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EDITORIAL

Sleep abnormalities in schizophrenia: pathophysiological significance[1]

The notion that sleep, dreams and psychosis are interrelated dates back to Hughlings Jackson, who, over a century ago, said, 'Find out about dreams, and you will find about insanity' (Jackson, 1958). The discovery in 1953 of the rapid eye movement (REM) sleep and its association with dreaming led to a surge of interest in the association between sleep and psychoses. Several sleep electroencephalographic (EEG) abnormalities have since been reported in schizophrenia; these include reduced total sleep, impaired sleep continuity, shortened (REM) latency, and reduced slow wave sleep (SWS, or delta EEG activity) (Keshavan *et al.* 1990*a*). Eleven of the 14 studies that compared REM latency between drug-free schizophrenics and normal controls (Gulevich *et al.* 1967; Stern *et al.* 1969; Dürrigl *et al.* 1973; Jus *et al.* 1973; Benson & Zarcone, 1985, 1993; Hiatt *et al.* 1985; Zarcone *et al.* 1987; Kempenaers *et al.* 1988; Keshavan *et al.* 1990*b*; Tandon *et al.* 1992) showed a reduction in REM latency in schizophrenic patients, though some studies (Feinberg *et al.* 1964; Caldwell & Domino, 1967; Ganguli *et al.* 1987) have not found such a reduction. In addition, a large meta-analytical study of controlled studies (Benca *et al.* 1992) confirmed this finding. Seven of 10 studies (Lairy *et al.* 1965; Caldwell & Domino, 1967; Jus *et al.* 1968; Kupfer *et al.* 1970; Traub, 1972; Hiatt *et al.* 1985; Benson & Zarcone, 1993) have shown a reduction of hand-scored SWS in schizophrenic patients, though there have been some negative studies (Ganguli *et al.* 1987; Kempenaers *et al.* 1988; Tandon *et al.* 1992). However, Ganguli *et al.* (1987) observed a significant reduction in delta wave counts in drug-naive schizophrenic patients, suggesting that hand-scored SWS may not be sensitive enough and automated counts may be a better marker of SWS deficiency in schizophrenia.

The implications of these findings for the diagnosis and pathophysiology of schizophrenia remain unclear. Disrupted sleep continuity, shortening of REM latency; and reduced SWS are also seen in affective disorders (Reynolds & Kupfer, 1987; Benca *et al.* 1992); the similarity between affective and schizophrenic disorders suggests that these findings may lack diagnostic specificity. There may, however, be some differences. While an increase in REM sleep in affective disorder is supported by findings of significant increases in REM density, time and percentage in controlled studies, no consistent changes have been seen in the amounts of REM sleep in schizophrenia (Benca *et al.* 1992). Thus, a combination of EEG sleep abnormalities (decreased REM latency and SWS deficits without appreciable alterations in REM sleep amounts) might be seen in schizophrenia. A clarification of the biological basis for such a constellation of findings could be instructive toward our understanding of the pathophysiology of schizophrenic disorders.

REM SLEEP

There may be several explanations for the observed shortening of REM sleep latencies in schizophrenic and affective disorders. First, it is conceivable that REM latency alterations in schizophrenia are related to the presence of depressive symptoms in schizophrenic patients. No such relationship between REM latency and affective symptomatology has been observed in schizophrenic patients, however (Tandon *et al.* 1992). There is a genetic overlap between these

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disorders, with many schizophrenic patients having family members with affective disorders and vice versa (Gershon *et al.* 1988). It is therefore possible that some schizophrenic patients may be biologically similar to affective disorder; such patients may be expected to have sleep findings similar to those in affective disorders. Preliminary data on this issue are contradictory (Keshavan *et al.* 1990*b*; Tandon *et al.* 1992). This hypothesis, therefore, needs further rigorous testing.

