REVIEW ARTICLES

Dopaminergic Syndromes of Sleep, Mood and Mentation: Evidence from Parkinson's Disease and Related Disorders

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We reviewed sleep and dream-related clinical symptoms in a set of four neurologic disorders (Parkinson's Disease, REM Behavior Disorder, Narcolepsy and Depression) characterized by severe reductions in dopaminergic function. Sleep findings included excessive daytime sleepiness (EDS), increased rapid eye movement sleep times (REM%), increased REM density or bursts of REMs, reduced REM latency periods, and sleep onset REM (SOREM). Clinical symptoms included perseverative or rigid thinking and personality styles, frontal lobe impairment, increased complaints of, or vulnerability to negative affect, and increased vivid and unpleasant dreams. The increased vulnerability to unpleasant dreams was particularly interesting as descriptions of dream content were strikingly similar across all 4 disorders. Dreams of feeling threatened or being attacked by animals or dangerous creatures were very frequent. We hypothesize that the cluster of sleep, dream and cognitive changes associated with these four disorders can be explained by assuming that lowered dopaminergic tone leads to a disinhibition of REM physiology and amygdalar activity and that this disinhibition of REM and amygdalar function yields unpleasant dreams, negative affect, and frontal lobe impairment. Careful study of the cluster of co-occurring symptoms identified here may illuminate 1) the ways in which dopamine might function in regulation of sleep states, and 2) aspects of the neurology of dream content. **(Sleep and Hypnosis 2002;4(3):119-131)**

Key words: *REM sleep, dopamine, Parkinson's disease, REM sleep behavior disorder, narcolepsy, depression, dreams*

INTRODUCTION

In this paper we call attention to a cluster of sleep and dream-related clinical symptoms that appear to be due, in part, to dopaminergic dysfunction and to co-occur reliably in a group of neurological and sleep-related disorders. We will examine the role of dopamine in motor function, cognitive function, sleep, mood and personality. These functions will be examined through an analysis of four diseases where dopamine dysfunction has been identified as a major component of the underlying pathophysiology. The diseases to be examined include Parkinson's disease (primarily considered a disorder of movement), depression (primarily considered a disorder of mood), narcolepsy (a sleep disorder with a

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primary emphasis on REM dysfunction) and REM behavior disorder (also, primarily a disorder of REM function). We will specifically look at the overlap of symptoms in these four disorders.

We believe that study of this cluster of co-occurring symptoms will illuminate the ways in which dopamine might function in regulation of sleep states. In addition, we believe that study of these co-occurring symptoms will reveal interesting aspects of the neurology of dream content as one of the distinguishing traits of these 4 disorders is the abundance of vivid, emotionally intense and unpleasant dreams where the dreamer experiences him/her self as being threatened or attacked. In our discussion of the target disorders we divide the relevant symptom clusters into sleep-related symptoms and "clinical" (motor, mood and mentation) symptoms. Sleep findings include excessive daytime sleepiness (EDS), increased rapid eye movement sleep times (REM%), increased REM density or bursts of REMs, reduced REM latency periods, and sleep onset REM (SOREM). Clinical symptoms include perseverative or rigid thinking and personality styles, frontal lobe impairment, increased complaints of, or vulnerability to negative affect, and increased vivid and unpleasant dreams. There may also be varying degrees of impairment in normal regulation of the postural atonia normally associated with REM sleep.

REM sleep is an integrated physiologic process characterized by both tonic and phasic components. Tonic aspects of REM include EEG low voltage fast activity, muscle atonia, high arousal thresholds, hippocampal theta and penile erections. Phasic aspects of REM include REM bursts, intermittent muscle twitches, and PGO waves (pontine-geniculate-occipital electrical spikes). Of course vivid dreams are typically reported when subjects are awakened from REM. Recently a number of PET and MRI studies of the sleeping brain have revealed that REM demonstrates high activation levels in pontine, midbrain tegmentum, limbic and amygdalar sites, anterior cingulate and deactivation of prefrontal areas, parietal cortex and posterior cingulate (1-4). Crucially, these imaging studies have consistently revealed exceptionally high activation levels in the amygdala during REM.

