(Vazquez & Baghdoyan 2001). Moreover, our laboratory has shown a slight increase of dopamine and a significant decrease of glutamate release in nucleus accumbens during REM sleep when compared to waking (Léna et al. 2004; 2005). Both neurochemical variations, even possibly separated from each other, are known to induce psychotic symptoms in normal subjects (Buffenstein et al. 1999; Grace 1991; Heresco-Levy 2000; MacKay et al. 1982). In addition, both dopamine agonists and glutamate antagonists induce vivid dreaming (Reeves et al. 2001; Solms 2000), reinforcing the proximity of underlying waking and REM sleep hallucination mechanisms. Now, the major neurochemical difference between waking and REM sleep is the silence of noradrenergic and serotonergic neurons in the latter stage (Aston-Jones & Bloom 1981a; Hobson et al. 1975; McGinty et al. 1974; Rasmussen et al. 1984). Our hypothesis is that the decrease of noradrenaline and/or serotonin is probably indirectly at the origin of the entire forebrain neurochemical functional state, which is responsible for the psychotic-like mentation of REM sleep. It is noteworthy that a similar deficit of noradrenaline (Friedman 1999; Linner et al. 2002) and/or serotonin (Silver et al. 2000; Van Hes et al. 2003) has been described in schizophrenia, characterized by a more general so-called glutamate-trimonoamine imbalance (Pralong et al. 2002). Here also, basic neurochemical data and clinical pharmacological results observed in forebrain functioning are in agreement with the PAD model.

The mechanism of possible dream intrusion into waking as an inducing factor of hallucinations (Kelly 1998) as indicated in the PAD model could be also related to a noradrenaline and possibly serotonergic deficit. Indeed, these neurons mainly inhibit cortical neurons (Foote et al. 1975; Frederickson et al. 1971; Krnjevic & Phillis 1963; Nelson et al. 1973; Phillis et al. 1973; Reader et al. 1979; see also, more recently, Araneda & Andrade 1991; Manunta & Edeline 1999), but they increase their signal-to-noise ratio (Aston-Jones & Bloom 1981b; Foote et al. 1975; McCormick 1992), thereby enhancing their performances. Because these monoaminergic neurons are silent during REM sleep, the resulting disinhibition process probably impairs mental functioning. This disinhibition is also reflected in the forebrain by the failure of prepulse inhibition as shown by the N_{100} evoked component (Kisley et al. 2003). At outcome of REM sleep, noradrenergic neurons (at least) begin to fire again a few seconds prior to awakening (Aston-Jones & Bloom 1981a), reestablishing the waking modality of brain functioning and probably favoring more or less rapid dream memory elimination. Freud (1925/1955) called this forgetting of dreams the *mystic writing-pad* process. When this physiological censorship fails, there is "an over-welling of dream into reality," as described by the great French poet Gérard de Nerval (1808–1855) (Marel & Marel 1967) when he drifted into madness. The fact that the waking hallucinations, as recalled in the PAD model, mainly involve unfamiliar images as opposed to memory contents, again suggests a connection with dreaming generating processes, since the dreamer often faces strangers.

It could be possible that the neurobiological support of waking hallucinations carefully analyzed in the PAD model represents an attenuated form of the common electrophysiological, tomographic, and neurochemical background of schizophrenia and REM sleep hallucinatory activity (Gottesmann 2005).

The emergence of proto-objects in complex visual hallucinations

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Abstract: There is little to refute in Collerton et al.'s argument that recurrent complex visual hallucinations involve multiple physiological mechanisms, and the target article's proposed PAD model implicitly incorporates this concept, advancing the field. The novel concept in this model is the intrusion of hallucinatory proto-objects into relatively preserved scenes. The weakness of the model is the lack of physiological detail for this mechanism.