Secondly, there may be common neurochemical mechanisms mediating the sleep findings in schizophrenia and affective disorders. Cholinergic mechanisms, which have been postulated to underlie shortened REM latency sleep in affective disorders (Sitaram *et al.* 1980) may be involved in schizophrenia as well (Tandon & Greden, 1989). At least seven studies have shown to date that patients with affective disorder have a rapid (supersensitive) induction of REM sleep with cholinergic agonists (Gillin *et al.* 1991). Schizophrenic patients have been described to show a similar rapid (supersensitive) REM sleep induction with the oral muscarinic cholinergic agonist RS-86 (Riemann *et al.* 1991) and a reduced prolongation of REM latency with the muscarinic antagonist biperiden (Tandon *et al.* 1991). There is also preliminary evidence for increased plasma cholinesterase (ChE) activity (Mahadik *et al.* 1989) and an inverse relation between plasma ChE and REM latency in schizophrenic patients (Keshavan *et al.* 1992). Increased cholinergic activity may thus be one possible explanation for the shortened REM sleep latency in affective and schizophrenic disorders. On the other hand, dopaminergic and noradrenergic (van Kammen *et al.* 1990) systems which are presumably hyperactive during acute episodes of schizophrenia, are inhibitory to REM sleep, while cholinergic mechanisms enhance REM sleep. The timing of onset of REM sleep is, however, mainly cholinergically mediated (Gillin *et al.* 1978). Thus, while cholinergic hyperactivity would explain the shortened REM latency, the concomitant NE/DA overactivity would counter the cholinergically-mediated REM sleep increases (explaining the absence of increased REM sleep in schizophrenia).

Thirdly, it is also possible that REM latency reductions in schizophrenia results from a deficit in SWS (Borbély, 1982; Feinberg *et al.* 1988). The latter possibility is supported by observations of an inverse relation between daytime naps (which lead to reduced night-time SWS) and REM latency (Campbell & Gillin, 1987). Kupfer & Ehlers (1989) have proposed that two distinct factors ('roads') may lead to shortening of REM latency in affective illness: type 1, a 'trait' marker, due to SWS deficiency, perhaps related to genetic vulnerability to affective illness and developmental factors, and type 2, an 'episode' marker, due to REM pressure, perhaps related to stress and illness severity. The lack of consistent changes in REM sleep amounts and the findings of reduced SWS in schizophrenia suggests that a mechanism similar to the Road I to REM latency might operate in schizophrenia. In this sense, the SWS deficits may be the *primary* sleep abnormality in schizophrenia.

SLOW-WAVE SLEEP

What is the pathophysiological significance of SWS deficits in schizophrenia? Some clues to this may derive from the studies of the ontogeny of sleep during normal adolescence, and in the context of a neurodevelopmental framework for schizophrenia (Feinberg, 1982; Waddington, 1993). One of the essential characteristics of schizophrenia is its onset in adolescence. Human adolescence is associated with a substantial reorganization of the brain structure and function, resulting in an initial increase and a subsequent decrease of cortical synaptic density proceeding through adolescence (Huttenlocher, 1979). This is paralleled by reductions in synaptic density, brain cortical volume, regional brain metabolism and deep sleep during the second decade of life (Feinberg, 1982, 1990). It has been proposed that such a process of programmed synaptic elimination, or 'pruning', may be exaggerated in schizophrenia (Feinberg, 1982; Hoffman & McGlashan, 1993). If this is true, first, one would expect deficits in these parameters in schizophrenia; observations of decreased grey matter volume, in magnetic resonance imaging (MRI) studies (Zipursky *et al.* 1992), possibly increased neuronal density, which may be related to loss of neuropil comprising of synapses (Selemon *et al.* 1993), and of decreased SWS in schizophrenia, as reviewed above, are consistent with this possibility. Secondly, one would expect an association between SWS deficits and indicators

of cerebral dysfunction in schizophrenia. Indeed, SWS deficits have been found to be associated with negative symptoms (Ganguli *et al.* 1987), cognitive impairment (Orzack *et al.* 1977), and with cerebral ventricular enlargement (van Kammen *et al.* 1988). Negative symptoms, cognitive impairments and ventriculomegaly are considered to reflect trait related alterations, which appear to be present at and may even precede illness onset, thus supporting the notion of neurodevelopmental abnormalities of schizophrenia (Mukherjee *et al.* 1991; also see Waddington, 1993 for a review). Decreased SWS in schizophrenia may therefore be related to alterations in brain structure and function perhaps related to such a neurodevelopmental abnormality.

