Neuroscience and Biobehavioral Reviews 190 (2026) 106921

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Stress, path integration, and the entorhinal cortex

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ARTICLE INFO

Key Words:
Stress
Cortisol
Path-integration
Entorhinal cortex
Alzheimer's disease

ABSTRACT

The stress induced release of glucocorticoids influences neural excitability and plasticity in the hippocampus. Surprisingly the entorhinal cortex (EC), an adjacent region, has received little attention in stress research, even though it is also rich in glucocorticoid receptors. Grid cells in the medial EC play a decisive role in path integration (PI). Interestingly, the EC is a brain region damaged very early in Alzheimer's disease (AD). Three recent studies investigated the associations between stress, cortisol and PI. In the first study chronic stress was associated with poorer PI. Acute stress induction impaired PI in the second study. In the third study cortisol administration impaired PI and reduced grid like representations in the EC as measured via fMRI. These findings have important implications. Future research on stress and spatial navigation should take the EC into account. Moreover, chronic stress is associated with an increased risk for AD. The findings suggest that the direct effect of cortisol on the EC may partially underly these clinical findings. Directions for future research are discussed.

Stress is an omnipresent phenomenon in our lives. Stressful events can cover a broad spectrum ranging from a deadline at work all the way towards traumatic experiences like a car crash or a burglary. While the acute stress response is characterized by mostly adaptive features chronic stress is associated with an increased risk for physical (e.g., coronary heart disease) and mental (e.g., major depression) disorders. In situations of stress the organism reacts with a rapid activation of the sympathetic nervous system (SNS) and a somewhat slower response of the hypothalamus-pituitary adrenal (HPA) axis (Joëls and Baram, 2009). This causes the release of catecholamines from the adrenal medulla (mostly adrenalin and to a smaller amount noradrenalin) and glucocorticoids (mostly cortisol in humans but typically corticosterone in laboratory rodents) from the adrenal cortex. These lipophilic steroid hormones can pass the blood brain barrier. In the brain they can bind to mineralocorticoid and glucocorticoid receptors thereby influencing neural excitability and plasticity. Here effects on the amygdala, the hippocampus (HC), and the prefrontal cortex (PFC) have been especially well investigated (Joëls et al., 2008; Schwabe and Wolf, 2013).

Indeed, stress has been shown to influence the entire information processing stream. It increases vigilance by activating the neuronal salience network. This appears to go hand in hand with impaired selective attention, mediated by the executive control network (Hermans et al., 2014). Further, stress prioritizes habitual stimulus-response behavior (the "inner autopilot"), mediated by the striatum, at the expense of cognitive/rational goal-directed behavior, known to rely on the PFC (Goldfarb and Sinha, 2018; Schwabe and Wolf, 2013). Memories of stressful events are typically especially strong reflecting the beneficial effect of the stress hormones NA and CORT on memory consolidation (Roozendaal et al., 2006; Wolf, 2019). In contrast to these beneficial effects impairments in memory retrieval and spatial navigation have been observed in rodents and humans alike (Brown et al., 2020; Wolf et al., 2016).

Surprisingly a region close to the hippocampus, namely the entorhinal cortex (EC) has received little attention in cognitive stress research so far. However, this brain region is also rich in glucocorticoid receptors (Sarrieau et al., 1986). The EC plays a decisive role in path integration (PI), a navigation strategy that is especially relevant in the absence of spatial cues (McNaughton et al., 2006). PI involves integration of self-referential movement information to estimate the current position and orientation in relation to the starting point of a trajectory (Wang, 2016). On the neuronal level, PI has been related to head-direction cells and grid cell firing in the medial EC. Specifically, the characteristic arrangement of grid cell firing fields in a regular hexagonal pattern may provide a general spatial metric of distances (McNaughton et al., 2006). In contrast the lateral EC is important for associative memory (Morrissey and Takehara-Nishiuchi, 2014; Wilson et al., 2013). In presence of spatial cues, however, additional neural systems tuned to the specific type of cue (e.g., boundary or landmark)

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https://doi.org/10.1016/j.neubiorev.2026.106921
Received 23 June 2026; Received in revised form 6 August 2026; Accepted 19 August 2026
Available online 20 August 2026

are recruited, including hippocampus and posterior cingulate/retrosplenial cortex (Bierbrauer et al., 2020). These additional systems may stabilize grid cell firing and/or support complementary navigational strategies. Because processing in the striatum, especially the caudate nucleus, is involved in landmark-based navigation and appears to dominate under acute stress (Schwabe and Wolf, 2013), the presence of spatial cues likely moderates stress hormone effects on either performance or strategy use during navigational processes.

