

Exploring a Role for Sleep in Neural Development and Psychiatric Disease

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Sleep is perhaps the most enigmatic of all behaviors, without any clear known purpose though conserved from fruit flies to rodents to humans. It has long been appreciated that abnormal sleep and mental illness are intimately related, and sleep disruptions are diagnostically relevant across many psychiatric disorders [1]. While we have gained some insight into the neurobiological and molecular underpinnings of sleep [2], there is still a limited understanding of why sleep occurs, what happens when sleep is disrupted, and why sleep changes are linked to nearly all psychiatric disorders. Advances in each of these areas are needed to successfully address sleep abnormalities in humans and begin to identify the potential role of sleep in maintaining mental health.

Not only do all studied species appear to sleep, but nearly all sleep more throughout early development—a period of robust synaptic plasticity and neural growth [3-5]. Thus, it appears that the need to sleep early in development is heightened, but why? Researchers as far back as the 1960s postulated that sleep plays an important role in brain maturation [6], and more recent evidence supports the hypothesis that sleep is involved in synaptic plasticity and remodeling both in the developing and mature brain [7,8]. If sleep plays a specific role in normal brain development, dysregulation of early sleep (due to stress, chaotic homes, overstimulation, etc.) might represent a potential risk factor for later neural dysfunction, and a potential point of therapeutic intervention in psychiatric disease. Already, some evidence suggests this might be the case. For instance, sleep deprivation in young rodents leads to deficits in synaptic plasticity and long-lasting cognitive and behavioral sequelae [9]. Moreover, sleep abnormalities are pervasive in neuro-developmental disorders such as autism and some forms of mental retardation [10]. Is it possible that sleep disruption might be a contributor to abnormal neural development in these disorders rather than only an effect? Fragile X Syndrome is the most common form of inherited mental retardation, and humans with this disease as well as multiple animal models exhibit abnormal sleep characteristics [11-13]. A *Drosophila* mutant lacking the protein product absent in humans with this disorder (Fragile X Mental Retardation Protein, FMRP) sleeps more than controls, while over-expression results in less sleep [11]. Current theories suggest that sleep dysfunction results from abnormal synaptic plasticity, i.e. without FMRP, synaptic pruning is defective, so sleep is increased as a homeostatic response to increase plastic events that should normally occur during rest [14]. Yet, while deficits in synaptic pruning are observed in humans with Fragile X syndrome, a hypersomnolent phenotype is rarely reported [12], raising the possibility that plasticity deficits might not result in a drive to sleep more. Perhaps instead, sleep abnormalities in Fragile X disease might lead to a more general disrupted balance between synapse development and pruning. Presuming FMRP is one of many synapse-pruning signals, restoring normal sleep in Fragile X Syndrome could help mitigate neurocognitive burdens of this disease.

Understanding the role of early sleep has taken on even greater importance recently, as many adult psychiatric diseases are increasingly thought to derive from early neuro-developmental abnormalities, likely resulting from environmental stressors in the setting of genetic

susceptibilities [15]. Schizophrenia, depression, and bipolar disorder are all characterized by sleep abnormalities but little effort has focused on the long term psychiatric impact of abnormal sleep during early development. Recent work in *Drosophila* has demonstrated that sleep deprivation by mechanical stimulation in young flies causes profound behavioral deficits later in life, including changes in learning and memory but also courtship and response to social enrichment [16]. Remarkably, even more prolonged mechanical sleep deprivation in mature flies does not cause such long lasting and diffuse impairments, again suggesting a critical role of sleep in development [16]. With the genetic tractability of *Drosophila* now being employed to tackle even more complex behaviors such as aggression [17], the stage is set to utilize the fly system to examine non-invasively how sleep deprivation and other behaviors are intertwined. A focus on the effect of early sleep disruptions on neurodevelopment, along with exploration of mechanistic underpinnings, is likely to yield tremendous insights into sleep functions during development in both health and disease.

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