We hypothesize that PD, RBD, narcolepsy and depression are all characterized by a generalized disinhibition of REM physiology and that this REM physiology includes an over-inhibited prefrontal cortex and a disinhibited amygdalar complex. That is why each disorder manifests enhanced REM values (REM%, REM density, latency to REM, vivid dreams and SOREM etc), and de-activated or impaired prefrontal functions and negative affect. The disinhibition of REM creates the clinical symptoms, including the unpleasant dreams, in these four disorders. The REM disinhibition may be due, in part, to reduction of dopaminergic inhibition of the amygdalar complex functions. We discuss this hypothesis in the final section of this paper. We turn, first, however, to a review of doapminergic effects on sleep and a discussion of relevant sleep and clinical symptoms in our four target disorders.

DOPAMINE AND SLEEP

Until very recently the neurotransmitter dopamine (DA) was not thought to play a significant role in modulation of sleep functions. This was due largely to early claims that endogenous DA transmission varied little between sleep/wake states. It has long been recognized, however, that administration of dopaminergic agents to patients or animals tended to enhance wakefulness (5,6), thus implying that reducing dopaminergic tone would reduce wakefulness and enhance sleep. After decades of neglect these clinical observations are now being tested in experimental animal models and these experiments have produced convincing evidence for the claims that dopamine is

crucially involved in regulation of sleep wake states. Recent studies by Wisor et al. (6) are illustrative: Using polygraphic recordings and caudate microdialysate dopamine measurements in narcoleptic dogs, Wisor et al., (6) have shown that the wake-promoting antinarcoleptic compounds modafinil and amphetamine increase extracellular dopamine without affecting other putative wake promoting substances/receptors like hypocretin receptor 2. In addition, manipulations of the dopamine transport molecule, DAT, confirm DA's central role in maintaining wakefulness. Wisor et al also showed that DAT knock-out mice suffered from excessive levels of sleepiness and were unresponsive to the normally potent wake-promoting action of modafinil, methamphetamine, and the selective DAT blocker GBR12909. In summary, reduced levels of dopamine transmission appear to be associated with excessive sleepiness and conversely normal levels of DA are critical for maintaining wakefulness.

Evidence from human clinical disorders also suggests that DA significantly modulates aspects of sleep state and may carry clinical implications for a number of sleep-related disorders. In what follows we first review the dopaminergic-related clinical symptoms occurring in 4 neurologic disorders with sleep changes. These are Parkinson's Disease (PD), REM behavior disorder (RBD), narcolepsy and depression. We then offer a hypothesis as to why this particular set of symptoms manifest themselves repeatedly across these 4 disorders. We conclude with a brief discussion of implications of the hypothesis for a theory of REM sleep functioning.

DISORDERS

PARKINSON'S DISEASE (PD)

PD is an idiopathic, neurodegenrative disorder characterized by rigidity, bradykinesia, gait disorder, and sometimes tremor.

PD dopamine deficit

The primary pathology in PD involves loss of dopaminergic cells in the substantia nigra (SN) and in the ventral tegmental area (VTA; 7). These two subcortical dopaminergic sites give rise to two projection systems important for motor, affective and cognitive functioning. The nigrostriatal system, primarily implicated in motor functions, originates in the pars compacta of the SN and terminates in the striatum. The meso-limbic-cortical system contributes to cognitive and affective functioning. It originates in the VTA and terminates in the ventral striatum, amygdala, frontal lobes, and some other basal forebrain areas. Dopamine levels in the ventral striatum, frontal lobes, and hippocampus are approximately 40% of normal (7-10). The degree of nigro-striatal impairment correlates with degree of motor impairment while VTA-mesocortical dopaminergic impairment correlates positively with the degree of affective and intellectual impairment (11-13) in affected individuals. As many as 40% to 60% of the cells in the substantia nigra must be lost before motor signs of disease become evident. Remaining neurons of the substantia nigra may also evidence the pathologic feature of Lewy bodies (cytoplasmic eosinophilic insolvent protein inclusions).

Prefrontal impairment in PD

Prefrontally-based executive cognitive functions and attentional control functions appear to be impaired in PD (14-21). Perseverative cognitive tendencies are also often reported. There is, for example, a well-established PD attentional switching deficit on certain verbal fluency paradigms -namely 'category alternation paradigms' where the patients are required to generate names in one category for about a minute and then switch to another category. Patients do not shift as readily as controls (14-16,21-24).