The concept, advanced by Collerton et al. in the target article, that recurrent complex visual hallucinations (RCVH) have a common underlying physiology regardless of the syndrome they occur in is a tantalizing and testable construct. This construction of an integrated and unified conceptual framework for the analysis of RCVH is needed, as morbidity directly relates to their persistence and increasing intensity. As reviewed, many models have been proposed to explain the generation of RCVH, with few of these models proving completely satisfactory. The Perception and Attention Deficit (PAD) model developed by Collerton et al. requires four coexisting features: (1) impaired attentional binding (abnormal lateral frontal activity); (2) poor sensory activation of a correct proto-object (abnormal ventral visual stream activity); (3) relatively intact scene representation (coactivation of frontal cortex and the ventral visual stream system); and (4) bias perception for intrusion of a hallucinatory proto-object (increased temporal versus frontal activity). This PAD model is extremely similar to the new integrative model proposed by Diederich et al. (2005). Diederich and colleagues suggest that poor primary vision, reduced activation of primary visual cortex, aberrant activation of associative visual and frontal cortex, lack of suppression or spontaneous emergence of internally generated imagery through the ponto-geniculo-occipital system, intrusion of rapid-eye-movement dreaming imagery into wakefulness, errative changes of the brainstem filtering capacities through fluctuating vigilance, and medication-related overactivation of mesolimbic systems contribute to recurrent visual hallucinations (Diederich et al. 2005). The argument in both papers that multiple factors are required for the phenomenon is very convincing, as hallucinations do not occur with poor sensory activation and perception or impaired attentional binding alone. The main difference between the models is the dominant concept of the proto-object in PAD.

Of course, a model requires testing to prove its worth. Collerton et al. suggest that the PAD model could be tested pychophysiologically for the coexistence of active hallucinatory versus correct perceptual proto-object images by combining perceptual tasks and visual cortex imaging and contrasting hallucinations with non-hallucinatory periods. However, it is not clear what the physiological predictions would be for firm proof of principle versus falsification. In fact, the major limitation of the PAD model is the lack of sufficient detail for a viable testable common physiological mechanism for the key phenomenon of the proto-object. At this level, the authors admit that the properties of proto-objects are not well defined and therefore hallucinations cannot yet be mapped onto these undefined properties. At present, the PAD model is cohesive for other ancillary aspects of hallucinations, and the authors have physiological suggestions for testing these ancillary predictions from their model. Examples include that recurrent complex visual hallucinations occur with impaired attention and object perception in association with frontal and ventral visual stream dysfunction, and that modification of cholinergic tone will precipitate or diminish the hallucinations, with the corollary that imaging cholinergic dysfunction associates with the phenomenon. Does this give sufficient physiological detail to understand the main phenomenon – the emergence of proto-objects? Not at this

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stage, and still only at a whole organ level, significantly limiting the refinement of treatment options.

Two kinds of "memory images": Experimental models for hallucinations?

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Abstract: Collerton et al. postulate that in a variety of different clinical conditions, hallucinations are derived from object schema lodged in long-term memory. I review two new experiments in which *memory images* can be easily triggered in neurologically intact subjects. These examples of making visible items in memory may provide experimental models for genesis of hallucinations.

Collerton et al. have abstracted from a variety of clinical entities some common traits of hallucinations and have proposed a plausible theoretical framework to account for the circumstances in which these images most often arise. Yet, at the core of their model, the location and physiological nature of the *schematic images* that feed hallucinations remain uncertain.

Are hallucinations akin to the images evoked by electrical stimulation of sites in the temporal lobe (Penfield & Perot 1963)? Or are they derived from more widely distributed networks, including the prefrontal cortex? Discovering how those visual images arise from memory is especially difficult because hallucinations arise unpredictably. Perhaps fMRI or pharmacological analyses of hallucinations would be advanced by studying analogous phenomena in a reliable and safely evoked manner in a laboratory setting. I review here two novel "memory image" phenomena, which might provide useful models for hallucinogenesis.

About 30 years ago I experienced remarkable intrusions of well-formed images at bedtime: the vivid replay of neuron waveforms that I had seen during hours of microelectrode recording earlier that day. Recently, I asked several visual scientists for such anecdotes and netted six recollections similar to my own. Three persons recalled seeing at night sharp images of patterns on computer screens, used earlier that day for psychophysical tests of experimental subjects. One man, driving home in the early morning, nearly swerved his car to avoid colliding with such an apparition. Naturalistic phenomena also appeared. One man, who had spent the afternoon picking avocados, was treated to an array of green blobs at night. Another saw images of swimming fish after a sporting day, and another recalled images of tree branches picked up while helping his tree-surgeon father.

