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INTRODUCTION

The fields of neuropharmacology and psychopharmacology are known to be highly connected, despite our severe lack of knowledge in these fields. One of the many overlaps between the two fields is sleep, which itself entails many mechanisms and events which are, as of yet, unexplainable. From the perspective of either field, one of the most mysterious events occurring during sleep is dreaming. From the cause of dreams to their content, little is known about them or their more sinister subclassification: nightmares. In this field of disturbed dreaming, neuropharmacology makes a large intrusion into the organized theory of psychology. It has been shown via drug studies that some drugs can cause disturbed dreaming as a side effect of their neuropharmaceutical action or as a backlash of withdrawal (Pagel, 2010a, 2010b). Additionally, it has been shown that REM sleep is linked to dream production (Nofzinger, 1997). These windows into the dream world leads to the suggestion that part of the mechanism for causing dreams is disturbed by certain drugs resulting in hyper-bizarre psychotic dreaming. Perhaps, the specific mechanism that tries to fit the nonsensical stream of neurological data to with the brain's compilation of expected physical action and reaction has been faulted by the drug, thereby producing such psychotic dreaming known as nightmares.

Link between Drugs and Dreaming

Pharmacological disturbances of dreaming are a rare but proven phenomenon. Disturbances have been reported by many psychiatric drugs, as well as by the antihistamine Chlorpheniramine, nicotine and others (Pagel, 2010a, 2010b). Barbiturates and alcohol, on the other hand, cause disturbed dreaming upon withdrawal of administration (Barrett and McNamara, 2007c). Drugs with neurological pharmacodynamics are most likely to cause disturbed dreaming (Pagel, 2010a, 2010b). In one extreme case, Chantix, a drug designed to help smokers quit, caused the death of one of its users (Westfall). Patients using Chantix have described dreams which are both vivid and hyper-bizarre. Clearly, there is some connection between sleep, dreaming and drugs.

Proposed Mechanism for Onset of sleep

Sleep begins with and is defined as the loss of consciousness. The brain gradually reduces its level of activity through sleep stages one through four, also known as NREM or non-REM sleep. Instead of remaining deactivated until awakening, the brain goes into the fifth stage of sleep known as REM sleep for its characteristic Rapid Eye Movement. This statement is a gross understatement of the complicated neurological and biochemical processes which occur during the transition into REM sleep.

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While awake and asleep, cells perform metabolism. They derive energy through the complex processes of glycolysis and the Kreb's cycle which convert one molecule of glucose to six of carbon dioxide and six of water (Merdian, 2009).

$$C6H1206 \quad \rightarrow \quad 6\,CO2 \quad + \quad 6\,H20 \quad + \quad 38\,ATP$$

The energy is transferred in the bond of a third phosphate group in the molecule adenosine triphosphate (ATP). The bond is broken to release energy which is used to drive many intracellular reactions via the following reaction (Merdian, 2009):

$$ATP \quad \rightarrow \quad ADP \quad + \quad Pi \quad + \quad Energy$$

Adenosine triphosphate is converted to adenosine diphosphate (ADP) and an inorganic phosphate group (Pi). The process can be repeated, converting the adenosine diphosphate to adenosine monophosphate (AMP) with an additional inorganic phosphate group.

$$ADP \quad \rightarrow \quad AMP \quad + \quad Pi \quad + \quad Energy$$

This second process is not naturally desired but can be forced by chemicals like caffeine (Zhang, 2009). Since while awake the body produces more metabolites than it can cart away, some of these metabolites build up. The increased concentrations of ADP and AMP cause the cell to slow its own metabolism to give itself time to lower the concentration of these metabolites and regenerate the ATP necessary to drive many cellular processes (Roth and Schwartz, 2008).

Another way the body causes the unconsciousness we call sleep is through the buildup of inhibitory neurotransmitters. γ-aminobutyric acid (GABA) and glycine (a derivative of α – ketoglutarate, an intermediate in the Kreb's cycle) are two inhibitory molecules whose effects can be felt throughout the brain. It has been shown that while awake, the concentrations of these chemicals rise, perhaps because they are metabolites of normal cellular processes. Since metabolism rates increase in times of intense use, the implication is that the rate of the production of metabolic byproducts increases. Therefore, in times of intense thought, GABA and glycine have an increased production. Eventually, when levels reach a specific threshold, the inhibitory effects become noticeable; slowing thought and, in high enough concentrations, induce unconsciousness (Watson et. al., 2010; Datta and McLean, 2007).