The frontal lobe-related cognitive deficits associated with PD appear to be due at least in part to the dopaminergic deficit. Levodopa (LD) has been shown to significantly improve performance of PD patients on ECF tests such as the Wisconsin Card Sort Test (WCST; 25), the Tower of London (TOL) planning test (26), verbal fluency tasks (23) and various other forms of intellectual functioning linked to ECFs (27). These LD-induced performance changes in ECFs occur even after motor components of the tasks are eliminated or minimized. Lange et al. (26,28) found that PD patients were dramatically impaired on 'frontal' or executive function tests (Tower of London task, set shifting, working memory, and spatial attention span) only when withdrawn from L-dopa medication. Performance on non-frontally-mediated tests such as visual memory tests was not impaired when patients were off LD.

Personality rigidity in PD

PD patients are also reported to exhibit a withdrawn, rigid and inflexible personality style (27,29) even well in advance of the first motor manifestation of the illness.

Negative affect in PD

Depression is acknowledged to be a common concomitant of PD with as many as 40% of patients displaying some signs of endogeneous depression (27).

Dreams in PD

There are very few studies of dreams of PD patients. We focus only on non-demented PD patients. Cipolli et al (30) reported a correlation between Mini Mental State scores and length of dream report and event story structure within the dream. Our clinical impression is that dreams reported by PD patients are typically vivid and unpleasant especially after LD administration. Our hypothesis predicts a predominance of unpleasant dreams among PD patients with signs of REM disinhibition (see below).

Sleep symptoms in PD

Sleep functions are also often abnormal in PD (31). In the mid-late stages of the disease polysomnographic study demonstrates increased amounts of stage 1 and REM and reduced amounts of stage 3 and 4. In a subgroup of patients one sees a markedly different set of sleep changes from the standardly reported profile of sleep fragmention and insomnia. Instead one sees excessive daytime sleepiness (EDS), increased REM%, reduced REM latency, increased REM density and SOREM (Footnote: Jankovic (32) seems to attribute this latter sleep profile to a thalamocortical arousal state abnormality but we will present a different hypothesis below). Using the Epworth self-report of sleepiness scale, Ondo et al (33) found that approximately 50% of 303 patients with PD evidenced significant sleepiness (ESS scores > 10) and the level of sleepiness was similar for patients on differing medication regimes (pramipexole, ropinirole and pergolide). Ulivelli et al., (34) reported pergolide-induced sleep attacks and increased REM in PD patients. Tan et al (35) recently reported that irresistible sleepiness was present in about 14% of a population of Chinese patients with PD. Using the multiple sleep latency test (MSLT), a standardized measure of physiologic sleep tendency across five daytime nap opportunities, Arnulf et al (36) found "pathologic" sleepiness in 50% of their PD patients (mean sleep latency of MSL<5 minutes), and a narcolepsy-like profile in 39% (MSL <8 minutes and >2 SOREM). These sleep related changes were not consistently correlated with disability ratings or medication regimes. Apparently, PD pathology itself accounts for a substantial proportion of excessive daytime sleepiness in PD. Nevertheless, these studies must be interpreted with caution as it is not

clear that a clear distinction was made between hypersomnia-an increased need for sleep over the 24 hour day vs. EDS which might be related to nocturnal sleep inefficiency.

REM SLEEP BEHAVIOR DISORDER (RBD)

Patients with idiopathic RBD typically complain of a history of vivid unpleasant dreams and excessive movements in sleep. They typically do not evidence a degenerative dementia until very late stages of the disease. We focus on phenomenology of sleep and dreams in non-demented RBD patients. The sleep-related movements in RBD may be violent enough to induce physical injury. There appears to be enactment of violent dream content and a concomitant failure of REM-related muscle atonia. Like Jouvet's (37,38) pontine lesioned cats, who were thought to exhibit oneric behaviors that were normally under output inhibition, these patients are thought to suffer from a similar disinhibition of selective brainstem motor pattern generators. The disinhibition, in turn, is thought to be due to a pathologic process that affects pontine and some basal ganglia sites and other midline structures.

