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Why people see things that are not there: A novel Perception and Attention Deficit model for recurrent complex visual hallucinations

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Abstract: As many as two million people in the United Kingdom repeatedly see people, animals, and objects that have no objective reality. Hallucinations on the border of sleep, dementing illnesses, delirium, eye disease, and schizophrenia account for 90% of these. The remainder have rarer disorders. We review existing models of recurrent complex visual hallucinations (RCVH) in the awake person, including cortical irritation, cortical hyperexcitability and cortical release, top-down activation, misperception, dream intrusion, and interactive models. We provide evidence that these can neither fully account for the phenomenology of RCVH, nor for variations in the frequency of RCVH in different disorders. We propose a novel Perception and Attention Deficit (PAD) model for RCVH. A combination of impaired attentional binding and poor sensory activation of a correct proto-object, in conjunction with a relatively intact scene representation, bias perception to allow the intrusion of a hallucinatory proto-object into a scene perception. Incorporation of this image into a context-specific hallucinatory scene representation accounts for repetitive hallucinations. We suggest that these impairments are underpinned by disturbances in a lateral frontal cortex–ventral visual stream system. We show how the frequency of RCVH in different diseases is related to the coexistence of attentional and visual perceptual impairments; how attentional and perceptual processes can account for their phenomenology; and that diseases and other states with high rates of RCVH have cholinergic dysfunction in both frontal cortex and the ventral visual stream. Several tests of the model are indicated, together with a number of treatment options that it generates.

Keywords: Blindness; Charles Bonnet; cholinergic; cortical release; delirium; dementia; dream intrusion; hallucination; Perception and Attention Deficit (PAD) model; schizophrenia.

1. Introduction

Is this a dagger which I see before me,
The handle toward my hand? Come, let me clutch thee:
I have thee not, and yet I see thee still.
Art thou not, fatal vision, sensible
To feeling as to sight? or art thou but
A dagger of the mind, a false creation,
Proceeding from the heat-oppressed brain?
I see thee yet, in form as palpable
As this which now I draw.
—Macbeth, Act II Scene 1

"I see people who are not there. I see people in the street with clipboards, sometimes it's the same person turning up, little fat chap, looks like Mickey Rooney."
—M.D. (A person with visual hallucinations associated with schizophrenia)

More than one million adults in Britain, while awake, repeatedly see people, animals, or objects that appear real but are not visible to others. Perhaps half as many again have similar experiences on the borders of sleep. Few, though, express their experiences quite so eloquently, or indeed publicly, as Shakespeare's Macbeth. For many, hallucinations are emotionally neutral or even comforting experiences (e.g., Diederich et al. 2000; Grimby 1993; 1998; Paulson 1997; Risser & Powell 1993; Tien 1991). For others, they are distressing and disabling symptoms of major illnesses (e.g., Goetz 1999; O'Reilly & Chamberlaine 1996). A general functional model may aid our understanding of these phenomena and ultimately lead to better help for these latter groups (e.g., Collerton & Dudley 2004).

Single experiences of visual hallucinations are so com-

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mon as to be considered normal. McKellar (1957) reports single hypnagogic hallucinations in 63% of students, and Ohayon (2000) reports that "almost everybody" has experienced at least one hypnopompic or hypnagogic hallucination. In this target article, we will be focusing on those people who have recurrent and potentially pathological hallucinations. Recurrent complex visual hallucinations (RCVH) are uncommon in non-pathological populations, with estimates in the 0.3% range for one or more per month (Ohayon 2000). Increasing frequency is associated with greater pathology (Ohayon 2000), as is longer persistence. Holroyd and Rabins (1996) and Gauntlett-Gilbert and Kuipers (2003) describe how they may persist in eye disease and schizophrenia over many years.

We will also primarily deal with complex, or formed, hallucinations of people, animals, and objects. Classically, these are differentiated from simple hallucinations of dots, lines, flashes, and amorphous shapes, as well as from panoramic hallucinations of landscapes (Cutting 1997, p. 84). Since these latter may result from different mechanisms (see, e.g., Cole 1999; Manford & Andermann 1998; and sect. 3.1 here), we will address them only in passing.

Recognition of hallucinations as potentially pathological biological phenomena dates from at least the medieval period. There are ninth-century Persian descriptions of *shaqhiqheh*, a headache associated with visual hallucinations (Gorji & Ghadiri 2002). In Europe, Charles Bonnet described them in the eponymous eye disease in 1769 (Schultz & Melzack 1991).[1] In recent times, several distinct models of visual hallucinations have been developed from the perspectives provided by mechanistic understandings of different disorders such as eye disease (e.g., ffytche & Howard 1999; Menon et al. 2003; Santhouse et al. 2000; Schultz & Melzack 1991), epilepsy (e.g., Kolmel 1993; Levine & Finklestein 1982; Rabins et al. 1991), sleep disorders (e.g., Arnulf et al. 2000; Manni & Mazzarello 2001; Manni et al. 2002; Nomura et al. 2003; Risser & Powell 1993), psychosis (e.g., Flynn 1962; Horowitz 1975; Slade & Bentall 1988), and Parkinson's disease (Barnes et al. 2003). These have been largely successful in accounting for hallucinations in specific disorders but struggle to generalise outside of the areas where they were developed.

