10.1016/j.neurobiolaging.2019.08.007.
[57] A. Sarrieau, M. Dussaillant, M. Moguilewsky, D. Coutable, D. Philibert, W. Rostène, Autoradiographic localization of glucocorticosteroid binding sites in rat brain after in vivo injection of [3H]RU 28362, Neurosci. Lett. 92 (1988) 14–20, https://doi.org/10.1016/0304-3940(88)90734-3.
[58] F. Chersi, N. Burgess, The Cognitive Architecture of Spatial Navigation: Hippocampal and Striatal Contributions, Neuron 88 (2015) 64–77, https://doi.org/10.1016/j.neuron.2015.09.021.

[59] G. Coughlan, J. Laczó, J. Hort, A.-M. Minihane, M. Hornberger, Spatial navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease? Nat. Rev. Neurol. 14 (2018) 496–506, https://doi.org/10.1038/s41582-018-0031-x.
[60] H. Braak, D.R. Thal, E. Ghebremedhin, K. Del Tredici, Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years, J. Neuropathol. Exp. Neurol. 70 (2011) 960–969, https://doi.org/10.1097/NEN.0b013e318232a379.
[61] E.H. Corder, A.M. Saunders, W.J. Strittmatter, D.E. Schmechel, P.C. Gaskell, G. W. Small, et al., Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families, Science 261 (1993) 921–923, https://doi.org/10.1126/science.8346443.
[62] A. Bierbrauer, L. Kunz, C.A. Gomes, M. Luhmann, L. Deuker, S. Getzmann, et al., Unmasking selective path integration deficits in Alzheimer's disease risk carriers, Sci. Adv. 6, eaba1394. (2020), https://doi.org/10.1126/sciadv.aba1394.
[63] L. Kunz, T.N. Schröder, H. Lee, C. Montag, B. Lachmann, R. Sariyska, et al., Reduced grid-cell-like representations in adults at genetic risk for Alzheimer's disease, Sci. (N. Y., N. Y.) 350 (2015) 430–433, https://doi.org/10.1126/science.aac8128.
[64] A.S. Mitchell, R. Czajkowski, N. Zhang, K. Jeffery, A.J.D. Nelson, Retrosplenial cortex and its role in spatial cognition, 2398212818757098, Brain Neurosci. Adv. 2 (2018), https://doi.org/10.1177/2398212818757098.
[65] K. Hardcastle, S. Ganguli, L.M. Giocomo, Environmental boundaries as an error correction mechanism for grid cells, Neuron 86 (2015) 827–839, https://doi.org/10.1016/j.neuron.2015.03.039.
[66] Y.H. Jeong, C.H. Park, J. Yoo, K.Y. Shin, S.-M. Ahn, H.-S. Kim, et al., Chronic stress accelerates learning and memory impairments and increases amyloid deposition in APPV717I-CT100 transgenic mice, an Alzheimer's disease model, FASEB J. 20 (2006) 729–731, https://doi.org/10.1096/fj.05-4265fje.
[67] N.J. Justice, The relationship between stress and Alzheimer's disease, Neurobiol. Stress 8 (2018) 127–133, https://doi.org/10.1016/j.ynstr.2018.04.002.
[68] R.S. Wilson, S.E. Arnold, J.A. Schneider, Y. Li, D.A. Bennett, Chronic distress, age-related neuropathology, and late-life dementia, Psychosom. Med. 69 (2007) 47–53, https://doi.org/10.1097/01.psy.0000250264.25017.21.
[69] G. Arsenault-Lapierre, H. Chertkow, S.J. Lupien, Seasonal effects on cortisol secretion in normal aging, mild cognitive impairment and Alzheimer's disease, Neurobiol. Aging 31 (2010) 1051–1054, https://doi.org/10.1016/j.neurobiolaging.2008.07.011.
[70] B. Lehallier, L. Essioux, J. Gayan, R. Alexandridis, T. Nikolcheva, T. Wyss-Coray, et al., Combined Plasma and Cerebrospinal Fluid Signature for the Prediction of Midterm Progression From Mild Cognitive Impairment to Alzheimer Disease, JAMA Neurol. 73 (2016) 203–212, https://doi.org/10.1001/jamaneurol.2015.3135.
[71] C.-W. Huang, C.-C. Lui, W.-N. Chang, C.-H. Lu, Y.-L. Wang, C.-C. Chang, Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease, J. Clin. Neurosci. 16 (2009) 1283–1286, https://doi.org/10.1016/j.jocn.2008.12.026.
[72] T. Stalder, C. Kirschbaum, Analysis of cortisol in hair—state of the art and future directions, Brain Behav. Immun. 26 (2012) 1019–1029, https://doi.org/10.1016/j.bbi.2012.02.002.
[73] H. Fliege, M. Rose, P. Arck, S. Levenstein, B.F. Klapp, Validierung des "Perceived Stress Questionnaire" (PSQ) an einer deutschen Stichprobe, Diagnostica 47 (2001) 142–152, https://doi.org/10.1026//0012-1924.47.3.142.
