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Commentary on **J. Allan Hobson, Edward F. Pace-Schott, & Richard Stickgold (2000). Dreaming and the brain: Toward a cognitive neuroscience of conscious states. BBS 23(6):793–842.**

Abstract of the original article: Sleep researchers in different disciplines disagree about how fully dreaming can be explained in terms of brain physiology. Debate has focused on whether REM sleep dreaming is qualitatively different from nonREM (NREM) sleep and waking. A review of psychophysiological studies shows clear quantitative differences between REM and NREM mentation and between REM and waking mentation. Recent neuroimaging and neurophysiological studies also differentiate REM, NREM and waking in features with phenomenological implications. Both evidence and theory suggest that there are isomorphisms between the phenomenology and the physiology of dreams. We present a three-dimensional model with specific examples from normally and abnormally changing conscious states.

Drug induced alterations in dreaming: An exploration of the dream data terrain outside activation-synthesis

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Abstract: Two meta-analyses of pharmacological research are presented, demonstrating that psychoactive drugs have consistent effects on EEG and sleep outside of their effects on REM sleep, and demonstrating that drugs other than those affecting sleep neurotransmitter systems and REM sleep can also alter reported nightmare occurrence. These data suggest that the neurobiology data terrain outside activation-synthesis may include sleep and dream electrophysiology, cognitive reports of dreaming, effects of alterations in consciousness on dreaming, immunology and host defense, and clinical therapies for sleep disorders.

The most accepted approach to addressing the obvious complexity of known components of central nervous system (CNS) electrophysiology and neurochemistry is to approach analysis of the system deductively, using selected data from many different areas to support a theoretical construct. Unfortunately, if this approach is utilized to present a purportedly broad-based review for prospective theorists in the field, data that are inconsistent or noncontributory to that theoretical construct (an amended activation-synthesis hypothesis) are excluded and ignored. This approach attempts to guarantee that future researchers and theorists in sleep and dreaming will work within the constraints of that model – a model currently requiring extensive restructuring and remodeling to encompass the experimental data of its supporters (see Nielsen 2003; Hobson et al. 2003). This commentary presents pharmacological data from two of these excluded areas: (i) psychoactive drug alteration of sleep stages and background EEG frequencies inclusive of alterations in REM sleep (REMS), and

Table 1 (Pagel). *Psychoactive drug effects on sleep and EEG frequencies*

Medication Class	EEG Frequency Effects	Sleep Stage Effects
Amphetamines	Increased – beta: Decreased – theta, Delta	Increased sleep latency: Decreased deep sleep
Benzodiazepines	Changes in delta amplitude	Decreased REMS REMS rebound on withdrawal Increased stages 1 & 2
Ethanol	Diffuse slowing	Decreased REMs, sleep latency, REMs rebound on withdrawal
Lithium	Episodic slowing	Increased stage 4
Opiates	Increased delta: Decreased alpha	Increased stage 4
Pheothiazines	Increased theta: Decreased alpha, sigma	(+/−)
Gamma hydroxy butyrate	Increased delta	Decreased stage 1 Increased stages 3 & 4
L-dopa	(0)	Decreased REMS Increased stage 1, sleep latency

Anti-Depressant Class	Drug		
Tricyclic	Trimipramine Nortriptyline Doxepin Amoxapine Amitryptyline Imipramine Amoxapine Protriptyline	Increased beta Decreased delta	Increased REMS latency Decreased REMS (++), sws latency Deep sleep, sleep latency
Non-tricyclic sedating	Desimprinine Maprotiline Mirtazapine	Increased-beta	Increased REMS latency Decreased -sws latency, REMS (++), sleep latency
Maoi	Phenelzine Tranylcypromine	(0)	Increased stage 4 Decreased REMS latency, REMS (+++)
Ssri	Fluoxetine Paroxetine Sertraline Fluvoxamine Citalopram hbr	Increased alpha and eog activity stage 1,	Increased REMS latency, sleep latency, stage 1 Decreased REMS
Ssri + tricyclic	Venlafaxine	(0)	Increased REMS latency Decreased sleep latency, REMS
Da-na-ssri	Bupropion	(0)	Increased REMS latency, sleep latency
Non-tricyclic Non-ssri	Nefazodone	(0)	Increased REMS Decreased sleep latency
5ht 1a agonist	Buspirone	(0)	Increased REMS latency: Decreased REMS

Note: (0) = not studied; (++) = higher levels of effect; (+/−) = reports of both negative and positive effects: delta (1.0–1.5 Hz), theta (7–9 Hz), alpha (8.5–10 Hz), sigma (12–16 Hz), beta (22–27 Hz). (Adapted from Pagel 1993; 1996.)