We have generated a new Perception and Attention Deficit (PAD) model, initially to account for hallucinations in a recently recognised disorder, dementia with Lewy bodies (McKeith et al. 2003), in which RCVH are exceptionally common. We will show how this model cannot only be successfully generalised to RCVH in other neurodegenerative disorders, but also how it has the potential to account for consistencies in the experience of RCVH in non-degenerative disorders and for non-pathological RCVH occurring during the transition between sleep and waking.

In doing this, we accept that active, ceaseless, complex, dynamic interactions between the visual systems and other brain areas lead to subjective perception. Many dysfunctions, either relative or absolute, in one or more areas might lead to consequent effects in others that are experienced as different types of hallucinations. Hence, perhaps, the great variability in type, content, frequency, and associated phenomena of RCVH (Brasic 1998; Kolmel 1993; Schultz et al. 1996). Like others (e.g., Behrendt & Young 2004; Manford & Andermann 1998), we do not see that it is the role of a general model to account for all this limitless variety. If we believe that visual dreams, hallucinations, volitional images, and perception reflect the activity of the same system operating under different constraints, then the role of a general model (if such can be found) is to identify the constraints that produce hallucinations. Thus, it should explain consistencies between different experiences. To this end, our strategy has been to draw out the similarities between different experiences in different disorders, averaging data wherever possible. Though this runs the risk of creating apparent commonalities where none truly exist, and obscuring as much as it illuminates, we feel that this is justified in an attempt to bring greater order to what has been a fragmented field of enquiry.

2. Defining and assessing recurrent complex visual hallucinations

Investigating normal visual imagery is challenging (Reisberg et al. 2003; Schwitzgebel 2002). Investigating halluci-

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natory visual imagery is perhaps even more so (Taylor et al. 1986), not least because there is no consensus definition or classification (Cutting 1997). Hallucinations are generally defined as perceptions without stimuli (Asaad & Shapiro 1986; Brasic 1998; Kolmel 1993). In contrast, illusions or misperceptions are incorrect perceptions of stimuli (Brasic 1998; Kolmel 1993). Horowitz (1975) takes an intermediate position and defines a hallucination as an "image experience in which there is a discrepancy between subjective experience and actual reality." As definitions, these do not formally distinguish between self-generated imagery, dreams, and hallucinations. They are also at odds with constructive models of subjective perception (e.g., Behrendt & Young 2004; Friston 2002a; 2002b; Rees 2001). These see a loose relationship between stimuli and perception, with many aspects of normal perception occurring in the absence of current sensory input. Indeed, an argument can be made, albeit not entirely convincingly (Clark 2002), for normal perception being mostly hallucinatory. For the purposes of this article, we will therefore sidestep these definitional problems and operationally define recurrent complex visual hallucinations (RCVH) as repetitive involuntary images of people, animals, or objects that are experienced as real during the waking state but for which there is no objective reality.

Between 75% and 90% of hallucinators do not spontaneously reveal their experiences (Nesher et al. 2001; Scott et al. 2001; Teunisse et al. 1996), with a good proportion not identified during routine assessments (Bracha et al. 1989). When hallucinations are identified, there is a lack of validated tools for the subjective or objective assessment and classification of hallucinatory experiences.

Differentiating between hallucinations and illusions or misperceptions is also challenging. Thus, there are instances where misinterpretations seem very unlikely, for example, hallucinating a person sitting on a chair; and there are those where misperception appears likely, for instance, mistaking one person for another. However, there can be significant difficulties in a grey zone of intermediate experiences in which patterns on walls or cushions, for example, metamorphose into faces. Additionally, many patient groups with high rates of apparent hallucinations, such as psychosis or dementing illnesses, also have high rates of other visual or communication problems (see sect. 3.1; Ballard et al. 1999; O'Brien et al. 2000). For example, Horowitz (1964) describes how patients with schizophrenia can attach meaning to simple visual hallucinations and hence report them as if they were complex; as instances, reporting lines as "vicious snakes" or dots as "two armies struggling over my soul." Compounding these problems are the great variations between studies in the methods used to identify, assess, classify, and report hallucinations.

Despite these caveats, we believe that there is enough epidemiological, phenomenological, pathological, psychological, and imaging evidence to allow us to develop and test general models of RCVH. We will now review that evidence.

3. People who see things

Many, many diseases, brain lesions, pharmacological agents, and psychological states are reportedly associated with RCVH (for qualitative reviews, see Anderson & Rizzo 1994; Asaad & Shapiro 1986; Brasic 1998; Kolmel 1993; Manford & Andermann 1998).