A similar sequence occurs with the prostaglandin (PG) known as PGD2. This particular chemical is produced via the cyclooxyenase (COX) pathway. For whatever reason this pathway is activated, whether because of an interaction of a glial cell with a neuron or because of another glial function, the levels of PGD2 peak before sleep. Interestingly enough, the same peak forms for two cytokines, Tumor Necrosis Factor A (TNFa) and Interleukin-1 beta (IL-1β). It is not surprising then that these chemicals have been said to be involved in the production of non-REM sleep.

Activation Synthesis Model

REM sleep, on the other hand, has a more subtle cause (Watson et. al., 2010; Datta and McLean, 2007). REM sleep is not triggered by the production of a specific chemical; rather, it is the absence of specific neurotransmitters that trigger the awakening of REM sleep (Pace-Schott et. al. 2003). The REM sleep trigger begins at the beginning of sleep, when the levels for certain neurotransmitters begin to fall from waking levels, causing a change in the chemical balance in the brain. The levels continue to fall throughout the brain's descent through the first four sleep stages. When the levels for serotonin and norepinephrine, neurotransmitters implicated in memory and understanding, fall past a specific inhibitory threshold, neurons in the pontine brainstem reticular formation begin to produce an excitatory neurotransmitter (Hobson and McCarley, 1977). These neurons produce acetylcholine which is involved in memory and attention. The acetylcholine be-

gins to wake up the brain, moving in a wave anteriorly and superiorly. The next brain section to wake up is the rest of the reticular formation, which responds by firing inhibitory signals to all sensory input. All motor neurons also receive hyper-inhibitory messages with the exclusion of those whose axons project into the intrinsic and extrinsic muscle of the eyes (Datta and McLean, 2007).

The process of keeping the brain locked within itself is an active suppression of the brain. The net effect keeps the mind resting and prevents it from becoming conscience while the brain itself becomes active to waking levels. This process moves in step with the wave of activation that sweeps up the brain. During and after the cholinergic self-activation of the brain, the activated neurons send out random signals which the now-activated brain treats as outside input, even though the sensory neurons are inhibited as previously stated. The mind attempts to fit this to a common storyline, but it lacks serotonin and norepinephrine, two chemicals which assist the brain in organizing data in a coherent manner. The resulting fusion with the brain's own signal results in the presentation of the bizarre data stream known as a dream (Hobson, 2010)

AIM Model

The REM sleep model just described is known as the Activation-Synthesis model (Hobson, 2010). It states in short that REM sleep is composed of the activation of the brain, followed by the synthesis of internally generated information. A newer model describes sleep in terms of a three-dimensional cube (Hobson, 2010). See figure 1, slightly modified from their source.
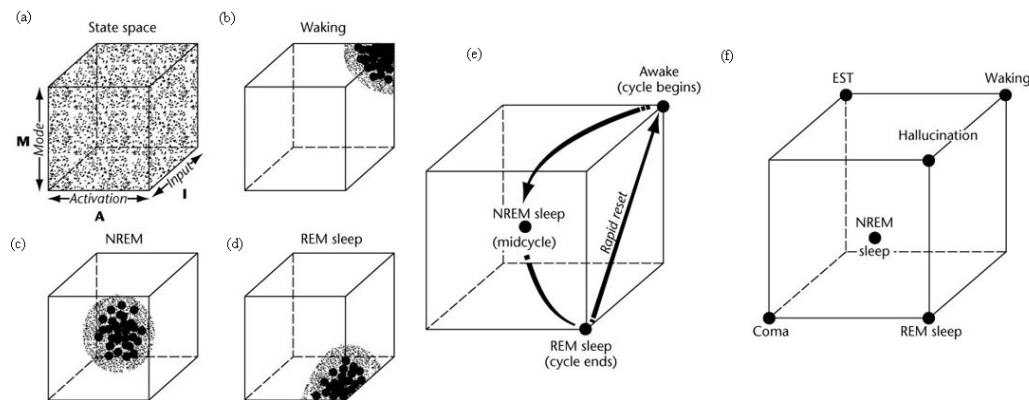

Figure 1: A visual representation of the three aspects of the AIM model when superimposed upon a cube (Hobson, 2010).