(ii) medications reported to induce nightmares in clinical trials and case reports. It is hoped that this information will prove useful to both theorists and researchers involved in the study of the neurobiology of the dream state.

Psychoactive drug effects on sleep stages and EEG frequencies. Medications that clinically produce psychoactive effects alter the recording of the electroencephalogram (EEG), the recording of brain electrical potential changes. Specific EEG epiphenomenon (e.g., seizure activity, PGO spikes) are well described, yet the origin of background EEG frequencies, which characterize the EEG particularly during sleep, remain a topic of open debate (Christakos 1986; Elul 1971). In general, drug-induced EEG changes are associated with characteristic behavioral effects (Hermann & Schaerer 1986; Itil 1981). This association has been utilized in developing therapeutic approaches for new medications producing characteristic EEG effects (Mandema et al. 1992). Typically, psychoactive medications alter background EEG frequencies as well as the occurrence, frequency, and latency of the various sleep stages including REM sleep, as charted in Table 1 (Pagel 1993; 1996; Pagel & Helfter 2003). Dream reports can be ob-

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Table 2A (Pagel). *Medications Affecting CNS Neurotransmitter Systems Reported to Induce Nightmares in Clinical Trials and Case Studies*

Affected Neuroreceptor Drug	Patient Reports of Nightmares – Evidence Base Clinical Trials (CT) Case Reports (CR)	Probability Assessment of Drug Effect
ACETYLCHOLINE – Cholinergic Agonists		
Donepezil	CT [3/747 report disordered dreaming]	Possible
Rivastigmine	CT [1/100–1/1000 report disordered dreaming	Possible
Tacrine	CT [1/100–1/1000 (2076) report disordered dreaming	Possible
NOREPINEPHINE – beta blockers		
Atenolol	CT [3/20 patients]	Probable
Betaxolol and carbachol [opth.]	CR [1] – de-challenge	Possible
Bisopropol	CT [3/68 patients] : CR [1] – de-challenge	Probable
Labetalol	CT [5/175 patients]	Probable
Oxprenolol	CT [11/130 patients]	Probable
Propranolol	CT [8/107 patients]	Probable
– Norepinephine effecting agents		
Atomoxetine	CT [4/269 abnormal dreams compared to 3/263 placebo group]	Possible
Deserpidine	CT – disordered dreaming listed as side effect	Possible
Guanethidine	CT [4/48 patients] Probable	
Methyl dopa	CT [infrequent reports of nightmares]	Possible
Tramadol	CR [1] – de-challenge Possible	
SEROTONIN – SSRI		
Fluoxetine	CT [1–5% – greater frequency in OCD and bulemic trials: CR [4] – de & re-challenge	Probable
Escitalopram oxylate	CT [Abnormal dreaming – 1 % 999 patients]	Probable
Nefazodone	CT [3% (372) versus 2% control] Probable	
Paroxetine	CT [4% (392) versus 1% control] Significant	
Sertraline CT [1/100–1/1000] Possible		
Agents effecting serotonin & norepinephrine		
Protriptyline	CT – nightmares listed as side effect	Possible
Trazadone	CR [reports abnormal dreams] Doubtful	
Risperidone	CT [1% increased dream activity – 2607 patients]	Probable
Venlafaxine	CT [4% (1033) versus 3% control] Probable	
DOPAMINE – agonists		
Amantadine	CT [5% report abnormal dreams]: CR [1]	Probable+
Bupropion	CR [1] – de-challenge Possible	
Cabergoline	CT [1/188 patients]: CR [1] – de-challenge	Possible
Levodopa	CT [2/9 patients]	Probable
Pergolide	CT [2.7% (189) report abnormal dreams versus 4.5% placebo]	Doubtful
Ropinirole	CT [3% (208) report abnormal dreaming versus 2% placebo]	Probable
Selegiline	CT [2/49 reporting vivid dreams]	Probable
– Amphetamine-like agents		
Bethanidine	CT [2/44 patients]	Probable
Fenfluramine	CT [7/28 patients]: CR [1] de & re-challenge	Probable
Phenmetrazine	CT [3/81 patients]	Probable
GABA		
Flunitrazepam	CT [1/127 patients]	Possible
Gabapentin	CT [1/100–1/1000 (2074) report abnormal dreams]	Possible
Gaba hydroxy buterate	CT [nightmares >1% 473 patients]	Probable
Nitrazepam	CR [2]	Possible
Triazolam	CT [7/21 patients]	Probable
Tiagabine	CT [3/2531 patients]	Possible
Zopiclone	CT [3 – 5/83 patients]	Probable

KEY: (+)Listed under multiple drug classification

tained on awakening from all stages of sleep. Potential electrophysiological correlates for dreaming clearly exist outside adapted versions of the activation-synthesis hypothesis based on the postulate that REM sleep equals dreaming.