3.1. Associated states and diseases

The prevalence of hallucinations shows distinct variation between conditions (Fig. 1). Some of this will reflect random or systematic biases. For example, reported rates of RCVH in eye disease range from below 1% to above 10% depending partially on selection and exclusion criteria (Shiraishi et al. 2004); and some disorders with particularly high rates (i.e., dementia with Lewy bodies, see McKeith et al. 2003; and narcolepsy, see Aldrich 1996) have visual hallucinations as one possible diagnostic criteria. There is a need for direct, within-study comparisons between different disorders. Even so, it is striking that acquired eye disease, occipital stroke, and sensory deprivation, all causes of restricted visual input, have similar low rates of RCVH (3–18%). Disorders with more distributed dysfunction, for example, those associated with disturbed consciousness (e.g., narcolepsy and delirium), some dementing illnesses (dementia with Lewy bodies, Parkinson's disease with dementia, and vascular dementia), and schizophrenia have high rates (30–59%). Table 1 shows that, where data exist, frequencies are in some cases reversed for simple hallucinations. Thus, simple hallucinations are relatively frequent in sensory deprivation and eye disease, but infrequent in dementia, delirium, and Parkinson's disease. This double dissociation between simple and complex hallucinations suggests two things to us. First, that each type of hallucination has a single primary cause, and second, that these causes are separable within the visual system.

These estimates of frequency within categories can be combined with estimates of the frequencies of these categories in, for example, the UK adult population to give an admittedly crude indication of associations with RCVH in the general population (Fig. 2). Normal hypnopompic (on waking) and, especially, hypnagogic (on falling asleep) hallucinations are, overall, the most frequent types. Broadly speaking, four groups of disorders – delirium, age-related dementia, schizophrenia, and acquired eye disease – stand out as being most frequently associated with RCVH. In contrast, some disorders that have been used to support general models (thalamic and pedunculopontine hallucinosis; see Noda et al. 1993; Risser & Powell 1993); stimulation of the subthalamic nucleus (Diederich et al. 2000); and fatal familial insomnia (Gallassi et al. 1996; Tabernero et al. 2000) are much rarer.

A number of risk factors for RCVH within specific disorders have been reported (Table 2), though there have been no cross-category comparisons and there are some contradictions (e.g., whether depression in Parkinson's disease is or is not associated with hallucinations). Increasing intellectual impairment is a consistent risk factor as is poor vision, though significantly, hallucinations cease in eye disease when all vision is lost (Menon et al. 2003). Impaired alertness or sleep abnormalities are also a recurring theme, even aside from delirium and narcolepsy. This suggests either that these categories overlap, or as others have also suggested (e.g., Cole 1992; Menon et al. 2003; Pappert et al. 1999), there may be a consistent set of features that predispose an individual patient to developing RCVH – namely, intellectual impairment, poor vision, and disturbed alertness.