[74] T. Stalder, S. Steudte-Schmiedgen, N. Alexander, T. Klucken, A. Vater, S. Wichmann, et al., Stress-related and basic determinants of hair cortisol in humans: A meta-analysis, Psychoneuroendocrinology 77 (2017) 261–274, https://doi.org/10.1016/j.psyneuen.2016.12.017.
[75] S.N. McLennan, A. Ihle, S. Steudte-Schmiedgen, C. Kirschbaum, M. Kliegel, Hair cortisol and cognitive performance in working age adults, Psychoneuroendocrinology 67 (2016) 100–103, https://doi.org/10.1016/j.psyneuen.2016.01.029.
[76] M.M. Pulopulos, V. Hidalgo, M. Almela, S. Puig-Perez, C. Villada, A. Salvador, Hair cortisol and cognitive performance in healthy older people, Psychoneuroendocrinology 44 (2014) 100–111, https://doi.org/10.1016/j.psyneuen.2014.03.002.
[77] J.C. Feeney, A.M. O'Halloran, R.A. Kenny, The Association Between Hair Cortisol, Hair Cortisone, and Cognitive Function in a Population-Based Cohort of Older Adults: Results From The Irish Longitudinal Study on Ageing, J. Gerontol. A Biol. Sci. Med Sci. 75 (2020) 257–265, https://doi.org/10.1093/gerona/gly258.
[78] L.J. Weckesser, K. Schmidt, M. Möschl, C. Kirschbaum, S. Enge, R. Miller, Temporal stability and effect dynamics between executive functions, perceived chronic stress, and hair cortisol concentrations, Dev. Psychol. 57 (2021) 1149–1162, https://doi.org/10.1037/dev0001193.
[79] L.L. van den Heuvel, S. Suliman, E. Bröcker, S. Kilian, T. Stalder, C. Kirschbaum, et al., The association between hair cortisol levels, inflammation and cognitive functioning in females, Psychoneuroendocrinology 136 (2022), 105619, https://doi.org/10.1016/j.psyneuen.2021.105619.
[80] S.E. Oumohand, D.D. Ward, M.M. Boenniger, N. Merten, C. Kirschbaum, M.M. B. Breteler, Perceived stress but not hair cortisol concentration is related to adult cognitive performance, Psychoneuroendocrinology 121 (2020), 104810, https://doi.org/10.1016/j.psyneuen.2020.104810.
[81] E.S. Epel, A.D. Crosswell, S.E. Mayer, A.A. Prather, G.M. Slavich, E. Puterman, et al., More than a feeling: A unified view of stress measurement for population science, Front. Neuroendocrinol. 49 (2018) 146–169, https://doi.org/10.1016/j.yfrne.2018.03.001.
[82] P.D. Gajewski, S. Getzmann, P. Bröde, M. Burke, C. Cadenas, S. Capellino, et al., Impact of biological and lifestyle factors on cognitive aging and work ability in the dortmund vital study: protocol of an interdisciplinary, cross-sectional, and longitudinal study, JMIR Res Protoc. 11 (2022), e32352, https://doi.org/10.2196/32352.
[83] C.J. Merz, O.T. Wolf, Sex differences in stress effects on emotional learning, J. Neurosci. Res 95 (2017) 93–105, https://doi.org/10.1002/jnr.23811.
[84] S. Levenstein, C. Prantera, V. Varvo, M.L. Scribano, E. Berto, C. Luzi, et al., Development of the perceived stress questionnaire: A new tool for psychosomatic research, J. Psychosom. Res 37 (1993) 19–32, https://doi.org/10.1016/0022-3999(93)90120-5.
[85] E. Russell, G. Koren, M. Rieder, S. van Uum, Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions, Psychoneuroendocrinology 37 (2012) 589–601, https://doi.org/10.1016/j.psyneuen.2011.09.009.
[86] G.A.A. Cooper, R. Kronstrand, P. Kintz, Society of Hair Testing guidelines for drug testing in hair, Forensic Sci. Int 218 (2012) 20–24, https://doi.org/10.1016/j.forsciint.2011.10.024.
[87] W. Gao, C. Kirschbaum, J. Grass, T. Stalder, LC-MS based analysis of endogenous steroid hormones in human hair, J. Steroid Biochem Mol. Biol. 162 (2016) 92–99, https://doi.org/10.1016/j.jsbmb.2015.12.022.
[88] P. Berens, CircStat: a MATLAB toolbox for circular statistics, J. Stat. Soft 31 (2009) 1–21, https://doi.org/10.18637/jss.v031.i10.
[89] R Core Team. R: A language and environment for statistical computing.: R Foundation for Statistical Computing, Vienna, Austria; 2021.
[90] D. Bates, M. Mächler, B. Bolker, S. Walker, Fitting linear mixed-effects models using lme4, J. Stat. Soft 67 (2015) 1–48, https://doi.org/10.18637/jss.v067.i01.
[91] A. Kuznetsova, P.B. Brockhoff, R.H.B. Christensen, lmerTest package: tests in linear mixed effects models, J. Stat. Soft 82 (2017) 1–26, https://doi.org/10.18637/jss.v082.i13.
