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Editorial\$Author's introduction

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The effects of stress on the dorsal raphe nucleus of the reticular formation and its role in the aetiology of disparate medical and neuropsychiatric disorders

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Introduction

The reticular (Latin *reticulum*, small net or mesh) formation of the brain stem of vertebrates has roles in a constellation of seemingly diverse functions, including: coordination of the movements of the head and body via stimulation and inhibition of voluntary movements and reflex movements; respiration; blood pressure; sensory gating, including in respect of pain; psychological processes such as arousal and attention; sleep and dreaming; and muscle tone (1). An important component of the vertebrate reticular formation is the raphe (Greek *rhaphé*, seam) group (accordance to the Olszewski-Brodal nomenclature). The mesencephalic nucleus raphe(s) dorsalis, or dorsal (rostral) raphe nucleus, projects widely to parts of the frontal, parietal and occipital cortices and to functionally related cerebellar cortical regions (2); these projections release the tryptophan-derived neurotransmitter serotonin (5-hydroxytryptamine or 5-HT), while the nucleus itself exhibits pacemaker activity. Thus the dorsal raphe nucleus has widespread actions.

Since 2001, Arnold E. Eggers has published a series of fascinating papers hypothesising that some physiological effects of stress give rise to increased activity of

neurones of the dorsal raphe nucleus. In turn, excitotoxic hippocampal damage ensues, which leads to a loss of the normal negative feedback control of the activity of this raphe nucleus. By turns, this may cause, or contribute to the aetiology of, a range of seemingly disparate medical and neuropsychiatric disorders, including, *inter alia*: migraine (selective serotonergic over-activity) (3); hypertension (increased set-point) (4, 5); stroke (stimulation of platelet activation) (6); temporal lobe epilepsy (faulty neuronal resonators) (7); schizophrenia (an extension of David Horrobin's membrane phospholipid hypothesis in which overdrive of 5HT_{2A/2C} receptors leads to increased cerebral cytosolic phospholipase A₂ activity) (8-10); and post-traumatic stress disorder (excitotoxic hippocampal damage followed by neurogenesis) (11). Further hypotheses are likely to follow as more details of this nucleus are discovered; in this regard, it is unlikely to have escaped Eggers' attention, for example, that serotonin neurones in the dorsal raphe nucleus have recently been shown to encode reward signals (12).

In this special issue of *Medical Hypotheses*, the opportunity has been taken to bring together several inter-related papers on the above theme authored by Eggers over a 15-year period and previously published in this journal. In these papers, Eggers skilfully brings compelling evidence to bear in support of his underlying thesis. For each implicated medical and neuropsychiatric disorder, the hypothesis is not only testable, but lays out a clear set of potential therapeutic interventions. It is to be hoped that the experiments suggested by Eggers' papers will be carried out. The words of the Founding Editor of this journal, David F. Horrobin, published in the very first issue of the first volume, are apposite: 'I follow Karl Popper in seeing the virtues of improbability. If a hypothesis which most people think is probably true does turn out to be true (or rather is not falsified by crucial and valid experimental tests) then little progress has been made. If a hypothesis which most think is improbable turns out to be true then a scientific revolution occurs and progress is dramatic.'

Many and probably most of the hypotheses published in this journal will turn out in some way to be wrong. But if they stimulate determined experimental testing, progress is inevitable whether they are wrong or right. Moreover the history of science has repeatedly shown that when hypotheses are proposed it is impossible to predict which will turn out to be revolutionary and which ridiculous. The only safe approach is to let all see the light and to let all be discussed, experimented upon, vindicated or destroyed.’(13)

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