This last individual is now a neuroanatomist and sometimes sees dendritic trees at bedtime. I lately discovered that very similar anecdotes were recounted by Hanawalt (1954), but the phenomenon appears not to have been systematically studied until recently. These recurring images appear similar to the dream intrusions studied by Stickgold et al. (2000) in volunteers who played a video game for several hours and witnessed the same specific images recurring at night. Another experiment form that lab (Merabet et al. 2004) may provide a safe method of increasing receptivity to those recurring images, as the blindfolding of volunteers for only 48 hours led to a high incidence of hypnagogic imagery.

Next, I present data from my own experiments on a rare visual phenomenon as an experimental analogue to the proto-objects postulated by Collerton et al. to be the source of hallucinated forms. About 1% of the academic population may experience *visual persistences* (VPs): vivid positive afterimages of single objects lasting for 15 to 30 seconds after brief fixation and eye closure (Ingle 2005). Although VPs are formed from just-seen objects or drawings and are not derived from long-term memories, new unpublished experiments reveal that certain VPs can reliably trigger *memory images* (MIs). This happened routinely when each of 5 subjects (including myself) formed a VP of an uppercase letter rotated 45 degrees from the vertical. Within 2 or 3 seconds, the VP of the sideways letter rights itself. One does not see the letter rotate, but the upright orientation suddenly replaces the first image. This intrusion from memory of the "canonical" orientation occurs as well with numerals and small faces (photos or schematic drawings).

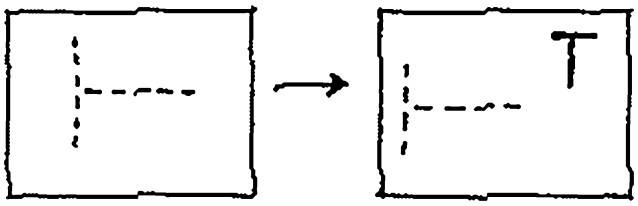


Figure 1 (Ingle). Fixation of a dashed sideward *T* leads to a *visual persistence* (VP) of the unfamiliar pattern. Within 2 or 3 seconds, a *memory image* (MI) of an upright *T* appears on the same index card.

A second example of substitution of an MI for a VP occurs when sideways letters or faces are used to create VPs. After the brief delay, the subject sees two images: the same sideways VP plus the upright MI. Two persons, tested with letters, saw the upright MI overlap with the original VP, whereas three others saw the MI set just to the right of the original VP (Fig. 1). We then found that these MIs are not all simply rotated versions of the VP. First, when the letter (e.g., a sideways *T*) is made of dashed lines, the upright T is seen with solid lines. Second, when the sideways letter is of a less familiar color (purple or yellow-green) the upright letter appears black or grayish. Yet, a familiar ink color (red) is duplicated in the upright MI. These phenomena invite further experiments to determine how much viewing of a given color, line-texture, or font may be necessary for that feature to appear in the MI.

Since the specialization of the fusiform region of temporal cortex for upright faces is now established (Yovel & Kanwisher 2004), I suggest than an analogous specialized representation for upright letters exists for humans (who read regularly) and that this representation readily intrudes upon the VP representation derived from the tilted letter. Although fMRI experiments have found some degree of localization for activations by single letters (e.g., Joseph et al. 2003), our experiments suggest that even better localization might be found by comparing responses of upright to rotated letters. As reliable as letters, numerals, and faces have been in triggering MIs, we have yet to see such effects using tilted or rotated VPs of line drawings of common objects such as fish, cars, bottles, cups, or horses. It seems likely that for these items there are not enough neurons dedicated to the identification of their canonical orientations.

Monoamines in RCVH: Implications from sleep, neurophysiologic, and clinical research

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Abstract: The role of brain monoamines may be important for the neurobiology of the alterations of visual alertness in recurrent complex visual hallucinations (RCVH). This is evidenced by sleep research, neurophysiologic, and clinical data. Hence, the mechanisms of RCVH may not be simply explained by acetylcholine underactivity only.

The novel Perception and Attention Deficit (PAD) model for recurrent complex visual hallucinations (RCVH), proposed by Collerton et al. in the target article, examines a large body of data

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