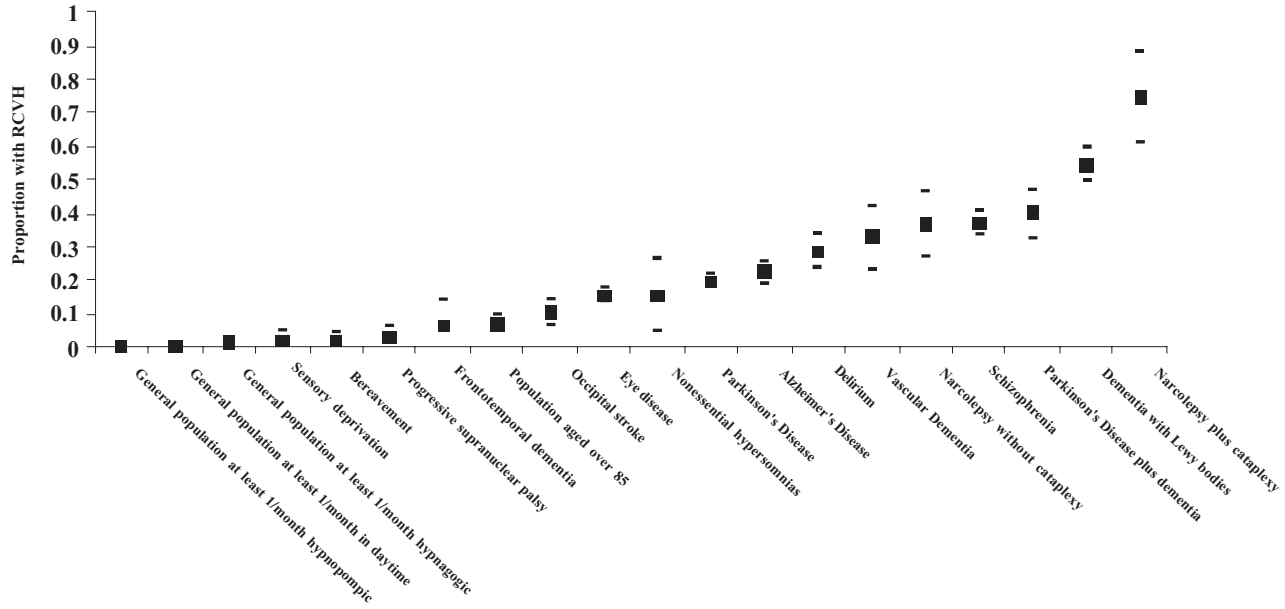


Figure 1. Reported frequencies of RCVH within different normal and pathological states. Values are averaged proportions (weighted by sample size) plus or minus 95% CI. Disparate methodologies and subject groups will account for some of the variation between groups. Both random and systematic biases cannot be excluded at present. Sources: dementia with Lewy bodies (Aarsland et al. 2001a; Ballard et al. 1995b; 1999, including six reviewed studies; 2001); Parkinson's disease (Aarsland et al. 2001a; 2001b; Barnes & David 2001; Cummings 1991; Fenelon et al. 2000; Goetz 1999; Holroyd et al. 2001; Sanchez-Ramos et al. 1996); Parkinson's disease plus dementia (Aarsland et al. 2001b; Neimark et al. 1996); progressive supranuclear palsy (Aarsland et al. 2001b); eye disease (Brown & Murphy 1992; Holroyd et al. 1992; Kolmel 1993; Lepore 1990; Scott et al. 2001; Soros et al. 2003); Alzheimer's disease (Ballard et al. 1995b; 1999; 2001; Bathgate et al. 2001; Cummings et al. 1987; Holroyd & Sheldon-Keller 1995); vascular dementia (Ballard et al. 1995b; Bathgate et al. 2001; Cummings et al. 1987); delirium (Cutting 1997; Webster & Holroyd 2000); sensory deprivation (McKellar 1957; Schulman et al. 1967); general population (Lindal et al. 1994; Ohayon et al. 1996; 2000); occipital stroke (Anderson & Rizzo 1994; Kolmel 1993; Vaphiades et al. 1996); people over 85 (Ostling & Skoog 2002); schizophrenia, including paraphrenia (Bracha et al. 1989; Cutting 1997; Howard et al. 1994; Ndetei & Singhe 1983; Zarroug 1975); narcolepsy and essential hypersomnias (Aldrich 1996); frontotemporal dementia (Bathgate et al. 2001); bereavement (Grimby 1993).

3.2. Pharmacologically induced hallucinations

Evidence that the phenomenology of RCVH is more consistent with hallucinations induced by anticholinergic drugs than by drugs acting on 5-HT, noradrenergic, glutamate, or GABA systems has been reviewed previously (Perry 2002; Perry & Perry 1995), although one notable difference is that drug-induced hallucinations occur with both eyes open and with eyes closed.

Antimuscarinic drugs used in ophthalmology, anaesthesia, heart disease, or motion sickness, and also used ritualistically or recreationally, most frequently induce hallucinations of people and animals in normal individuals (reviewed Perry & Perry 1995; see also Balikova 2002; Cheng et al. 2002; Gopel et al. 2002; Han et al. 2001; Tune 2000; Tune & Egeli 1999; Winawer 2001), especially in the young and elderly (in whom cortical cholinergic activity is lower than in adults; Perry et al. 1992). Nicotinic, as well as muscarinic, receptors may be involved since toxic quantities of tobacco can induce hallucinations (Thomas 2002).

In Parkinson's disease, antimuscarinic agents such as atropine can induce hallucinations (Cummings 1991; Hyson et al. 2002). There is also a limited amount of evidence that patients with dementia with Lewy bodies are vulnerable to potentially hallucinogenic effects of neuroleptic medication with anticholinergic side effects (Scheepmaker et al. 2003). There is consistent evidence that antimuscarinic drugs induce delirium with hallucinations, especially in the elderly (Han et al. 2001; Tune 2000). Endogenous antimuscarinic activity in plasma has been reported in elderly medical patients with acute illness – a population at risk for delirium. This activity, which was not identified chemically, was detected using a broad spectrum anti-muscarinic receptor assay (Flacker & Wei 2001; Mussi et al. 1999). Delirium has also been reported as a result of nicotine withdrawal in heavy smokers (Mayer et al. 2001). Recent reports that the anticholinergic side effects of neuroleptic medication contribute to the cognitive deficits of schizophrenia (Minzenberg et al. 2004) raise the possibility that RCVH in this disorder are at least partially iatrogenic.

The case for a dysfunctional cholinergic basis for RCVH is strengthened by their symptomatic reduction in dementia with Lewy bodies, Alzheimer's disease, Parkinson's disease, and delirium by drugs which increase synaptic acetylcholine (physostigmine, donepezil, rivastigmine, galantamine; see McKeith et al. 2000; Bullock & Cameron 2002; Fabbrini et al. 2002; Maclean et al. 2001; Reading et al. 2001; Rosler et al. 1998; Zesiewicz et al. 2001).

