

## Significance of REM Sleep in Depression: Effects on Neurogenesis

Laura Palagini\*<sup>1</sup>, Angelo Gemignani<sup>2</sup> and Mario Guazzelli<sup>1</sup>

<sup>1</sup>Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, Pisa, Italy School of Medicine, Via Roma 67 Pisa 56100, Italy

<sup>2</sup>Department of Physiological Sciences, University of Pisa, Extreme Centre, Scuola Superiore Sant'Anna and Institute of Clinical Physiology Research National Council, Pisa, Italy

Disturbances of sleep are typical of depression and are observed in between 50% and 90% of depressed subjects [1]. Most patients with depression complain of insomnia and have well-described sleep disruptions, which belong to the core symptoms of the disorder [2]. Sleep disorders in depression have stimulated many sleep studies and for many decades sleep research has been a major pillar of neurobiological investigations into depression's cause, onset and course. Since 1960s polysomnographic sleep research has demonstrated that besides disturbances of sleep continuity a constellation of sleep EEG changes is present in depression [3,4]. Especially Rapid Eye Movement activity has been the favorite focus of sleep EEG studies in depression and studies on its significance indicate that a strong link exists between dysregulation of REM sleep, REM latency, REM density, and the cause, onset and course of major depressive disorders. These alterations might act as trait dependent marker of depression and have been considered biological marker for depression. Especially shortened REM sleep Latency might be both a prodrome of major depressive episodes [2] and a consequence or complication of depression [2,5]. In fact REM alterations often persist beyond the clinical episode indicating heightened vulnerability to depressive relapse or recurrence, negative affecting treatment response independent of treatment method [2,6]. Moreover because the majority of antidepressants irrespective of their chemical class suppress REM sleep, it has been hypothesized that REM sleep suppression might be considered a key mechanism underlying treatment response and might be considered necessary if an antidepressant effect is obtained. Recently REM deregulations have been described to have a role in the production of the core symptoms of mood disorder contributing to the core features of cognitive distortion including self-worth [7] and to negative emotional memories consolidation. Studies have in fact demonstrated that there is a failure of sleep dependent emotional brain processing in REM sleep in depression which seems to support the development of clinical depression [8]. In addition, REM sleep is physiologically abnormal in persons at risk for depression. In fact several high risk studies including healthy relatives of patients with depression have demonstrated that REM sleep, particularly REM density changes, are present before the disorder's onset and predict its development.

Several theoretical models have been developed to explain REM sleep abnormalities in depression and they might be implicated in the pathogenesis of depression. Indeed Circadian Rhythm abnormalities have been hypothesized to explain REM sleep abnormalities in depression i.e. the Two Process Model, "S-deficiency" [9] the "Phase-advance" hypothesis [10], genetically driven [11] and the "hypocretine deficit hypothesis" [12], REM sleep dysregulation have been historically posed as a causal process of depression [13]. In fact the "Monoamine Hypothesis," "ACh-hypersensitivity" in depression indicate a key role of REM sleep dysregulations as specific features of this disorder due to cholinergic hyperactivity [14] which might be under genetic control. More recently REM sleep dysregulation have been hypothesized to contribute to neurometabolic alterations in depression. Recently McNamara et al. [7] suggest that one proximate mechanism that does directly yield the pathophysiologic pattern of hyperactive paralimbic/ ventromedial Prefrontal Cortex (vmPFC) and

hypoactive dorsomedial prefrontal cortex (dPFC) in mood disorders might be "REM hyperactivation or dis-inhibition" driven. A key role of REM sleep alterations in the pathogenesis of depression have been also indicated within the defect of brain maturation hypothesis. A novel concept for the etiology of depression proposes that a dysfunction of neural plasticity might represent a final common pathway underlying the biological and clinical characteristics of the disorder. Changes in neurogenesis might be linked to the pathophysiology of depression. In fact a decrease in neurogenesis has been shown in animal models of depression, and shift in brain plasticity might be stress related [15]. Recently it has been hypothesized that one mechanism that does directly yield the pathophysiologic pattern in mood disorders affecting neurogenesis is stress-related REM hyperactivation or dis-inhibition [16,17]. Moreover available data favor the hypothesis that the increase of stress hormones, due to sleep loss of depression and REM-stress related affects adult neurogenesis and it may endanger hippocampal integrity [18], thereby leading to cognitive dysfunction and contributing to the development of mood disorders (allostatic load) [16,17]. REM sleep changes in depression might be under a genetic control and are mediated by complex neurobiological modifications that involves noradrenergic, serotonergic, cholinergic systems and the stress system which might affect adult neurogenesis and brain plasticity. Recently REM sleep alterations have been considered not only biological scars but true endophenotypes for depression [4,19]. In fact in the search of new "vulnerability markers" or "endophenotypes" for depression changes during the REM sleep period have been reconsidered of potential interest.

Concluding from historical studies to more recent ones we might hypothesized that REM sleep might play an important key role in depression onset, course, cognitive emotional symptoms, expression and treatment response. Moreover REM sleep dysregulation might contribute to neurometabolic alterations in depression and are involved in the pathogenesis of depressive disorders. Especially it seems that REM sleep changes in depression might be under a genetic control and are mediated by host of genetic, neurochemical and neurobiological factors which might affect neurogenesis and brain plasticity of depressed patients. For all these evidences in the search of new "endophenotypes" changes during the REM sleep period have been reconsidered of potential interest. Clearly REM sleep dramatically modulates physiological, emotional and cognitive states of the human

**\*Corresponding author:** Palagini Laura, Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, School of Medicine, University of Pisa, Via Roma, 67, 56100, Pisa, Italy, Tel: 39-050993165; E-mail: [lpalagini@tiscali.it](mailto:lpalagini@tiscali.it), [l.palagini@ao-pisa.toscana.it](mailto:l.palagini@ao-pisa.toscana.it)

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being. Indeed as Prof. Siegel wrote “we will continue to ask the question “why do we have REM sleep?” [20]. Research efforts are needed to identify the REM sleep specific genetic, molecular and neurobiological pathways that contribute to depression.

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