



The dreaming brain/mind: a role in understanding complex mental disorders?

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Abnormalities in the sleep/wake cycle and within sleep itself have extensively been studied in a broad range of psychiatric and neurodegenerative disorders. Despite increasing evidence for a mechanistic overlap between the disruptions of circadian timing control and neuropathology, the relationship remains unclear (Wulff et al., 2010). One possible way to address this problem from a psychiatric perspective is to compare the phenomenological correlate of sleep with the waking mentation observed in patients. Indeed, so-called “positive” symptoms such as abnormal senso-perceptual experiences or thought processes ranging from ideas of reference to highly structured delusions, share substantial similarities with dream phenomenology. The same process by which psychotic patients progress from salience attributed to irrelevant stimuli to a new, highly relevant meaning, appears to occur in dreams, where a single hallucinatory image can convey “an immediate emotionally compelling meaning that is not related to the image in any obvious way” (Feinberg, 2011). With the exception of the rare experience of lucidity, the dreamer has no recognition of his objective status, i.e., being asleep and vastly detached from the external environment; dream images produced uniquely by endogenous neural activity are interpreted as coming from the external world; heightened and often incongruous emotions are coupled with a decrease in ego functions which ultimately leads to instinctual behaviors and severe impairment in reality testing (Hobson, 2009). The striking similarity between these aspects of dreaming and psychosis has been observed by most of the founding pioneers of the modern approach to psychopathology. Indeed, it is largely unknown that Emil Kraepelin extensively studied his own dreams with the aim of progressing his understanding of schizophrenic thought disorder (Engels et al., 2003). Recent advances in neuroscience have led

few contemporary researchers to bind these complex phenomena, with electrophysiological, neurochemical, and cerebrofunctional data now pointing to shared patterns across dreaming and psychotic experiences (Hobson, 2004; Gottesmann, 2006).

One relevant issue in the scientific study of dreams is bound to the limits of our current understanding of cerebral activation patterns across different stages of sleep. Despite early observations binding dreams to REM sleep physiology, it is now widely accepted that dreams occur across all stages (Nir and Tononi, 2010). However, mental activity across sleep does differ, ranging from simple thought-like experiences to full-blown hallucinoid dreams, which have been shown to be underpinned by NREM and REM polysomnographic patterns respectively (McNamara et al., 2010). Although a direct correlation between dreaming and underlying neurofunctional modifications remains a challenge for sleep/dream researchers, some studies have shown a relative hyperactivation of cerebral regions related to emotional and affective life (i.e., amygdala and anterior cingulate cortex) and a relative hypoactivation of the frontal cortex, mainly in its dorsolateral prefrontal regions, during REM sleep (Nir and Tononi, 2010). This functional condition of the brain is mediated by a complex and interactive neurochemical pathway within which a strong increase of cholinergic activity is coupled with the reduction of serotonergic and noradrenergic firing rates. Mesolimbic dopaminergic activation has also been hypothesized to occur in dream sleep in absence of serotonergic inhibition (Gottesmann, 2002). Indeed, a raise in cortical dopamine activity has been causally linked to the generation of nightmares, possibly implying an intensification of cholinergically driven characteristics of REM sleep-related dream mentation. In order to account for the relevant findings which link REM sleep to dream phenom-

enology, bursts of “covert” REM sleep have been hypothesized to underlie mental activity during other stages. This observation is based on the correlation between hallucinatory subjective experiences and EEG configurations containing elements of both REM and NREM. Moreover, the most vivid NREM mentation reports have been collected when transient EMG suppressions and phasic muscle twitches, which are typical of REM sleep, were recorded during sleep onset (Nielsen, 2000).

Prefrontal hypometabolism and limbic/paralimbic hypermetabolism have been reported in both waking schizophrenic and manic psychotic subjects (Molina et al., 2005; Minzenberg et al., 2009; Brooks III et al., 2010). On the neurochemical level, positive symptoms have been hypothesized to result from abnormal regulation of NMDA-dependent synaptic plasticity by transmitters like dopamine, acetylcholine and serotonin (Stephan et al., 2009). Long-term potentiation (LTP), a key mechanism of synaptic consolidation, is similarly thought to rely on glutamatergic transmission, with sleep spindles having been recognized as a possible neurophysiological correlate of the consolidation dialog between the hippocampus and neocortical structures during sleep (Diekelmann and Born, 2010; Fogel and Smith, 2011). In this regard, it seems interesting to note that sleep spindle density has been found to be reduced in schizophrenic subjects (Ferrarelli et al., 2007). Indeed, procedural and declarative memory consolidation impairment has been correlated to sleep disturbances in these patients (Manoach et al., 2010; Seeck-Hirschner et al., 2010). The mixed findings that have historically emerged from sleep studies in this population could at least in part be attributed to the complex nosographical boundaries of the disorder. In our view, abnormalities in sleep-dependent consolidation mechanisms should be considered in relationship