Drug-induced nightmares. The effects of medications on dreaming are not generally included in clinical trials and case reports, except as reports of nightmares – vivid and terrifying mental experiences occurring during sleep. Recent pharmacological

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Table 2B (Pagel). *Other Drug Classes Reported to Induce Nightmares in Recent Case Reports and Clinical Trials*

Drug Class Drug	Patient Reports of Nightmares Clinical Trials (CT) Case Reports (CR) – Evidence Base	Probability Assessment of Drug Effect
ANESTHETICS		
Ketamine	CR [1]	Possible*
midazolam	CT [<1%]	Possible*
ANTI-INFECTIVES & IMMUNO-SUPRESSANTS		
amantadine	CT [5% reporting abnormal dreams]: CR [1]	Probable+*^
ciprofloxacin	CR [1] – de-challenge	Possible^
erythromycin	CR [2] – de-challenge	Possible
Fleroxacin	CT [7/84 patients]	Probable^
ganciclovir	CR [1] – de & re-challenge	Probable*^
gusperimus	CT [13/36 patient]	Probable
ANTI-EPILEPTICS		
Ethosuximide	CT [reports of night terrors]	Possible*
Lamotrigine	CT [1/100–1/1000 report abnormal dreams]	Possible*^
valproic acid	CR [1] – de-challenge	Possible*^
Zonisamide	CT [1/100–1/1000 report abnormal dreams]	Possible^
ANTI-PSYCHOTICS		
chlorpromazine	CR [1] – de-challenge	Possible*^
Clozapine	CT [4%]	Probable*^
Thiothixene	CR [3] – de-challenge	Possible*^
ANTI-HISTAMINE		
chlorpheniramine	CT [4/80 patients]	Probable*^
ACE INHIBITORS		
Captopril	CR [1]	Possible*^
Enalapril	CT [.5–1% abnormal dreaming – 2987 patients]	Probable*^
Losartin potassium	CT [>1% dream abnormality – 858 patients]	Probable*^
Quinapril	CT	Probable*^
OTHER AGENTS – NO PROPOSED MECHINISM		
buprenorphrine	CR [1] – de-challenge	Possible
Digoxin	CR [1] – de & re-challenge	Probable
Naproxen	CR [1] – de & re-challenge	Probable*^
Verapamil	CR [1] – de & re-challenge	Probable^

KEY – (+)Agents listed in multiple classes: (*) Agents inducing daytime sedation as a side effect to use:
(^) Agents inducing insomnia as a side effect to use.

A qualitative probability assessment is used to determine the probability that nightmares are drug induced by these agents based on the Naranjo et al. (1981) algorithm ranging from definite – probable – possible – doubtful [57]. The association between each medication and described side effect (nightmares or alterations in dreaming) in clinical trial reports is rated from significant ($p < .01$), to probable (reported by >1% of population relative to controls), to possible (less than 1% difference compared to control orin studies without controls) to doubtful (minimal evidence for side-effect/drug association). This study does not include data concerning drugs for which no effects on dreaming or nightmares are reported, because of concerns as to the significance of negative reports. Older (before 1990) clinical trial data is not included since clinical trial reports for agents known to induce nightmares per case reports (examples: tricylic antidepressants, amphetamines, and benzodiazepines often did not include reports of nightmares or disturbed dreaming. [This assessment approach is used for drugs in Tables 2A and 2B.]

literature describing drug effects on dreaming consists primarily of reports of nightmares as a side effect of medication or as a symptom of medication withdrawal (Table 2A).

Data from human clinical trials and case reports (Table 2) indicates that reports of altered dreaming and nightmares are consistently associated with agents exerting pharmacological effects on dopamine, serotonin, and norepinephrine. Beta-blockers are the agents most likely to result in patient complaints of nightmares. The strongest clinical evidence found in this meta-analysis for the association of a drug with nightmare induction is for the SSRI paroxetine (Pagel & Helfter 2003). Most agents affecting dopaminergic neuroreceptors have been reported in clinical trials to induce nightmares in some patients. Medications altering these neurotransmitter systems are likely to induce reports of nightmares and disordered dreaming for patients taking those medications. These neurotransmitters may function in a reciprocal interaction involving a wide spectrum of neurotransmitters interacting in an intricate modulation of the cardinal sleep stages – REM and non-REM sleep (Pace-Schott 2003).