The model postulates that there are a theoretically infinite number of possible states for the brain to exist in. The space is a cube whose three dimensions are A (activation), I (input) and M (mode or modulation)(Figure 1a). Activation refers to the level of neuronal activity in comparison to waking levels. Input is indicative of the amount of outside input the brain receives. Modulation describes the likelihood of the events in the dream sequence being written to the person's memory. In theory, this could be determined by the ratio of serotonin and norepinephrine to acetylcholine in the brain, but a safe way to test for it has not been found for humans (Pagel, 2010a).

When all three dimensions are put together, it is found that a healthy waking brain would be found in the upper right corner, farthest away from the observer, with high levels of A,I and M (Figure 1b). A sleeping brain not in REM would be somewhere in middle, representing some A, I and M (Figure 1c). In REM sleep, the brain represents with high A but very low I and M (Figure 1d). A typical sleep cycle is also represented (Figure 1e). Hallucination, a period of high memory

and activation but low input (high A, M and low I), might be illustrated as being in the upper right corner closest to the observer (Figure 1f) (Pagel, 2010a).

Drugs or adverse conditions would force the brain to deviate from the path it normally travels. This could easily be demonstrated on this graph of sleep trajectory, showing how useful this model is (Pagel, 2010a). The one problem with using this model as a sole description of REM sleep is that it cannot describe the reason for the deviation or, for that matter, the trajectory in general. It tells about the state of the brain, not what the brain is doing. It can tell us what state is most likely to have dream occurrence, but it cannot tell us about the dream content. At the moment, it can show what state the brain is in, not why it is there. It is a factual model, not an explanatory model. To explain the effects of drugs on dreaming requires an explanatory model of the causes of dreaming.

RAT Theories

The set of theories that is most easily derived from the REM sleep mechanism explained above is known as the Random Activation Theories or RATs. These refer back the events following the activation of the reticular formation before REM sleep. It is simplest to say that random neuronal firing in the reticular formation activates the corresponding sectors in the brain, which in turn generate the random images that the brain then attempts to filter down and make sense of. Valli and Revonsuo (2009), in their study on sleep, ask two obvious questions. If the brain is randomly activated, they should be nowhere near as organized that they actually are? They should be highly chaotic and completely nonsensical. Secondly, why can sleep researchers point to specific events or characteristics that repeat in multiple people? If the brain really was entirely randomly generated, there should be no clearly identifiable sleep structures.

Attractor Model

A newer model, the Attractor model, posits the polar opposite of the random activation theories. It claims that not only is there a structure to dreaming, but that the structure itself is the hypothesized "fit mechanism" which fits a dream to conventional rules of observed reality. Memories from the waking hours may be delivered as input for the brain via the Continuity Hypothesis, which is a new hypothesis beginning to form around a strong correlation between waking events and their presence in dreams (Valli and Revonsuo, 2009). Input delivered in this manner or derived from some other source finds its way into the brain. The input is recognized by the brain which activates the input's own neuronal network. However, since recognition, even while awake, is based in some degree or another on the context of the recognition, it can require more input to activate a specific network over one very similar to itself. For example, little additional information is needed to recognize the difference between a hamster and a goldfish. Much more information, in other words much more activation is necessary to differentiate between a pair of identical twins. Enough input must be gathered to make the distinction. The recognition, depending on the power of activation, shows up in conscious level of the brain, feeding itself and its own context in the dream sequence. Items in the dream sequence receive activation signals in power levels proportional to the extent and power with which they show up in the dream sequence. Activated items, in turn, activate their contexts which results in the activation of a situation likely to follow the current context. These self-activated contexts show up in the sequence while simultaneously, the events which are unlikely to follow receive deactivation signals. If left to itself, this cycle would, in theory, generate an entire storyline which would make plenty of sense (Barrett and McNamara, 2007a).