RBD dopamine deficit

Very little data exist on neurochemical pathophysiology of RBD but given its strong comorbidity with PD, dopaminergic dysfunction is probable. RBD has been found to occur in about 47% of PD patients (39), both in treated and untreated patients, with some patients reporting symptoms before the onset of PD. As mentioned above, a great deal of dopaminergic cell loss occurs before the first signs of motor dysfunction. Perhaps early dopaminergic cell loss promotes vulnerability to RBD. Albin et al., (40) determined the density of striatal dopaminergic terminals with [11C]dihydrotetrabenazine PET in six elderly subjects with chronic idiopathic RBD and 19 age-appropriate controls. In subjects with RBD, there were significant reductions in striatal [11C]dihydrotetrabenazine binding particularly in the posterior putamen implying significant dopamine deficit.

Frontal impairment in RBD

Patients with RBD exhibit a cognitive profile consistent with frontal lobe impairment. Ferman et al (41) compared cognitive performance of non-demented idiopathic RBD patients to a group of patients with Alzheimers Disease (AD) and found that patients with RBD evidenced greater deficits on attention/ concentration, perceptual organization, visual memory and verbal fluency tests than did the AD patients. Shirakawa et al (42) used magnetic resonance imaging and single-photon emission computed tomography of the brain to study neurologic basis of RBD. Blood flow in the upper portion of both sides of the frontal lobe and pons was significantly lower in patients with RBD than in a normal elderly control group.

Personality rigidity in RBD

Based on the hypothesis we describe below we predict a compulsive and rigid personality profile with perseverative and ruminative thinking styles. Olson et al (39) reported that 25.8% of their patients had histories of psychiatric disease or neurotic profiles, a figure somewhat lower than the 35% reported by Schenck and Mahowald (43).

Negative affect in RBD

Olson et al (39) reported that a significant percent of their series of 93 patients were depressed or had histories of depression.

Unpleasant dreams

Dream content in RBD typically involves the

patient under some sort of threat either against himself or his wife. Most patients report that they repeatedly experienced this RBD-related "nightmare" of being attacked by animals or unfamiliar people. The dreamer attempts to fight back in self-defense. Fear rather than anger is the usual accompanying emotion reported.

Sleep symptoms in RBD

Polysomnographic studies show loss of muscle atonia and thus the patients are in danger of acting out these unpleasant or violent dreams and thus causing injury to themselves or their bedpartners. According to Mahowald and Schenck (44) the overall sleep architecture is typically intact but most patients show increased SWS for their age. Schenk and Mahowald (43) found that 28 of 65 patients they evaluated evidenced increased REM percent (>25% of total sleep time). In the Olson et al study of 93 consecutive patients with RBD (39), 90 showed increased phasic activity in REM. No consistent reports of SOREMs have yet appeared, though we would predict this based on our hypothesis described below.

NARCOLEPSY

Narcolepsy is a disorder of excessive daytime sleepiness that typically is associated with cataplexy and other REM-related phenomena such as sleep paralysis, vivid dreams, and hypnagogic hallucinations. The cataplectic attack is usually triggered by intense emotion. Narcolepsy may be associated with expression of HLA-DR2, DQw6 DQB1-0602 and thus might be linked to HLA antigen and autoimmune disease. The positional cloning of the canine narcolepsy gene (canarc-1) indicated that the disorder was related to exon-skipping mutations in the gene that encodes one of the G-protein-coupled receptors for the neuropeptide hypocretins (Hcrtr2). Excitatory hypocretin neurons project most heavily to the locus coerlueus (LC). Thus a lowering in hypocretins could decrease LC activity thereby disinhibiting REM and producing narcolepsy, but the story is likely to be more complex as hypocretin neurons project diffusely throughout the forebrain and narcoleptics evidence no hypocretin deficits in their cerebrospinal fluid.