In contrast to anticholinergic drugs, those (such as LSD) that target 5HT2 receptors induce phenomenologically different visual hallucinations that involve distorted images and synesthesia (blending of sensory modulators; Abraham et al. 1996; Perry 2002), though mianserin and ondansetron (5HT2 receptor antagonists) are reported to reduce visual hallucinations in Parkinson's disease (Ikeguchi & Kuroda 1995; Zolden et al. 1995). GABA may also be implicated

Table 1. *Content of recurrent complex visual hallucinations*

	Complex hallucinations						Simple hallucinations	Panoramic hallucinations
PATIENT GROUP	Familiar people	Unfamiliar adults	Children	Animals	Inanimate objects	Multiple images		
Dementia with Lewy bodies	66[3]		8[3]	35[3]	11[3]		8[3]	
Parkinson's disease	15 (69 of all hallucinations unfamiliar)[1]			7[1], 10[2], 7[4], 8 (PDD)[3]	8[1], 4[4], 6[2], 3 (PDD)[3]		25[4], 4[2], 3 (PDD)[3]	
	11[4], 1[2]	13[4], 11[2]	3[2], 6 (PDD)[3]					
	40 (PDD)[3]							
Dementia (mixed diagnoses)	7[5]	20[5]	17[5], 5[8]	13[5], 6[8]	9[5]		0[5]	
	25[8]							
Eye disease		2[6], 2 (figures)[10], 8 (distorted faces)[10]	6[10], 1[16]	5[12], 3[13], 4[15], 1[16]	6[10], 9[12], 1[15], 1[13]	4[13], 13[24], 7[16], 12[12]	6[22], 2[16], 2[17], 18–20[10], 51[12], 17[19]	3[12],3[16], 6[22]
	1 (1 faces)[16]							
	21 (7 faces and body parts)[12], 11[13]							
	6[19], 13[22]							
Unselected population sample	2[11]	6[11]		1[11]			1[11]	
Delirium	27[9]			17[9]	11[9]		1[9]	
Schizophrenia (including paraphrenia)	20[9], 23[18], 58[21]			6[9], 3[18], 3[21], 6[11]	6[9], 3[18]	60[18]	64[14], 6[9], 31[11], 8[20], 50[14], 7[18]	
	18[11]	25[11]						
	64[14], 33[20]							
Stroke in visual pathways	22[17]						25[17]	
Alcohol abuse	79 (predominantly people)[14]						61[14]	
Sensory deprivation	6[23]						42[23]	

Figures are reported percentages of people who have hallucinations of each type out of all people who have that disorder. Because people may experience more than one type of hallucination, percentages may total more than 100%. Some sources (6, 7, 10, 15) reported rates only within those who hallucinated. In these cases, overall rates of 15% of people with eye disease having complex hallucinations and 25% with simple hallucinations were derived from other studies and used to calculate comparable figures.

Sources: (1) Holroyd et al. (2001); (2) Barnes & David (2001); (3) Aarsland et al. (2001a); (4) Fenelon et al. (2000); (5) Murgatroyd & Prettyman (2001); (6) ffytche & Howard (1999); (7) Brown & Murphy (1992); (8) Ballard et al. (2001); (9) Cutting (1997); (10) Santhouse et al. (2000); (11) Lindal et al. (1994); (12) Lepore (1990); (13) Nesher et al. (2001); (14) Deiker & Chambers (1978); (15) Pliskin et al. (1996); (16) Teunisse et al. (1996); (17) Vaphiades et al. (1996); (18) Gauntlett-Gilbert & Kuipers (2003); (19) Soros et al. (2003); (20) Howard et al. (1994); (21) Zarroug (1975); (22) Scott et al. (2001); (23) Schulman et al. (1967); (24) Needham & Taylor (2000).

PDD, Parkinson's disease with dementia.