Practically speaking though, there are streams of input coming to the brain from a variety of sources. Incoming items, therefore, in their respective contexts may have enough power to tip the sequence away from a previously activated network. Since this network is no longer all that likely because of the tip of balance, it begins receiving a few deactivation signals. The network becomes even less likely because it is being deactivated and in time, loses enough power so that it drops out of the sequence entirely. This answers the question of how to get a semi-sensical dream and defines a system which the brain uses while awake to utilize learned connections (Barrett and McNamara, 2007a).

This system, as any other neurological event, uses specific brain regions to carry out its task. However, it has been demonstrated that during sleep, loss of connection between these regions can occur resulting in the malfunction of the attractor give and take. The normal activations and inhibitions do not occur, resulting in illogical connections (Barrett and McNamara, 2007b). Logically, enough broken connection would result in a bizarre, jerky and radically changing dream sequence.

AND Model

The Attractor model, as just described, has been incorporated in a slightly modified form into a more general dream and nightmare model referred to as the AND (Affect Network Dysfunction) model. This model is unlike the models seen before in that it follows the path of a specific unit. The working unit of the AND model is known as the fear memory. It may be formed via classic Pavlovian conditioning (Knight et al., 2009). This type of conditioning entails the pairing of a stimulus to an otherwise abnormal response. The paradigm example of classical conditioning was performed on a dog. One normal reaction of a dog is to salivate with the presentation of food. The experiment was conducted by ringing a bell every time food was given. The dog salivates, as per its normal reaction. With the constant repetition of this food-presentation, bell-ringing pair, the animal begins to associate the ringing of the bell with the appearance of food. Eventually, when this coincidence has been repeated a sufficient number of times, at the mere ringing of a bell, the dog will begin to salivate because it now associates the bell with food presentation. This is known as classical Pavlovian conditioning (Cohen, 2010).

Fear memories, as stated above, may be formed by a normal conditioning pattern with the pairing of an event or memory with fear. Such memories can also be formed by one sudden traumatic event such as the case with Post Traumatic Stress Disease (PTSD) patients. Levin and Nielson (2007a, 2007b, 2009), in their explanation of the AND model, describe a three step process of events which occur in nightmare formation. The first step, Memory Element Activation, works in a manner very similar to the Attractor model as described above. The single difference between the two models is that, in contrast to the Attractor model, in the AND model, only elements of a scene are activated, but the entire scene will not be activated simultaneously. Typically though, as long as the memories activated are not fear-causing elements, the second phase is not required, and the process is likely to remain at the first phase until fear-causing elements come along (Levin and Nielson 2007a, 2007b, 2009).

When fear-causing elements are activated, the process continues to the next step. This second segment is called Memory Element Recombination. The mechanism by which it occurs is not well understood but functionally it combines the fear-causing elements with other unlikely elements. This recombination is then displayed in the dream sequence. The fear-causing elements still

cause some level of fear, but continued cycles of recombination and reality simulation somehow defuse the fear (Marin and Quirk, 2004).

It is thought that the reason for the presentation of the recombined memory in a simulation so real as to parallel reality is to induce the awake but contained brain to exhibit the same responses it would if it were fully awake. Additionally, it allows the brain to change the memory in the method it was formed, creating a more permanent fix. What Levin and Nielson cite as proof to the mechanism they propose, demonstrates the reality of this concept. A highly similar process is now being used in the treatment of PTSD. Exposure therapy - imagining the scene in which the trauma occurred - seems to works extraordinarily well in the reduction of nightmares in such patients (Levin and Nielson, 2009).

Table 1.

Neurotransmitters and their Effects on the Brain	
Neurotransmitter	**Effects**
ACH (acetylcholine)	Injection in the pontine reticular formation increases REM sleep, while intravenous administration yields the prevention of REM sleep
Dopamine	Increases wakefulness while decreasing NREM sleep
GABA	Increases sleep, but injection into the pontine reticular formation results in overall sleep reduction
Glutamate	Injection into select areas (research does not detail specific areas) gives increased wakefulness and REM sleep while reducing NREM sleep
Norepinephrine	Generally increases wakefulness and inhibits overall sleep. However, bilateral injection yields an increase in REM sleep
Serotonin	Injection of chemicals that synergize with (works together with or increase concentration of) serotonin tend to increase wakefulness and decrease overall sleep.