Interestingly, the EC is also among the first brain regions affected by tau pathology in Alzheimer's disease (AD; (Igarashi, 2023)), and deficits in PI have been proposed to be a particularly sensitive marker for early AD (Segen et al., 2022). These alterations occur prior to clear clinical symptoms. In a previous study, we employed a virtual homing task (the "Apple game", see Fig. 1) to probe PI with and without landmarks (pure PI (PPI) and landmark-supported PI (LPI), respectively) in healthy participants depending on their genetic risk for AD. We observed that participants at genetic risk for AD (APOE ε4 carriers) show selective deficits in PPI but not LPI, suggesting that early dysfunctions of the EC are unmasked in the absence of additional spatial cues. Moreover, with the help of functional magnetic resonance imaging (fMRI) grid-like representations in the EC were detected during the same PI task, and they predicted performance specifically during the PPI condition (Bierbrauer et al., 2020).

In a series of three human studies, we investigated the relationship between stress, GCs and PI using the Apple Game. The first study was conducted in a cohort of middle aged female participants and showed that two measures of chronic stress namely a questionnaire (Perceived Stress Questionnaire; PSQ) and hair cortisol measures (reflecting overall cortisol secretion during the last four months) were associated with poorer PI performance (see Fig. 2a; (Akan et al., 2023)).

Next, we investigated the effects of acute stress induced with the Socially Evaluated Cold Pressor Task on PI. As expected, participants in the stress group showed an increase in salivary cortisol levels, indicative of successful stress induction. Results revealed poorer PI performance in the stress group. The decrease in performance between LPI and PPI trials was substantially stronger in stressed participants. This finding illustrates an acute stress induced impairment in PI ((Akan et al., 2023); Fig. 2b).

The causal role of cortisol was finally investigated in a pharmacological fMRI study with young healthy males (Akan et al., 2026). Twenty milligrams of the stress hormone applied orally impaired PI, an effect this time independent of the presence of spatial cues (Fig. 2c). The univariate fMRI data analysis indicated a higher activation of the posterior cingulate and the right caudate nucleus in the LPI condition. Interestingly, cortisol led to increased activity in the caudate nucleus during LPI, suggesting a compensatory recruitment of this area. By contrast, the EC was only recruited during PPI under placebo but not under cortisol, suggesting an impairment of EC-dependent navigation strategies after cortisol administration. Multivariate neuroimaging analyses revealed grid-like representations in the right entorhinal cortex under placebo on the first treatment day, which were diminished by cortisol. Taken together, the study may suggest that a cortisol-induced disruption in grid cell function in the EC underlies at least in part impairments in path integration under stress. These three findings are the first to systematically investigate the impact of stress and cortisol on PI, a function mediated by the EC. The results appear to suggest that PI is a cognitive process especially sensitive to stress. As always, these novel results are in need of replications. Future studies may wish for example to investigate different PI paradigms, since our studies solely relied on the apple game.

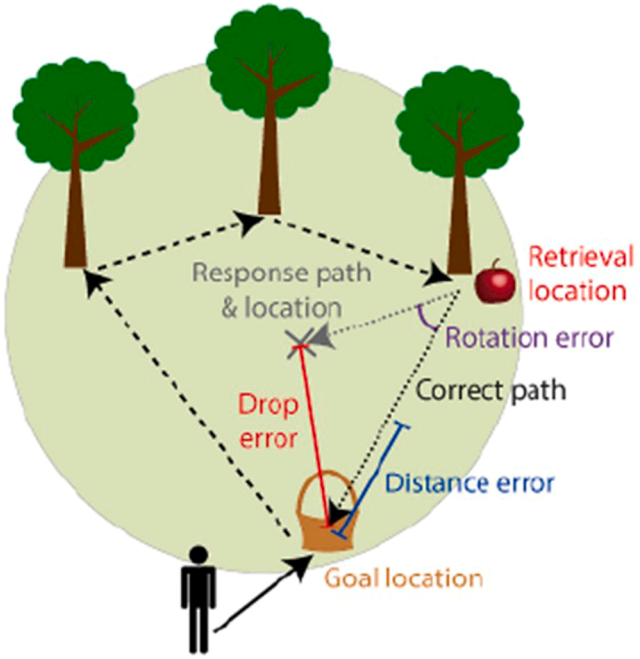

Fig. 1. Picture of the Apple Game used in the three studies.

The findings obtained have multiple implications. Future research on stress and spatial navigation needs to take the EC as a player into account. Previous research might have focused too strongly on the hippocampus and on a shift towards striatal processing under stress (Schwabe and Wolf, 2013). Mechanistic studies in laboratory animals on this topic could be very informative. For example, glucocorticoids were shown to influence spontaneous inhibitory post-synaptic currents in layer 2 of the medial entorhinal cortex (Hartner and Schrader, 2018).

Furthermore, stress effects on the EC may exacerbate early dysfunction of this area due to AD. Multiple longitudinal studies in older humans have observed that stress is associated with an increased risk for AD (e.g., (Wilson et al., 2005); see for a review (Eberly et al., 2026)). In fact, HPA-axis hyperactivity is a common observation in AD (Saelzler et al., 2021). Elevated cortisol levels might reflect chronic stress or could be secondary to the occurring neurodegeneration in key regulatory brain structures like the hippocampus (Eberly et al., 2026). As summarized by Burke and colleagues there are several pathways by which GCs can foster AD pathology. Chronic stress stimulates tau pathology, increases amyloid plaques, enhances neuroinflammation and impairs the blood-brain barrier (Burke et al., 2024). The studies in healthy participants discussed above suggest that a direct effect of cortisol on the EC may partially underly these clinical findings. A reduction of stress may thus alleviate early AD symptoms (Eberly et al., 2026). Future longitudinal studies as well as intervention studies are needed to put these hypotheses to test.