Dopamine deficit in narcolepsy

Catecholaminergic stimulants are commonly used to treat sleepiness in narcolepsy, implying that what is causing the sleepiness is reduction in catecholaminergic activity. Nishino et al., (5) reported that dopaminergic uptake inhibitors dose-dependently increased wakefulness in control and narcoleptic animals. The in vivo potencies of DA uptake inhibitors and modafinil (a drug used to treat narcolepsy) on wake significantly correlated with their in vitro affinities to the DA and not the NE transporter, suggesting that presynaptic activation of DA transmission is critical for the pharmacological control of wakefulness in narcoleptics and that dopaminergic tone is reduced in narcolepsy. While increased dopamine D2 receptor binding in basal ganglia has been reported in human narcolepsy, these studies were mostly based on post-mortem material from patients who were medicated for narcolepsy. A number of neuroimaging studies (45-47) have failed to find increased DA D1 and D2 receptor binding in basal ganglia of narcoleptic patients.

Frontal impairment in narcolepsy

Kaufman et al. (48) compared MRI-derived gray matter maps of 12 patients with narcolepsy with matched controls using voxel-based morphometry to ascertain whether there are other structural brain abnormalities. Patients with narcolepsy showed bilateral cortical gray matter reductions predominantly in inferior

temporal and inferior frontal brain regions. Relative global gray matter loss was independent of disease duration or medication history. No significant subcortical gray matter alterations were noted.

Personality rigidity and negative affect in narcolepsy

Narcolepsy is also associated with marked personality and cognitive changes. In a postal survey of 500 members of the UK narcolepsy patient association, which included the SF-36, a health and psychiatric symptom inventory, the Beck Depression Inventory (BDI), and the Ullanlinna Narcolepsy Scale (UNS), Daniels et al (49) found that narcoleptics had significantly lower median scores on all eight domains of the SF-36 and scored particularly poorly for the domain of social functioning. The BDI scores indicated that 56.9% of subjects had some degree of depression. There was little difference in symptom profiles as a function of receiving different types of medication. Similarly, Kryger et al (50) using the Province of Manitoba Health database, compared the diagnoses made in the year prior to initial sleep disorder diagnosis of 77 patients with narcolepsy and 1,155 matched controls. Narcoleptic patients were much more likely than controls to be diagnosed with mental disorders (Odds ratio (OR)=4.0645; 95% confidence limit (CL)=2.4671-6.6962; $p<0.0001$) and nervous system disorders (OR=5.0495; CL=3.0606 -8.3309; $p<0.0001$). Neurotic disorders (17% of cases), depression (16%), personality disorders (3%) and adjustment reaction (4%) were elevated in narcoleptics relative to controls. It is not clear whether these personality and affective changes are due to primary pathology of the disease or are reactive to chronic effects of the disorder. Given that the data apply to patients before they were diagnosed with narcolepsy it may be that the personality deficits are not simply reactive.

Unpleasant dreams in narcolepsy

Despite the increased REM percentages, nighttime sleep is often interrupted by awakenings and terrifying dreams (51,52).

Sleep symptoms in narcolepsy

Sleep changes have been extensively documented in narcolepsy (see 52 for review) and remarkably parallel those found in depression (described below) with reduced REM latencies, increased REM percent, increased REM densities and SOREM.

DEPRESSION

Depression is a major disorder of mood involving unpleasant or dysphoric affect, inability to experience pleasure, weight changes (usually loss), psychomotor retardation, feelings of worthlessness, diminished ability to think or concentrate with intrusive, repetitive thoughts and sleep disturbances. The sleep disturbances usually involve early morning awakenings, insomnia, nonrestorative sleep and disturbing, unpleasant and vivid dreams.

Dopamine deficit in depression

There are several lines of evidence suggesting a role of dopamine in depression which cannot all be reviewed here (see 53,54 for reviews). For our purposes it is interesting to note that early brain electrical stimulation studies of the ascending medial forebrain bundle involving the dopaminergic nuclei of the ventral tegementum and mesolimbic catecholaminergic systems that project into limbic and frontal lobes, revealed an integrated reward system mediating behavioral reinforcement, motivation and goal-directed behavior. This catecholaminergic reward system is believed to be the site of action for virtually all the major addicting substances. Hypoactivity in this system would certainly

induce dysphoric affect. Virtually all of the known addictions exert their addictive actions, in part, by prolonging the influence of dopamine on target neurons in this 'reward' system (55,56). VTA DA neuron responses appear to be necessary to facilitate formation of associations between stimuli that predict reward and behavioral responses that obtain reward (57). Thus, stimulation of dopaminergic terminals in the meso-limbic-frontal systems appear to constitute the substrate for a most potent reward/reinforcing system.