(Levin and Nielson, 2007b)

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The third step in the AND model, Emotional Expression, is not per se a next step, it is more like a parallel description of one byproduct of the model. The source of the emotion is simply the expression of the attempted fear extinction (Levin and Nielson 2007a, 2007b, 2009). As proof of the fact that the emotional display occurs, a nightmare is progressing. There are differences whether the nightmare is traumatic or not, but the actual differences are irrelevant to this discussion. In either case, fear memories, instead of being peacefully extinguished, can behave in one of a few ways. They can resist extinction, increase the amount of fear causing elements connected to itself or even cause the next nightmarish scene to arise in the dream sequence (Levin and Nielson, 2007b).

Resistance may be caused by a fault in one of a few places. One fault which may occur is that instead of following the normal path and activating scene elements, the brain (seemingly preferentially) activates the entire scene, causing the emotion content to be displayed and simultaneously preventing the extinguishing mechanism from acting. Alternatively, a dream may be activated correctly but during recombination, integrate more fear producing elements, causing a dream more fearful than its predecessor. The brain, effectively, enforces a dream scarier than the one it is trying to extinguish. A similar problem can occur with integrating distress-causing elements as well. When the dream is reactivated, instead of just the non-extinguished fear elements displaying themselves, the distress now inherent in the dream shows up as well. Since the distress may cause other dreams based around the same themes, this could be the beginning of a cyclic series of nightmares (Levin and Nielson, 2007b).

The AND model described above is one of two prerequisites to understand the hypothesis which this paper describes. Attention must now be turned from the overall theoretical understanding of the production of nightmares. The second prerequisite, knowledge of the neuropharmacology of dreaming and nightmare production, is required. ACH (acetylcholine), dopamine, GABA (γ-aminobutyric acid), glutamate, norepinephrine and serotonin are all mimicked by drugs (Levin and Nielson, 2007b). It is for this reason that they will be examined in terms of their effects on the sleep and nightmare production models.

Table 2.

Brain Sectors Discussed in the AMPHAC model	
Brain Sector	**Effect or Purpose**
Amygdala	Required for the acknowledgement and response to fear stimuli.
MPFC (Medial PreFrontal Cortex)	Produces fear extinction, helps in reducing activity in the amygdale
Hippocampus	Controls amygdala and MPFC in the regulation of fear conditioning by regulating fear contexts
ACC (Anterior Cingulate Cortex)	Regulates the severity of distress produced by distress components during emotional expression

(Levin and Nielson, 2007b)

AMPHAC Model

Based on the REM sleep model described above, many necessary logical derivations can be made provided that the basic premise of the AMPHAC model is understood. The AMPHAC (Amygdala, Medial Prefrontal cortex, Hippocampus and Anterior Cingulate cortex) model is an attempted explanation of dreaming and nightmares not from the cognitive theoretical standpoint of the AND theory but from an examination of neuronal structures involved in the process. The exact details will not be discussed; however, a brief summary of the four brain sectors involved is provided in the chart above. (Levin and Nielson, 2007b).

Proposition of Mechanism

Combining both the AMPHAC and AND theories with logical deduction, one can easily understand how an imbalance in neurotransmitter levels may cause disturbed dreaming. It can be said that an excess of a neurotransmitter with an excitatory function may cause the hyperactivation of the amygdala, resulting in an above normal fear expression, while an excess of a neurotransmitter with an inhibitory function may cause disturbed dreaming by overly down-regulating any of the control or regulatory sectors, blocking the ample production of fear extinction. On the other hand, logically, a lack of neurotransmitter has the same effect as an excess of a neurotransmitter of the opposite effect. A classification of the neurotransmitters may now be made.

