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## Cognitive Neuroscience: Why Do We Get Lost When We Are Stressed?

Arne D. Ekstrom

Department of Psychology and Evelyn McKnight Brain Institute, University of Arizona, 1503 E. University Blvd., Tucson, AZ 85721, USA  
 Correspondence: [adekstrom@arizona.edu](mailto:adekstrom@arizona.edu)  
<https://doi.org/10.1016/j.cub.2020.03.065>

**A recent study in humans shows that stress increases our reliance on familiar routes during navigation. This research explains how increases in cortisol, a biomarker of stress, disrupts navigation-related brain circuits, resulting in less efficient navigation.**

Anecdotally, many of us have experienced the deleterious effects of stress on how we navigate in everyday situations, for example, choosing to sit in traffic rather than risking a short-cut. Indeed, one study [1] suggested that even time pressure could lead to participants using more familiar routes and less accurate trajectories. Yet, stress is closely related to cortisol changes [2] and exactly how such neurobiological factors affect brain circuits in actively navigating humans remains unknown. In a recent experiment involving navigation in virtual cities, reported in this issue of *Current Biology*, Brown *et al.* [3] found that stress reduced the likelihood of participants employing efficient yet novel short-cuts. The reliance of stressed participants on familiar paths closely mirrored transient increases in cortisol and disruptions in activity in several brain areas important

to navigation and episodic memory retrieval. This new paper therefore helps to resolve a long-standing issue regarding navigation and stress: why do we seem to navigate less efficiently when we are under stress?

In their study, Brown *et al.* [3] used several important experimental manipulations to address how stress affects navigation and route planning. Participants first explored several distinct virtual towns over two different days by being guided on distinct routes. Along each route, participants saw distinct, clearly visible objects. On the third day, participants were assigned to a stress or control group, with those in the stress group receiving calibrated electric shocks to the ankle during navigation in the scanner. When participants were placed in the environment, they rotated to position themselves (the ‘planning period’) and then either navigated the

familiar route or found a specific goal object (for example, George Clooney) on ‘probe’ trials. Cortisol samples were collected at baseline (the ‘training period’) and at several points throughout the scan.

When faced with locating a novel goal object during probe trials, stressed participants were more likely to employ a familiar route and less likely to employ a novel short-cut compared to controls. For both familiar and probe trials, a region of interest (ROI) analysis revealed that stressed participants showed reduced activity in the hippocampus, lateral prefrontal cortex, and lateral intraparietal sulcus during the planning/orientation period. A whole brain analysis revealed additional reductions in the stress-group during the planning period in visual cortex, putamen, and the caudate nucleus. These findings thus suggest the



recruitment of a network of different brain regions important to route planning that were impacted by stress.

Based on functional localizers, Brown *et al.* [3] additionally trained a classifier to identify specific object categories participants saw during navigation. The authors found that, for periods preceding a shortcut, stressed participants showed lower classifier evidence for goals and proximal objects along the routes than control participants. Even during the familiar routes, stressed participants showed lower classifier evidence for familiar objects, suggesting deficits in how well they could prospectively plan their routes. Importantly, the stress-related disruptions in route planning and short-cuts closely mirrored transient increases in cortisol levels, which declined after about 30 minutes, suggesting that stress was particularly disruptive when exploration was most novel.

There are several important implications of these findings. First, the results directly tie together stress, increases in cortisol, and alterations in navigation-related behavior. Specifically, the findings suggest that stress most directly impacts the prospective planning of navigation, a process that previous research suggests involves active simulation of novel routes to find optimal short-cuts [4]. Second, the findings implicate both a reduction in local activity and alterations in distributed neural patterns within specific brain regions implicated in past studies as important to navigation. Of particular interest is that this distributed activity involved a network of different brain regions, several of which have been suggested as critical to both episodic memory retrieval and navigation [5,6]. Finally, the fact that stress led to the disruption of neural activity during the planning period for both novel and familiar routes suggests the critical relevance of this deliberation/decision process to successful navigation [4,7,8].

The Brown *et al.* [3] findings also have relevance to models of spatial navigation, particularly those that have hypothesized a switch in neural circuits for flexible spatial planning ('place strategies') *versus* more rigid route following approaches ('response strategies') with stress [9–11].

These models, in particular, suggest that such place strategies rely on the hippocampus, while response strategies depend on the caudate nucleus, with stress triggering a switch to caudate-based response strategies [12,13]. Interestingly, recent work in more ecologically enriched tasks like that used by Brown *et al.* [3] has challenged this strict dichotomy of neural labor. Specifically, rats navigating in situations that could involve either a 'place' or 'response' strategy to solve the eight-arm maze typically show a mixture of both, and lesions that should impair one system often have more complex effects [14,15].