Clinical trial and case report data are less clear in their support

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for the association of GABA and acetylcholine receptors with dreaming, and nightmare alteration with the reported nightmare/drug association rated as possible (rather than probable or significant) for the majority of drugs evaluated. The finding that different types of drugs known to affect the GABA receptor (agonists, modulators, and reuptake inhibitors) can result in patient complaints of nightmares and abnormal dreaming is suggestive that GABA may be a modulator of the neuronal populations involved in dreaming as proposed by Pace-Schott (2003) (Mallick 2001, Xi & Morales 1999). Agents that increase acetylcholine levels such as the acetylcholineserase inhibitors routinely utilized in patients with Alzheimer's disease would be expected based on animal models to increase REM sleep. The side effect of nightmares and/or altered dreaming secondary to the use of these agents is rarely reported (only 3 of 747 patients using donepizil in clinical trials reported changes in dreaming) (Pagel; in press).

Agents that alter an individual's conscious relationship to the external environment may alter reported dream and nightmare occurrence. Induction anesthetics induce an electrophysiological state that is not clearly sleep, as well as patient complaints of abnormal dreaming. Some of the agents reported to cause altered dreaming are: profolol, the barbituate thiopental, ketamine, and the opiate tramadol (Krissel et al. 1994; Marsh et al. 1992; Oxorn et al. 1997). The CNS side effects of daytime somnolence and/or insomnia may be an indicator for medications likely to induce disordered dreaming and nightmares (Table 2B).

Infectious diseases are sometimes associated with the complaint of nightmares. Sleep loss affects host defense and cellular immune function (Benca & Quintas 1997; Hall et al. 1998; Moldofsky 1995). These studies suggest that a clear, but currently poorly defined relationship may exist between host defense and infectious disease, and sleep/dreaming. Several of the agents reported in case reports and clinical studies to induce nightmares (fleroxacin, erythromycin, ciprofoxin, and ganciclovir) may induce nightmares by affecting sleep-related immunological response to infectious disease. This meta-analysis indicates that the neuropharmachological agents reported to induce nightmares in human studies differ from the agents modulating REM sleep in animal models. Drugs affecting acetylcholine, the primary modulator of REM sleep in animal models, are not reported to induce nightmares in clinical trials. Pharmachological agents affecting the negative neuro-modulators of REM sleep – norepinephrine and serotonin – are those most likely to induce nightmares in human subjects. Other medications appear to alter dreaming by affecting an individual's conscious relationship to the environment or to host defense and immunology.

Conclusion. The neurobiology of the human CNS is the most complex one yet addressed by theorists and researchers. Activation-synthesis as a theory of sleep and dreaming has been tremendously useful to the field, and its basic tenet – that the physiological events occurring in the brain during dreaming are associated with dreaming – remains absolutely valid. Theories are useful if they can be adapted or altered to achieve consistency with new data. Theories can be harmful if used to misrepresent the extent of knowledge or to limit the breath of study.

In this commentary, two meta-analyses of pharmacological research have been presented. The data on electrophysiological psychoactive drug EEG effects demonstrates that psychoactive drugs have consistent effects on EEG and sleep outside of their effects on REM sleep. The data on drug-induced nightmares demonstrates a complex system characterized poorly by neurotransmitter models limited to the modulation of one or several neurotransmitters at discrete CNS sites. This is experimental data obtained from humans in which the cognitive process of dreaming is addressed, rather than the associated state of REM sleep.

These data suggest that the neurobiology data terrain outside activation-synthesis may include sleep and dream electrophysiology, cognitive reports of dreaming, effects of alterations in consciousness on dreaming, immunology and host defense, and clinical therapies for sleep disorders.[1] Dream neurobiology is a field in which experimental data can be addressed inductively, a field open to new theories developed to explain data lying outside the structured paradigms of current theory. A philosophy that remains cogent for the CNS is that new research almost always shows this system to be more complex than previously thought.

Editors' Note: There is no Authors' Response to this commentary.