ACH promotes wakefulness and REM sleep. By promoting activity, ACH demonstrates an excitatory effect. In the pontine reticular formation, where sleep or inactivity is stimulated, an inhibitory role is played. The same logic prevails through the entire derivation. Dopamine increases waking and REM sleep. Since it serves the role of lengthening activation, it can be presumed to play an excitatory role. GABA, in contrast to ACH, generally plays an inhibitory role. In the pontine reticular formation however, it does exert an excitatory force. Glutamate increases wakefulness and REM sleep with the inhibition of NREM sleep demonstrating an excitatory role. Norepinephrine is excitatory, inhibiting sleep and increasing wakefulness. In the case of bilateral injection, norepinephrine increases REM sleep, fulfilling an exhibitory role. Serotonin is unusual as it increases wakefulness and decreases sleep. It could most likely be defined as excitatory.

Combining the nightmare model and the basic knowledge of neurotransmitters, a very logical conclusion arises. It is common knowledge that drugs affect neurotransmitter uptake, breakdown and concentration. For instance, L-dopa, a drug used in the treatment of symptoms for patients with Parkinson's disease is converted to dopamine (MedicineNet.com, 2004), Motrin prevents enzymes from working (Cerner Multin Inc, 2009b) and Klonopin increases the effects of GABA (Cerner Multin Inc, 2009a). It therefore stands to reason that drugs cause nightmares by effecting the neurotransmitter concentrations. The imbalance disturbs the nightmare model, inducing fear-filled dreams which we call nightmares.

This stands to explain why most drugs reported to cause nightmares are psychiatric drugs, for they affect the brain directly. Additionally, it is also understood why specific people report seeing nightmares. The normal pharmaceutically significant idiosyncratic effects of drugs (in other words the normal uncertainties of drug use) show their hand. Some people may not have such an interaction with the drug, while others may have too low of an M value (as per the AIM model as described above). There are many uncertainties with using drugs. Each one may contribute towards experiencing or not experiencing a drug-induced nightmare.

This hypothesis also serves to explain the post treatment nightmares. Drug tolerance, via the normal drug pharmacology, imitates the effects of neurotransmitters, producing the same re-

sults as an imbalance. The same idiosyncratic uncertainties which occur during drug treatment occur again. However, as the time since the last drug application increases, the neurons lose the tolerance, reducing the tolerance-caused imbalance. This would imply that as the time lengthens, the drug-induced nightmares would occur less frequently or with less fear experienced when a nightmare does come.

As implied in the paragraph above, this proposal should reveal itself to testing. Although dream and nightmare testing is fraught with faults as the patients themselves may color and disturb the actual events, the test would not involve specific details which could be susceptible to confusion. Such a test would involve asking volunteers to record nightmare occurrences following the termination of drug application. A high occurrence asymptotically approaching the normal nightmare levels would indicate that indeed, post treatment drug nightmares are being caused by the reducing tolerance. The implication of the statement would be that the same effect would be present during the actual drug application period.

CONCLUSION

The reported effects of Chantix and other drugs lay out rather bluntly that a drug interaction which causes nightmares and disturbed dreaming does exist. Dreaming, as explained above, is produced by the activation and attraction of similar scene contexts. Activated dream contexts rise into the dream sequence being experienced. If the activated scene contexts contain fear-causing elements, the brain subconsciously attempts to disarm these fear elements. At times, this mechanism can be faulty, resulting in a reinforcement of more fearful memory or a memory which incorporates distress elements as well. These distress elements, when remembered by day cause the distress that they activate possibly causing a nightmare cycle. The faulty mechanism could possibly be blamed on an imbalance of neurotransmitters. Such an imbalance could also be formed by the neuropharmaceutical effects of drugs, displaying itself as drug-induced nightmares. Naturally forming drug tolerances imitate the effects of a neurotransmitter imbalance as proposed above. This is the hypothesis presented in this paper and may be the mechanism for the production of drug-induced nightmares. Further testing would be necessary although empirically this hypothesis fits soundly. With this knowledge in hand, doctors and pharmacists can devise drug combinations which would reduce the causes of drug-induced nightmares thus making drug application all that much easier on the patient and hopefully lead to an easier and more complete recovery.

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