The results discussed (as always) leave several questions open. Acute stress is known to have a phase dependent effect on long-term memory with enhancing memory consolidation and impairing memory retrieval (Roozendaal, 2002; Wolf, 2017). The virtual homing game used in the three studies does not differentiate between these processes but rather tests repeatedly PI performance with and without landmarks.

Effects of glucocorticoids on long-term memory have been shown to rely on noradrenergic activation in the basolateral amygdala (BLA). This neuroendocrine interaction influences memory storage in the hippocampus. The role of the BLA for the stress-induced PI impairments detected in our studies remains to be investigated (Roozendaal et al., 2006).

Sex differences have been observed in the psychoneuroendocrine stress response and its effect on cognition (Merz and Wolf, 2017). Moreover, most mental and neurological disorders are characterized by sex differences in their prevalence. This is also the case for Alzheimer's disease with a higher prevalence in women (Cao et al., 2020). In our initial studies we investigated one sex only. Future research is needed to investigate the impact of gender, sex and gonadal steroids on the effects observed in the three studies.

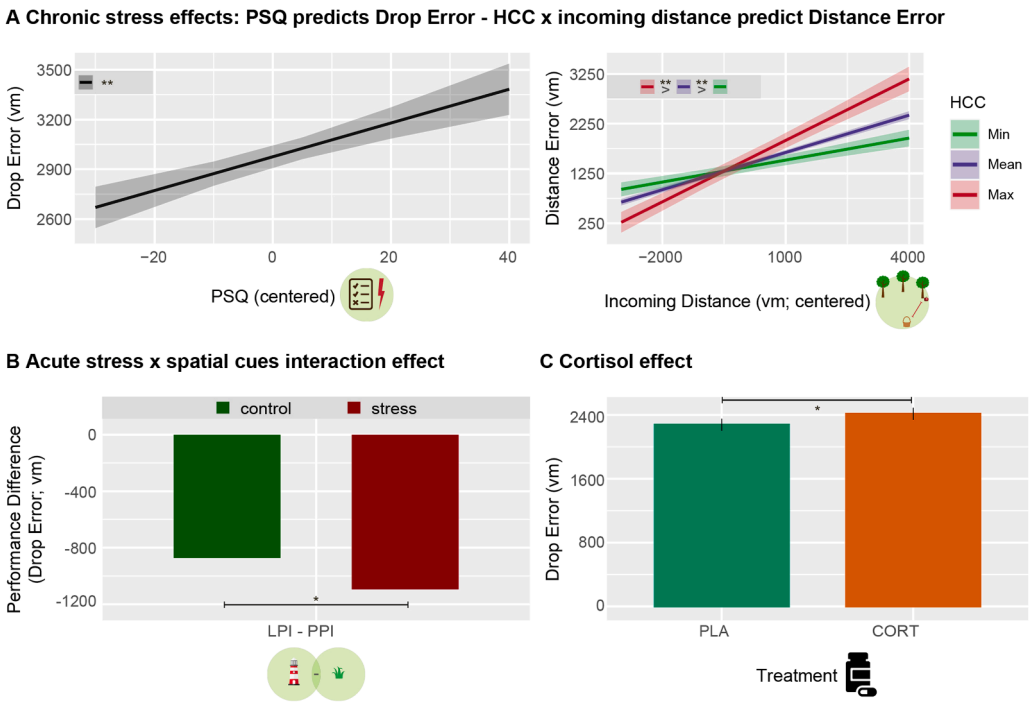

Fig. 2. Stress (hormone) effects on path integration. (A) Higher Perceived Stress Questionnaire (PSQ) scores were associated with more drop errors, whereas higher hair cortisol concentrations (HCC) strengthened the relationship between incoming distance and distance error (n = 52, (Akan et al., 2023)). (B) The difference in PI performance between both subtasks (path integration with or without landmarks; LPI - PPI) was larger in the stress group (n = 32), compared to the control group (n = 34), indicating a greater decline of performance when the landmark is no longer available (Akan et al., 2023). (C) A single cortisol administration led to an increase in drop errors. This was associated with a reduction in grid-like activity in the entorhinal cortex (n = 39, placebo-controlled crossover design (Akan et al., 2026)).

Taken together the present mini-review summarized recent findings on the impact of stress or stress hormones on PI in humans. They suggest that stress may impair PI via the effects of the stress hormone cortisol on grid like representations in the EC. Having said this these stress effects do not occur in isolation but are rather accompanied by changes at the network level (Brown et al., 2020; Hermans et al., 2014). The results obtained should stimulate future research in basic and clinical neuroscience.

Funding source

The work discussed in this review was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project no. 419039274 — FOR 2812 and the European Research Council (ERC, CoG 864164 GridRepresentations).

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