to positive symptoms rather than to the broader concept of schizophrenia, and one recent study seems to suggest that neurocognitive deficits do correlate with sleep spindle density in a population of psychotic patients belonging to several different diagnostic categories (Keshavan et al., 2011). Sleep-dependent processing of memory may be viewed as a continuous adaptation of the brain to the external environment, of which dreaming constitutes the subjective epiphenomenon. In this perspective, positive psychotic symptoms may be considered the subjective correlate of aberrant underlying consolidation processes. Indeed, several neurobiological findings seem to support the view that delusions occur when consolidation of prior beliefs is driven above new extinction learning by dopaminergic hyperactivity (Corlett et al., 2009). The neural plasticity which underlies continuous integration of information could be abnormal in several clinical conditions, leading to a phenomenological overlap between sleep and waking mentation. This conceptualization may be of use in explaining the broad variety of disorders within which psychotic symptoms occur, and the high correlation found between these symptoms and chronobiological disruptions. From a phenomenological point of view, the waking cognition of acutely psychotic subjects has been shown by our group to share similarly elevated levels of cognitive bizarreness with their own dream reports and those of a control population independent of diagnostic categorizations (Limosani et al., 2011).

The key similarity between dreams and psychosis evolves around the subject's inability to discern external reality from internally generated stimuli that arise to consciousness. Severe impairment of cognitive processes such as self-reflective awareness, abstract thinking and metacognition justify the impaired reality testing found in both mental states, converging on the crucial role of frontal regions. Promising findings have recently emerged from research into the neurobiological substrates of lucid dreaming (Voss et al., 2009; Dresler et al., 2011). Within this peculiar state of the brain/mind, the dreamer gains awareness into the internally generated origin of the experience and can in some cases volitionally control the dream. Dream lucidity has been hypothesized to occur "when wake-like frontal lobe activation is associated with REM-like

activity in posterior brain structures" (Voss et al., 2009). In other words, reactivation of frontal lobes within REM sleep appears to underlie awareness within the hallucinatory nature of one's experience. Although the multidimensional construct of insight has been shown to reflect a vast and complex neural circuitry in psychotic patients, frontal lobe processing is thought to play a critical role (Antonius et al., 2011). Disruption of synaptic plasticity in the prefrontal cortex has been confirmed in rodent models of schizophrenia and available antipsychotic medications are known to modulate LTP in this area (Goto et al., 2010). The atypical antipsychotic clozapine appears to improve insight phenomenologically and is often referred to as the most effective antipsychotic in clinical practice (Tiihonen et al., 2009). Clozapine, which produces fundamental changes in prefrontal cortex functioning in schizophrenic patients (Pallanti et al., 1999), has been shown to enhance LTP induction (Matsumoto et al., 2008) and to reverse stress-induced impairments of LTP induction in the hippocampus-PFC pathway (Dupin et al., 2006). Alongside pharmacological interventions, Cognitive Remediation Therapy has been shown to enhance activity in the prefrontal cortex of schizophrenic patients (Wexler and Bell, 2005). This type of treatment may also contribute to the reduction of psychotic symptoms, suggesting a relationship with the increase of synaptic plasticity in frontal structures obtained through cognitive skills training (Lecardeur et al., 2009).

Future directions for research may involve low-intensity scalp stimulation techniques that have been shown to modulate neuronal excitability. In a recent review, transcranial direct current stimulation (tDCS) in the DLPFC was reported to improve cognition in schizophrenic patients (Minzenberg and Carter, 2012).

Although interest in the relationship between dreams and psychosis has refluorished in recent research (Scarone et al., 2008; Lusignan et al., 2009; Yu, 2009; Noreika et al., 2010; Schredl, 2011; Zanasi et al., 2011), more experimental data are needed to understand whether or not the abundant findings which have only partially been discussed here can be reconceptualized in a framework linking sleep-dependent processing of memory to the onset of psychotic symptoms in genetically and

environmentally predisposed subjects. Similarities and differences in brain function will have to be addressed directly in the future by binding sleep and dream research with research in psychotic disorders within the same experimental framework.

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