[92] Lenth R.V. emmeans. Estimated Marginal Means, aka least square means, R package version 1.8.0; 2022.
[93] T. Evans, A. Bicanski, D. Bush, N. Burgess, How environment and self-motion combine in neural representations of space, J. Physiol. 594 (2016) 6535–6546, https://doi.org/10.1113/JP270666.
[94] L.R. Howard, A.H. Javadi, Y. Yu, R.D. Mill, L.C. Morrison, R. Knight, et al., The hippocampus and entorhinal cortex encode the path and Euclidean distances to goals during navigation, Curr. Biol. 24 (2014) 1331–1340, https://doi.org/10.1016/j.cub.2014.05.001.
[95] R.A. Epstein, E.Z. Patai, J.B. Julian, H.J. Spiers, The cognitive map in humans: spatial navigation and beyond, Nat. Neurosci. 20 (2017) 1504–1513, https://doi.org/10.1038/nn.4656.
[96] Y. Burak, I.R. Fiete, Accurate path integration in continuous attractor network models of grid cells, PLoS Comput. Biol. 5 (2009), e1000291, https://doi.org/10.1371/journal.pcbi.1000291.
[97] A.W. Lester, S.D. Moffat, J.M. Wiener, C.A. Barnes, T. Wolbers, The Aging Navigational System, Neuron 95 (2017) 1019–1035, https://doi.org/10.1016/j.neuron.2017.06.037.
[98] C.K. Enders, D. Tofighi, Centering predictor variables in cross-sectional multilevel models: a new look at an old issue, Psychol. Methods 12 (2007) 121–138, https://doi.org/10.1037/1082-989X.12.2.121.
[99] P.J. Gianaros, J.R. Jennings, L.K. Sheu, P.J. Greer, L.H. Kuller, K.A. Matthews, Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus, NeuroImage 35 (2007) 795–803, https://doi.org/10.1016/j.neuroimage.2006.10.045.
[100] J. Taverniers, T. Smeets, S. Lo Bue, J. Syroit, J. van Ruysseveldt, N. Pattyn, et al., Visuo-spatial path learning, stress, and cortisol secretion following military cadets' first parachute jump: the effect of increasing task complexity, Cogn. Affect Behav. Neurosci. 11 (2011) 332–343, https://doi.org/10.3758/s13415-011-0043-0.
[101] K.M. Kerr, K.L. Agster, S.C. Furtak, R.D. Burwell, Functional neuroanatomy of the parahippocampal region: the lateral and medial entorhinal areas, Hippocampus 17 (2007) 697–708, https://doi.org/10.1002/hipo.20315.
[102] L. Schwabe, O.T. Wolf, Stress and multiple memory systems: from 'thinking' to 'doing', Trends Cogn. Sci. 17 (2013) 60–68, https://doi.org/10.1016/j.tics.2012.12.001.
[103] C.F. Doeller, J.A. King, N. Burgess, Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory, Proc. Natl. Acad. Sci. USA 105 (2008) 5915–5920, https://doi.org/10.1073/pnas.0801489105.
[104] E.Y. Yuen, J. Wei, W. Liu, P. Zhong, X. Li, Z. Yan, Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex, Neuron 73 (2012) 962–977, https://doi.org/10.1016/j.neuron.2011.12.033.
[105] G. Sanacora, Z. Yan, M. Popoli, The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders, Nat. Rev. Neurosci. 23 (2022) 86–103, https://doi.org/10.1038/s41583-021-00540-x.
[106] J.P. Hartner, L.A. Schrader, Interaction of Norepinephrine and Glucocorticoids Modulate Inhibition of Principle Cells of Layer II Medial Entorhinal Cortex in Male Mice, Front. Synaptic Neurosci. 10 (2018) 3, https://doi.org/10.3389/fnsyn.2018.00003.
[107] P. Beed, A. Gundlfinger, S. Schneiderbauer, J. Song, C. Böhm, A. Burgalossi, et al., Inhibitory gradient along the dorsoventral axis in the medial entorhinal cortex, Neuron 79 (2013) 1197–1207, https://doi.org/10.1016/j.neuron.2013.06.038.

[108] A. Tomar, D. Polygalov, S. Chattarji, T.J. McHugh, The dynamic impact of repeated stress on the hippocampal spatial map, Hippocampus 25 (2015) 38–50, https://doi.org/10.1002/hipo.22348.
[109] W.S. Kremen, R.C. O'Brien, M.S. Panizzon, E. Prom-Wormley, L.J. Eaves, S. A. Eisen, et al., Salivary cortisol and prefrontal cortical thickness in middle-aged men: A twin study, NeuroImage 53 (2010) 1093–1102, https://doi.org/10.1016/j.neuroimage.2010.02.026.
[110] J.T. Sneider, D.A. Hamilton, J.E. Cohen-Gilbert, D.J. Crowley, I.M. Rosso, M. M. Silveri, Sex differences in spatial navigation and perception in human adolescents and emerging adults, Behav. Process. 111 (2015) 42–50, https://doi.org/10.1016/j.beproc.2014.11.015.