Clinical, neuroimaging and neuropsychologic studies all suggest dysfunction of this circuit in depression. Reduced CSF levels of HVA have been documented in significant proportions of depressed subjects (58,59), while anti-depressant medications may increase HVA levels. Anhedonia in particular appears to be related to low dopamine. D1 receptor agonists may reduce the reinforcement value of reward seeking behavior while D2 receptor agonists tend to have the opposite effect (increase reinforcement value). Thus, anhedonia in depression may be due to increased D1 receptor activity and/or decreased D2 activity (59).

Frontal impairment in depression

Major reviews of neuropsychologic effects of depression have repeatedly pointed to impairment of executive cognitive functions (60) and poor performance on tests that are classically thought to tap frontal lobe functions (61). In addition, a number of recent imaging studies have demonstrated reduced blood flow and cerebral metabolisms in frontal lobes of individuals who are depressed (62,63).

Personality rigidity in depression

Thinking and personality styles of depressed individuals have been characterized as inflexible, stereotyped, obsessional and perseverative (64).

Dreams in depression

Dreams of depressed patients are vivid and unpleasant. Cartwright et al (65) studied REM sleep and dreams of persons who were and were not depressed while undergoing divorce. Dreams of depressed people were vivid and evidenced increased "dream masochism" (the dreamer is deprived, attacked, excluded or fails). A follow-up study showed that early onset REM was correlated with the number of unpleasant dreams reported by depressed people. Regression analysis revealed that 54% of the variance in level of depression (as measured by the BDI) could be accounted for by number of unpleasant dreams and REM density of the first REM period.

Sleep in depression

Hundreds of polysomnographic and other sleep studies have now been performed on patients with depression. Reviews can be found in (66). The primary sleep changes in depression include sleep fragmentation or reduced sleep continuity, reduced slow wave sleep, reduced REM sleep onset latency, increased REM density, prolongation of the first REM episode and SOREM (66).

Hypothesis

We have shown that conditions such as depression, narcolepsy, REM behavior disorder and PD, are characterized by variable degrees of dopaminergic dysfunction,which is manifested by sleepiness, inappropriate intrusion of sleep onset REM (SOREM), increase REM% and REM density, and reduced REM latency. In addition, these four disorders share a striking set of mental changes including increased reports of vivid and unpleasant dreaming, high negative affect, frontal impairment and rigid or perseverative personality and thinking styles (see Tables 1-2).

Table 1. Polysomnographic Sleep Findings in target disorders.

	EDS?	REM%	REM density	REM latency	Slow-wave sleep %	SOREM?
Depression	?	↑	↑	↓	↓	yes
Narcolepsy	↑	↑	↑	↓	↓	yes
PD (subtype)	↑	↑	↑	↓	↓	yes
RBD	?	↑	↑	↓	↑	?

Arrows indicate consensus findings from a majority of studies and indicate direction of change relative to healthy control subjects. ↑=increase; ↓= decrease; →=no change; see text for references.

Table 2. Clinical findings in dopaminergic syndromes of sleep.

	personality	Vivid unpleasant dreams	Flat to unpleasant affect	Disinhibition of REM atonia	Mesocortical dopaminergic dysfunction	Frontal lobe impairment
Depression	Ruminative, perseverative	↑ "mascochistic" dream content (dreamer attacked or damaged)	↑	?	yes	yes
Narcolepsy	?	↑ (dreamer attacked and threatened)	↑	No (rather there is inappropriate increase in sleep paralysis)	some	Frontal and temporal
PD	Somewhat rigid and perseverative	↑	↑	?	yes	yes
RBD	?	↑ (dreamer under attack or threatened)	↑	↑	yes	yes

Arrows indicate consensus findings from a majority of studies as reviewed in the text and indicate direction of change relative to healthy control subjects. ↑=increase; ↓= decrease; →=no change.

