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# Stress, Brain Wiring and the Economy

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**Abstract**

Emerging links between lifestyle stress, psychological traits and the economy are explored by highlighting recent work in which stress has been shown to trigger enduring changes in neural cell metabolism via epigenetic mechanisms. One important target of such changes is the circuitry of the medial prefrontal cortex, which has been implicated in abstract construal, theory of mind functions, agency and other psychometric constructs associated with innovation and entrepreneurship. In an economy increasingly dependent on such psychological traits for its competitiveness our understanding of the impacts of stress on cognition and affect may be especially relevant to future prosperity. One recent approach to designing a pathway-based intervention for epigenetic dysfunction triggered by stress is discussed as an example.

**Keywords:** Stress; Epigenetic; Nephrilin; Rictor; Rac1; Oxidative stress; Abstraction; Agency; Innovation; Entrepreneurship

## Transgenerational Stress Burden and the Economy

The advent of shorter product cycles in an increasingly globalized economy raises troubling questions about the possible role of cumulative lifestyle stress (the 'stress exposome') on human psychological characteristics relevant to economic innovation. In particular, the exploding incidence of metabolic disease in advanced industrial societies — and the chronic metabolic stress implied therein — is of particular concern.

Recent findings showing that epigenetic marks from stressful events can reduce the threshold for subsequent stress insults, including in *future* generations, complicate this picture [1,2]. Epigenetic mechanisms are clearly implicated in such enduring effects, but although exposure to stress is associated with a number of psychiatric disorders little is known about the epigenetic mechanisms that underlie either the stress response itself or a subject's resilience to its effects.

## Cognition, Affect and Innovation

The role of personality in innovation is a subject of growing interest [3]. A recently developed inventory (eSAIL) measures psychometric constructs that have been linked to innovation, adoption of innovation, entrepreneurship and regional success in creating 'new economy' jobs [4-6]. In one study CEOs of small companies (less than 100 employees), for example, scored well above population averages on agency and positivity sub-scales of the eSAIL [5]. Interestingly, using the eSAIL and other relevant scales, one recent report shows that self-reported perceived chronic stress [7] is associated with statistically significant deficits in agency, abstract construal, RD (a construct previously linked to innovation) and theory of mind [8]. Stress also appears to be associated with higher apathy scores. One might expect the effects on apathy and agency scores to be reciprocal, even though the items used to measure the two constructs are quite different [9]. The stress study demonstrated that this was, in fact, the case. Stress may affect core circuits in the medial prefrontal complex that sub serve theory-of-mind functions [10], level of construal [11] and reward valence assessment [12], among others. All three of these functions appear to have been significantly impacted by chronic stress in the study cited above [8].

Correlation, however, does not prove a causal connection. Thus, demonstrating a biochemical link between stress and cognitive traits known to be relevant to innovation and entrepreneurship remains an active area of investigation. Understanding such links and how to modulate them could have significant effects on a society's economic competitiveness.

## Markers of Stress-Related Epigenetic CNS Plasticity

Altered prefrontal structural and functional plasticity is observed following early life adversity [13]. Chronic stress, in turn, is associated with a plethora of cognitive symptoms such as emotional dysregulation and impaired executive function that have been attributed to modifications in neuroanatomy in the orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC) and hippocampus (HPC) [14]. Genes such as the glucocorticoid receptor gene NR3C1, DNA-Binding Protein Inhibitor ID-3 (ID3), Glutamate Receptor (GRIN1) and Tubulin Polymerization Promoting Protein (TPPP), among others, have been implicated in stress-related epigenetic CNS plasticity [15,16]. BDNF has been implicated in the epigenetic effects of early life stress on the hippocampus [17]. Nevertheless, a "global" epigenetically dysregulated biochemical pathway in the CNS of stressed individuals has not been shown.

## Oxidative Stress: A "Global" Mechanism of Stress Plasticity?

A recent study showed that a severely stressful event (thermal injury) in rats generates enduring epigenetic changes in a pathway associated with mitochondrial oxidative metabolism, the Rac1/NADPH oxidase (Nox) pathway [18]. Markers of oxidative stress, such as 8-isoprostane and other markers of lipid peroxidation, are often elevated in neuroinflammation and CNS dysfunction [19,20].

In cellular housekeeping mode the Nox pathway is important to the maintenance of healthy oxidative metabolism and cellular survival. Yet it appears that prolongued and amplified activity of Nox in response to chronic or traumatic stress can cause injury and sustained dysfunction.

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This poses a fundamental problem in the design of possible interventions. Simply inhibiting Rac1 (or some other subunit of Nox) with a direct inhibitor might not be the best approach, given the essential cellular housekeeping functions of Nox. Ideally, an intervention would target just the mechanism that causes the up-regulation in Rac1 from stress, while leaving Rac1 basal activity alone.

In a number of recent studies the adaptor protein Rictor has been implicated as a key player in the mechanism of dysregulation consequent to stress insult. Rictor serves as a molecular scaffold for the maturation of protein kinase(s) C (PKC), Prex1 and, indirectly, p66shc. Both PKCs and Prex serve to hyper-activate Rac1. In some studies, nuclear translocation of Rictor appears to control both neuroinflammation and oxidative stress via Rac1 hyper-activation [18,21-24].

## Inhibition of Epigenetic Mechanisms of CNS Dysfunction

If Rictor does indeed control the stress-mediated "excess" activation of Rac1, perhaps the ideal global intervention for stress-mediated oxidative dysfunctions in neural cells would target Rictor complex selectively, i.e., without compromising the levels of Rac1 activation required for normal cellular function.

One molecule of particular interest, nephrilin peptide, has been used in a variety of stress models to accomplish exactly this. In one study, nephrilin injected into rats reversed an enduring elevation in PKC and calcitonin-gene related peptide (CGRP), a major regulator of neuroinflammation and pain, caused by traumatic stress in dorsal root ganglia [21]. Data from kidney tissues implicates both global (histone-3 acetylation) and local (DNA methylation) effects in the action of nephrilin in this model [18]. Similar epigenetic effects on dorsal root ganglia have not yet been demonstrated.

## Gaps in Knowledge

Although the above findings are provocative, much remains to be done before one may confidently join the dots between chronic stress, epigenetic modification, Rictor complex and CNS dysfunction specific to cognition/affect in innovation. It would be interesting to know, for instance, a fuller catalog of gene transcripts elevated in CNS tissues after serious stress insult and whether such changes endure via histone acetylation and DNA methylation. Survey data of this kind can point investigators in the direction of anatomical structures in the brain that are particularly relevant in the context of stress damage. Using imaging techniques, it should then be possible to image such brain areas during the performance of innovation- or entrepreneurship-related tasks, using stress as a cohort variable.

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