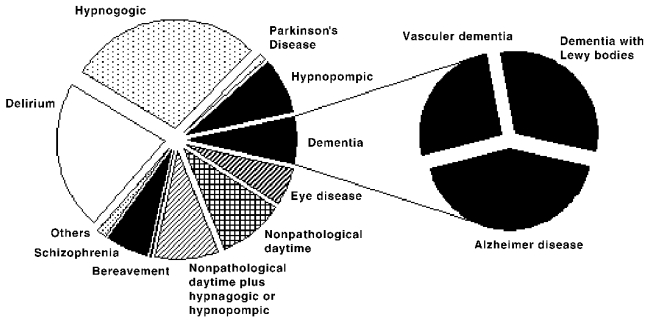


Figure 2. Estimated relative associations of RCVH in the adult population derived from reported frequencies within categories and prevalences of those categories. Data were calculated by multiplying the weighted average frequency of RCVH within each category (from Fig. 1) by estimates of prevalence of that category within the UK adult population (45.8 million; www.statistics.gov.uk). Estimates for the prevalence of specific categories are: dementia with Lewy bodies (150,000), vascular dementia (112,500), and Alzheimer's disease (412,500) (calculated from rates in Stevens et al. 2002); schizophrenia (1% of adult population; www.nelh.nhs.uk); delirium (22% [www.psych.org] of 9.6 million hospital inpatients, prorated from England figures; www.doh.gov.uk); repeated non-pathological day time (0.57% of population), hypnagogic (1.7%) and hypnopompic (0.5%) (Ohayon 2000; Ohayon et al. 1996); eye disease (1 million; www.rnib.org.uk); Parkinson's disease (120,000; parkinsons.org.uk); and bereavement (1% of the adult population; www.statistics.gov.uk). Others include rare disorders (under 0.5% of the population), or unsystematic series, or single case reports, for example, epilepsy, stroke, narcolepsy, pedunculopontine hallucinosis, fatal familial insomnia, and progressive supranuclear palsy. Because of variations between studies and disorders in definitions of RCVH, the data indicate approximate associations with RCVH rather than exact ratios. Estimating an average overlap among categories of a third gives a crude estimate of around 2 million adults with RCVH.

based on limited evidence of zolpidem induced visual hallucinations (Markowitz & Brewerton 1996), baclofen withdrawal (Harrison & Wood 1985), and delirium tremens (Brailowsky & Garcia 1999).

Agents such as mescaline that affect catecholaminergic systems, promoting the release of dopamine, are said to result in multi-coloured images of fantasy. The dopaminergic system is frequently implicated in disease-related visual hallucinations, especially in Parkinson's disease, on the basis of symptomatic treatment with neuroleptics such as clozapine (Devanand & Levy 1995; Molho & Factor 2001), which commonly target the D2 receptor subtype (although other pharmacological actions may be implicated), and on the basis of the induction of hallucinations by levodopa (L-dopa) (Cannas et al. 2001; Goetz et al. 2001a; 2001b; Holroyd et al. 2001). However, in Parkinson's disease, evidence that L-dopa is the principal contributing factor to hallucinations is not consistent, since increasing L-dopa medication does not increase hallucination prevalence (Goetz et al. 1997; 1998a). Among neuroleptics, olanzapine is reported to be superior in reducing hallucinations in Parkinson's disease, compared to haloperidol or risperidone (Edell & Tunis 2001) which could be related to the promotion of acetylcholine release associated with this type of drug (Ichikawa et al. 2002). In contrast to degenerative dementia, neuroleptics are not consistently effective in treating RCVH in the Charles Bonnet syndrome (Batra et al. 1997), and it remains to be determined if cholinergic agents are effective.

In conclusion, pharmacological data so far available indicate a primary role for cholinergic and secondary role for dopaminergic dysfunction in the aetiology of RCVH. Cholinergic hypoactivity alone, or dopaminergic hyperactivity if (and only if) cholinergic hypoactivity is already present, as underlying mechanisms are both consistent with the psychopharmacological evidence (above) and pathological data (sect. 7.6.2.2). In relation to the potential dual transmitter role, combined cholinergic and neuroleptic treatment is reported to be effective in reducing hallucinations in Alzheimer's disease (Bergman et al. 2003).

4. The character of recurrent complex visual hallucinations

4.1. Phenomenology

The content of RCVH is summarised in Table 1; and their phenomenology, in Table 3. As with estimates of the frequency of RCVH, there are contradictions and gaps in the data. Given the differences in methodology between studies and in the reporting abilities of different groups and the absence of direct comparisons of RCVH across disorders, it is unclear exactly how phenomenologically similar RCVH are in, say, eye disease, schizophrenia, and dementia. However, like previous reviewers (e.g., Behrendt & Young 2004; Brasic 1998; Cutting 1997; Horowitz 1975; Horowitz et al. 1968; Kolmel 1993; Manford & Andermann 1998; Siegel & Jarvik 1975), we consider that, in contrast to the variations in frequency of RCVH across disorders, the phenomenology of RCVH is more consistent. Together with the double dissociation between simple and complex hallucinations, this suggests to us that the wide range of factors associated with RCVH converge on a common target system.

4.1.1. Content. As we noted earlier in section 2, a distinction needs to be drawn between what is actually seen, which may be prosaic, and what is reported, which may be anything but. Many single case reports have emphasised the bizarre or incongruous nature of hallucinations (e.g., Needham & Taylor 2000; Silbersweig et al. 1995), but in our experience, within dementing illnesses (Mosimann et al., in press) and in systematic surveys (Cole 1992; Pliskin et al. 1996; Teunisse et al. 1996; Zarroug 1975), these are less common than rather commonplace images – a man sitting on a chair or a dog in the corner of the room, for example.

Hallucinations of people tend to be more common than are those of animals. Images of objects such as tables or cars are the least frequent. Unrecognised images are hallucinated as frequently as or more so than familiar ones (Table 1; Cole 1992). There is often a stereotyped or repetitive quality to the images. Commonly, the same image repeats itself on different occasions, though over time, many patients will experience a range of hallucinatory images. There is generally movement, although this is often stereotyped and restricted. The images rarely interact with or respond to the environment. The image is usually whole and sharply focused. It is normal sized or unusually small with a normal or unusually vivid colour. If there is distortion, this is usually of the face with a consistent exaggeration of the mouth and eye areas (ffytche & Howard 1999; Frucht & Bernsohn 2002).