As mentioned above we hypothesize that the four disorders reviewed, (PD, RBD, narcolepsy and depression) are all characterized by a generalized disinhibition of REM physiology and that this REM physiology includes an over-inhibited prefrontal cortex and a disinhibited amygdala. That is why each disorder manifests enhanced REM values (REM%, REM density, latency to REM, vivid dreams and SOREM etc), excessive daytime sleepiness, de-activated or impaired prefrontal functions and negative affect.

All four disorders evidence clinically significant dopaminergic dysfunction. We hypothesize that the disinhibition of REM physiology is due primarily to dopaminergic dysfunction, specifically the removal of dopaminergic inhibition on amygdalar sites. The disinhibited amygdala yields the affective and personality changes associated with the 4 disorders as well as the unpleasant dreams.

What is the evidence for these claims? We have reviewed the imaging evidence for the high activation levels of the amygdala during REM. More recently a number of studies have demonstrated regulatory functions of the amygdala with respect to REM. The amygdala has reciprocal connections with pontine regions involved in the control of REM sleep (67). Electrical stimulation of the central nucleus of the amygdala increases PGO wave frequency (68) and other signs of phasic REM (REM bursts). Carbachol injection within the same nucleus increases REM sleep duration and other

REM indices (68). Serotonin injection causes a rapid sleep change from SWS to REM (69). In sum activation of the amygdala yields activation of signs of REM. Morrison et al (67) review several lines of evidence which point to an important initiatory and regulatory role of the amygdala in REM.

Amygdaloid nuclei receive strong inhibitory dopaminergic input from the ventral tegmental area and the dorsal pars compacta of the substantia nigra (70). Within the amygdala dopaminergic fibers are most numerous in the central, basal and lateral nuclei-the primary regulatory regions (71). There are also connections from the amygdala to the ventral striatum which preferentially terminate in the nucleus accumbens (72).

Evidence from many different laboratories and a variety of animal species indicates that the amygdala specializes in processing of fear, anxiety and attention (see 73, for review of animal studies). Electrical stimulation of the amygdala elicits a pattern of behaviors that look like intense fear, aversion and attention. Lesions of the amygdala block innate or conditioned fear and aversion as well as various measures of attention. N-methyl-D-aspartate (NMDA) receptors in the amygdala are important in the acquisition of learned fear responses. The peptide corticotropin-releasing hormone acts on the amygdala to orchestrate fear and aversive states within the organism.

A lowering of the dopaminergic input to the amygdala from the ventral tegmental region will lead to heightened activation levels of the amygdala and thus the release of REM physiology along with signs of heightened amygdalar functioning such as creation of a generalized aversive state, and dreams of being under threat. The lowered dopaminergic tone also makes the individual more vulnerable to prefrontal lobe dysfunction given that the prefrontal cortex is innervated by mesocortical dopaminergic afferents (as reviewed above). The vulnerability to prefrontal impairment, in turn, promotes a restrictive and rigid personality style along with an inability to experience pleasure (anhedonia). In sum, the reduction in brain dopamine levels at the level of the amygdala leads to a disinhibition of REM and both the overall brain dopamine reduction and the disinhibition of REM yields prefrontal impairment. The individual is subjected to recurrent unpleasant dream-like episodes but lacks full ability to critically reflect on these dysphoric and dream-like experiences.

If these sets of co-occurring sleep and clinical symptoms are confirmed to be due to amygdalar and REM disinhibition, then REM suppression should effectively treat the symptoms, including the frontal dysfunction. This is a counter-intuitive prediction (deprivation of a physiologic process leads to better brain function) of our hypothesis that can be easily tested. Overnight REM deprivation, for example, should yield improvement on tests that tap frontal functions. Administration of anti-depressants should also help but degree of cognitive improvement may be blunted due to cognitive side–effects of these drugs. Both frontal function and affect should improve with degree of REM normalization (reduction of REM%, density, SOREMs etc).

Both clinical data and the recent series of neuroimaging experiments of REM sleep brain activation patterns suggests that prefrontal impairment should be considered an integral part of REM sleep physiology (just as REMs or desynchronized EEG patterns are). Thus, every manipulation done on REM will also have consequences for prefrontal function and vice versa. REM-related sleep disorders and parasomnias might be better understood if we considered these clinical phenomena in the light of dopaminergic and prefrontal impairment.

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