Similarly, the Brown *et al.* [3] findings, while supporting the idea that stress does result in a switch to familiar route following, showed that activity in the caudate nucleus was elevated in controls compared to stressed participants during route planning. This stands somewhat in contrast to the models cited above, which would predict greater activity in the caudate nucleus for route following in stressed participants. While future work is needed to better understand the role played by the caudate/putamen in navigation, the Brown *et al.* [3] findings suggest that the brain circuits triggered by stress during navigation are likely more complicated than a simple 'place' *versus* 'response' dichotomy [6].

Finally, the Brown *et al.* [3] results have important implications for models of cognition that attempt to account for the time dependent nature of the stress response [16–18]. Specifically, stress seems to have the most disruptive effects immediately on retrieval of episodic memories [19] and may wear off over time [18]. This meta-analytic finding is consistent with those from Brown *et al.* [3] suggesting that the disruptive effects on navigational planning occur within about the first 30 minutes of stress induction. In addition, the Brown *et al.* [3] findings suggest that, rather than having a unitary effect on brain circuits, such as disrupting executive control or attention [16], stress may have both disruptive and enhancing effects on different aspects of cognition at different time points [17]. Future work will be needed to better resolve this issue for navigation, as has been

done to some extent for episodic memory [18].

Another important future study on stress and navigation should consider both women and men: the Brown *et al.* [3] study involved only men based on an assumed greater homogeneity in their response to stress. Participant heterogeneity in navigation and stress are also important, however, to capturing a wider range of individual differences, an issue of growing interest in the field of navigation [20]. Overall, though, the study provides several important leads on how stress affects navigation. Perhaps most relevant to our everyday lives, the study provides an important reminder of why we might choose to fight traffic rather than choose a faster short-cut.

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## Tumourigenesis: Using Cytonemes to Engage Mesenchymal Cells in Epithelial Tumours

Marta Portela

Department of Biochemistry and Genetics, La Trobe Institute for Molecular Sciences, La Trobe University, Melbourne, Australia

Correspondence: [m.portelaesteban@latrobe.edu.au](mailto:m.portelaesteban@latrobe.edu.au)

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**A new study in *Drosophila* shows that inter-tissue communication between epithelial and mesenchymal cells via Notch signalling plays a role in EGFR-driven tumourigenesis of epithelial tissues.**

Cell–cell communication is a crucial process that regulates morphogenesis, cell differentiation, cell proliferation, and homeostasis of cells, tissues and organs within the body. The complexity of cell communication in multicellular organisms has been investigated for decades in physiology, in developmental biology, and in pathologies such as cancer, revealing more recently the importance of the communication between the tumour and its microenvironment [1]. Increasing evidence indicates that tumour progression results from the interaction between tumour cells and the surrounding normal cells that form the tumour microenvironment [2]. The most frequent tumours are malignant neoplasms of epithelial origin (carcinomas) that account for 90% of all cancer cases. Carcinomas express growth factors involved in the communication between cancer cells

and tumour-associated normal cells, whilst the microenvironment surrounding the tumour produces tumour-suppressive signals as long as tissue architecture and homeostasis remain controlled. However, if tissue architecture or homeostasis is lost, the altered microenvironment can itself become a potent tumour promoter [2]. A new study by Boukhatmi *et al.* [3], published in this issue of *Current Biology*, now shows that epithelial tumours use long-range membrane protrusions termed cytonemes to activate Notch signalling in the mesenchymal tissue to prevent its differentiation and promote tumourigenesis.

In multicellular organisms, there are at least four categories of chemical signalling: autocrine, where a cell secretes signalling molecules that can bind to receptors expressed on the same secreting cell; paracrine, where

cells can send signals to other cells nearby; juxtacrine, where a cell targets adjacent cells by direct cell contact, such as through gap junctions; and endocrine, where a cell targets a distant cell through hormones in the bloodstream [4]. Cancer cells often use autocrine signalling to stimulate their own survival and proliferation by secreting signals that act back on their own receptors; however, in complex multicellular organisms, short-range signalling is not sufficient to coordinate the behaviour of cells.

Recently, another communication mechanism was identified, which involves the exchange of signals via cytonemes by direct contact over long distances. The dynamic regulation of cytonemes facilitates signal transfer in complex environments [5]. Cytonemes have been identified as signalling-specialised structures in *Drosophila* and vertebrates, and are involved in different