RCVH are often associated with hallucinations in other sensory modalities at other times (Ballard et al. 1999;

Table 2. *Risk factors for recurrent complex visual hallucinations*

PATIENT GROUP	Sleep disorders	Cognitive impairment	Poor vision	Other risk factors *Nonrisk factors*
Parkinson's disease	Daytime somnolence[4], *sleep disturbance*[4]	Cognitive impairment[1,2,3,4], subsequent dementia with Lewy bodies, or Alzheimer disease[11]	Visual acuity[1,2], poor colour, and contrast discrimination[18]	Depression[1,2,3], disease severity[1,2,3,4], disease duration[2,4], age[4], previous psychiatric disease[11], *history of psychiatric disease*[1], *dose of anti-Parkinsonian treatment*[1,2,3,4], *duration of treatment*[1], *duration of disease*[1], *depression*[3]
Alzheimer's disease		More rapid decline[5], cognitive impairment[7,8], visual agnosia[19]	Relative occipital atrophy[6], visual acuity[7,19]	
Dementia with Lewy bodies		Cognitive impairment[8], overlapping figure identification[16], variability in attentional reaction time[17], *cognitive impairment*[3]	Occipital hypometabolism and preserved posterior temporal/parietal metabolism[10]	Absence of occipital white matter hyperintensities[9], *age*[3], *age at onset*[3], *anti-Parkinsonian medication*[3], *depression*[3]
Dementia (mixed diagnoses) with or without hallucinations	Nighttime disturbance[12],	Clock drawing[12], CAMCOG object recognition[12], diagnosis of DLB[12,15], diagnosis of not AD[12], *MMSE*[12], *total CDR*[12]	Near and far visual acuity[12,15,27], ambient illumination[12]	Age[15,27], female[27] *age*[12], *sex*[12], *illness duration*[12]
Eye disease	Fatigue[26]	Cognitive impairment[14,23], stroke[14]	Bilateral sequelae[13,30], bilateral visual impairment[14,31], acute onset of visual loss[14]	Living alone[14], loneliness[12], low extraversion[29], high shyness[29], female[28,30], level of disability[30], emotional distress[30], age[31], *history of psychiatric disorder*[14], *personality*[14]
General population daytime hallucinations	*Sleep disorders*[21]	Neurological disorders[21], dementia[22]	Poor vision[21,22]	Use of recreational drugs[21], anxiety[21], psychosis[21], depression[22], vivid day dreams[25], *bipolar disorder*[21], *alcohol use*[21], *hypnotics*[21], *depression*[21], *adjustment disorder*[21]
General population hypnagogic and hypnopompic hallucinations	Sleep disorders[20]			Anxiety[20], depression[20], psychosis[20]
Schizophrenia including paraphrenia			Poor vision[24]	

Italics indicate a nonsignificant relationship. Sources: (1) Holroyd et al. (2001); (2) Barnes & David (2001); (3) Aarsland et al. (2001a); (4) Fenelon et al. (2000); (5) Wilson et al. (2000); (6) Holroyd et al. (2000); (7) Chapman et al. (1999); (8) Ballard et al. (1999); (9) Barber et al. (1999); (10) Imamura et al. (1999); (11) Goetz et al. (1998a; 1998b); (12) Murgatroyd & Prettyman (2001); (13) Brown & Murphy (1992); (14) Holroyd et al. (1992); (15) Ballard et al. 1995a; (16) Mori et al. (2000); (17) Wesnes et al. (2001); (18) Diederich et al. (1998); (19) Holroyd & Sheldon-Keller (1995); (20) Ohayon et al. (1996); (21) Ohayon (2000); (22) Ostling & Skoog (2002); (23) Pliskin et al. (1996); (24) Howard et al. (1994); (25) Morrison et al. (2002); (26) Menon et al. (2003); (27) O'Reilly & Chamberlaine (1996); (28) Shiraishi et al. (2004); (29) Teunisse et al. (1998, 1999); (30) Scott et al. (2001); (31) Teunisse et al. (1995).

DWB, dementia with Lewy bodies; AD, Alzheimer's disease; MMSE, Mini Mental Status Examination; CDR, cognitive drug research.