How does one understand deficits in SWS in the context of the possibly reduced cortical synaptic density in schizophrenia? EEG waves are thought to reflect summed post-synaptic potentials in large assemblies of cortical neurons driven by a subcortical 'pacemaker' (Elul, 1972). Decreased synaptic density, therefore, could result in smaller EEG waves (and thus resulting in reduced SWS) by decreased membrane surface (fewer dendrites/neuron) causing a smaller voltage response to the synchronizing stimulus (Feinberg *et al.* 1990). Further, lower levels of interconnection would cause smaller aggregations of neurons to simultaneously change potential. Miles & Dement (1980) have suggested that the age-related reduction in delta sleep may be related to loss of oblique-horizontal dendrite system of layers 2, 3, and 5. Pyramidal cells, which may be involved in synchronous neuronal behaviour mediating delta sleep. Perhaps such an age-related neuronal decrement is exaggerated in schizophrenia.

Do SWS deficits reflect widespread brain dysfunction, or is there a regional specificity? Kraepelin (1919) originally proposed that schizophrenia 'attacks by preference the prefrontal cortex'. Interest in the role of the prefrontal cortex (PFC) in pathophysiology of schizophrenia has been rekindled by observations of consistently reduced metabolism in this region ('hypofrontality') from a variety of approaches, including positron emission tomography (PET) studies (Buchsbaum, 1993), single photon emission tomography (SPECT) studies (Andreasen *et al.* 1992), magnetic resonance spectroscopy (MRS) studies (Pettegrew *et al.* 1991), and electrophysiological studies of cortical coherence (Hoffman *et al.* 1991). The PFC is the site of most intense cortical brain activity during the awake state in normal humans, and the reverse is true during SWS. The delta EEG activity is most prominent in the PFC (Horne, 1992, 1993). Further, data from coherence analysis of EEG support the view that the PFC may play a role in the generation of SWS (Nielsen *et al.* 1991). The cognitive effects of sleep deprivation in normal subjects appear to resemble closely PFC dysfunction (Horne, 1993). These data, albeit circumstantial, suggest an association between hypofrontality and deficits in SWS, even though the direction of causation remains unclear.

DISCUSSION

Schizophrenia appears to be marked by a polysomnographic profile of shortened REM latency without alterations in REM sleep amounts and reduced amounts of slow-wave sleep. While similarity in these findings between schizophrenia and affective disorder reflects a lack of diagnostic specificity, these similarities perhaps suggest common neurobiological mechanisms. The changes in REM latency in these disorders might reflect similar alterations in cholinergic function. An intriguing alternative possibility is that the sleep EEG alterations reflect a neurodevelopmental abnormality, perhaps an excessive cortical synaptic pruning during adolescence, perhaps more so in the PFC. However, these possibilities must at this time be considered speculative. Future studies need to examine EEG sleep findings in schizophrenia, paying close attention to the state vs. trait differences and the question of whether these findings are present at illness onset. The neurochemical correlates of sleep changes and the effects of pharmacological challenges (dopaminergic, cholinergic, etc.) are a worthwhile aspect of enquiry. The neurodevelopmental aspects of sleep EEG, examining the maturational changes in sleep during adolescence in healthy and schizophrenic subjects need to be studied. Finally, the association between sleep changes and neuroanatomical and physiological alterations need to be examined using state-of-the-art imaging approaches such as MRI, MRS, and

PET studies. Such studies may help us to more fully exploit the use of sleep EEG as a window to the brain capable of providing clues to the pathophysiology of puzzling disorders such as schizophrenia.

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