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Commentary on **Esther Thelen, Gregor Schöner, Christian Scheier, & Linda B. Smith (2001). The dynamics of embodiment: A field theory of infant perseverative reaching. BBS 24(1):1–86.**

Abstract of the original article: The overall goal of this target article is to demonstrate a mechanism for an embodied cognition. The particular vehicle is a much-studied, but still widely debated phenomenon seen in 7–12-month-old-infants. In Piaget's classic "A-not-B error," infants who have successfully uncovered a toy at location "A" continue to reach to that location even after they watch the toy hidden in a nearby location "B." Here, we question the traditional explanations of the error as an indicator of infants' concepts of objects or other static mental structures. Instead, we demonstrate that the A-not-B error and its previously puzzling contextual variations can be understood by the coupled dynamics of the ordinary processes of goal-directed actions: looking, planning, reaching, and remembering. We offer a formal dynamic theory and model based on cognitive embodiment that both simulates the known A-not-B effects and offers novel predictions that match new experimental results. The demonstration supports an embodied view by casting the mental events involved in perception, planning, deciding, and remembering in the same analogic dynamic language as that used to describe bodily movement, so that they may be continuously meshed. We maintain that this mesh is a pre-eminently cognitive act of "knowing" not only in infancy but also in everyday activities throughout the life span.

Is the concept of object still a suitable notion?

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Abstract: The model and framework presented in the target article by Thelen et al. is an interesting effort that is able to account for the contextual variability in the A-not-B performance of 7–12-month-old infants. In the process of developing their framework, the authors discounted the concept of object as a useful notion in discussions of A-not-B performance. For Piaget and other developmentalists, the main evidence for the acquisition of the concept of object was the disappearance of A-not-B errors after age 12 months. However, the Thelen et al. model makes predictions of A-not-B outcomes over a much shorter, trial-to-trial time scale. Given the mismatch in the time scales over which analyses in the two approaches have been based, we wonder if the challenge to the concept of object has been misplaced.

Thelen et al. (2001) used the inconsistency of the results in the A-not-B paradigm, and the success of their model, to bring into question the utility of Piaget's (1954) *concept of object* as the predominant explanation for A-not-B performance. Nevertheless, we wonder whether the success of their model justifies rejection of the concept of object as an explanation for A-not-B performance. In addition to exploring this issue, we point out that although Piaget did not present a quantitative account of his empirical work, his framework can, at least in part, be considered dynamical. In other words, in many ways Piaget's outlook as a scientist of the developing mind may not differ as much from the viewpoint advocated by Thelen et al. as the authors portrayed.

What is the utility of the "concept of object"? The "concept of object" is generally defined as an awareness that an object continues to exist even when the actor no longer interacts with it, and when sensory input regarding the object has been removed. The A-not-B experimental procedure has been the predominant method used to study the concept of object and to track its changes with age. Briefly, the procedure requires participants to reach for a hidden object at a location A, and then to make a subsequent reach to an object hidden at a cued location B. Continued reaching at location A, committing the A-not-B error, has been taken as evidence of incomplete acquisition of the concept of object, whereas the acquisition of the concept of object has been reflected by the generation of cued reaches to location B. Thus, the level of A-not-B error provides a simple, parsimonious operationalization of the concept of object. Developmentalists, Piaget in particular, were interested in examining performance on this task because it reflected development toward adaptive, adult capabilities. In particular, a transition from the presence of A-not-B error to its disappearance became a landmark for identifying a critical transition in development. Namely, this transition marked the end of Piaget's stage IV to the beginning of stage V, during his sensorimotor period of development.

Between the ages of 7 and 12 months (Piaget's stage IV), variation in task parameters are related to variation in the degree of A-not-B error outcomes, but clearly there is evidence of the A-not-B error. Moreover, the A-not-B error disappears after about age 12 months (Piaget's stage V). Therefore, when considered over the course of development, and taking the literature as a whole, the basic effect and developmental trend *are* reproducible. Early in the Thelen et al. target article (sect. 2), the authors were apparently in agreement with this statement. However, in focusing on the between-experiment variability in A-not-B outcomes during the ages 7–12 months period, the authors (viz., their model) seem to have lost sight of the fact that the trend continues beyond that age, and in fact changes after about age 12 months. It is the appearance of this bifurcation in the developmental function, and not the pre-12-months-of-age between-experiment variability, that would seem to be the main evidence supporting the appearance of the concept of object. Therefore, if the concept of object is to be challenged from an analysis of the extant empirical data, then the authors have based their challenge on what seems to be a wrong view of the data.

In particular, the Thelen et al. model (e.g., Figs. 15–20 in the target article) accounts for how changes in task parameters and internal processes (e.g., memory) act on a short-term, trial-to-trial basis in the prediction of A-not-B performance. This time scale of analysis is much briefer than the time scale with which Piaget and other developmentalists were concerned. Given such a difference, we wonder if the authors were actually interested in addressing developmental processes regarding A-not-B performance. Perhaps Thelen et al. were more interested in adapting an already ex-

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