Table 3. *The phenomenology of recurrent complex visual hallucinations*

	Phenomenology																					
	Duration	Reaction			Appearance					Environment									Movement			
DISORDER	Lasts minutes	Neutral or positive emotion	No interaction with patient	Insight	Coloured	Normal or small	Sharply formed	Part of visual field	Complete image	Occurs at specific time	Occurs in specific place	Common in evening	Poor light	No immediate trigger	Associated with inactivity	Not associated with sleep	Fits in with Context	Mainly open eyes	Intrinsic movement	Image moves around	Image moves with eyes	Disappears with eye movement
Eye disease	√[1,4,14,28]X[18,19]	√[4,19,6,27]X[17]	√[1,5]	X[3,9]√[19]	√[1,4,14,19,6,28]	√[1,2,14,19]	√[1,4,17,18,6,28]	√[1,7,13,17,28]X[14]	√[1,4,6]	X[14,27]	√[4]	√[4,13]X[27]	√[4]	√[4,18]	√[4]	√[4,28]	√[4]	√[4,18,27]	√[4,6,17]X[18]	X[4]√[6]	X[4]√[17]	X[17]√[14]
Stroke	√[14]			√[26]	X[14]	√[14]	√[14]	√[14]	√[26]	X[14]		√[6]							X[14]			√[10,14]
Psychosis		X[8,5]√[2,3]		√[8,20]	√[13]		√[8]		√[20]				√[8]	√[8]	√[8,9]X[13]		X[8]√[5]	√[5]	√[8]		X[8]	
Peduncular hallucinosis	X[14,13]	√[15]		√[15]	√[15]		√[15]	√[13] X[14]				√[13,14]							√[15,17]	√[15]		
Dementia with Lewy bodies	√[15,25]	√[25]			√[25]	√[25]	√[25]	√[13,25]				X[25]	X[25]	√[25]		√[25]		√[25]	√[25]			X[25]
Parkinson's disease	√[21]X[22]	√[12,24]		√[23]	X[21]	√[22]		√[21]				X[23]√[24]	√[21]					√[21]	√[21]			X[21]
Alcohol		X[21,2]				√[13]																
Thalamic hallucinosis	√[11]							√[11]														
Deep brain stimulation		√[16]			√[16]			√[16]			√[16]								√[16]	√[16]		
Total √ reports	9	11	2	6	10	8	10	12	5	0	2	6	3	4	3	3	2	6	9	3	1	3
Total X reports	5	5	0	2	2	0	0	2	0	3	0	3	1	0	1	0	1	0	2	1	2	3

Sources are a mixture of quantitative and qualitative descriptions. To combine these, we have used a quantitative distinction between whether a feature occurs 50% or more of hallucinations (√), or less than 50% (X), and a qualitative report that a feature is characteristic (√) or not (X) of hallucinations in that disorder. Sources: (1) Nesher et al. (2001); (2) Deiker & Chambers (1978); (3) Pliskin et al. (1996); (4) Teunisse et al. (1996); (5) Asaad & Shapiro (1986); (6) Schultz & Melzack (1993); (7) Fernandez et al. (1997); (8) Gauntlett-Gilbert & Kuipers (2003); (9) Delespaul et al. (2002); (10) Vaphiades et al. (1996); (11) Noda et al. (1993); (12) Godwin-Austin (1999); (13) Manford & Andermann (1998); (14) Kolmel (1993); (15) Risser & Powell (1993); (16) Diederich et al. (2000); (17) Santhouse et al. (2000); (18) Schultz et al. (1996); (19) Paulson (1997); (20) Zarroug (1975); (21) Barnes & David (2001); (22) Holroyd et al. (2001); (23) Fenelon et al. (2000); (24) Gold & Rabins (1989); (25) Bowen et al. (unpublished data); (26) Anderson & Rizzo (1994); (27) Shiraishi et al. (2004); (28) Scott et al. (2001).

Deiker & Chambers 1978; Fenelon et al. 2000; Gauntlett-Gilbert & Kuipers 2003; Goetz 1999; Holroyd et al. 2001; Howard et al. 1994; Needham & Taylor 2000; Noda et al. 1993; Ohayon 2000; Simard et al. 2003; Zarroug 1975). Thus, people with visual hallucinations may have auditory hallucinations of voices, but it is very rare to hallucinate a figure that talks (Gauntlett-Gilbert & Kuipers 2003).

4.1.2. Time and place. Episodes of RCVH tend to be of the order of minutes, rather than seconds or hours, with an abrupt onset with no apparent trigger. Offset is equally sudden. Sometimes they disappear on changes in the visual environment, though often again there is no apparent cause. They more rarely occur with eyes closed (Barnes & David 2001; Melzack 1991; Menon et al. 2003; Schultz & Schultz et al. 1996; Shiraishi et al. 2004; Teunisse et al. 1996).

By definition, the commonest hallucinations of normal life, hypnopompic and hypnagogic, are associated with falling asleep or waking. Similar associations with times of low arousal (sitting or otherwise resting) have been reported in Parkinson's disease (Fenelon et al. 2000), schizophrenia (Delespaul et al. 2002), and eye disease (Lalla & Primeau 1993), though in schizophrenia as in delirium, hallucinations have also been reported to be accompanied by over-arousal (Manford & Andermann 1998). Associations with times of low (as opposed to bright or absent) illumination have been reported in dementia (Murgatroyd & Prettyman 2001) and eye disease (Lalla & Primeau 1993; Teunisse et al. 1996), and it seems plausible that hypnagogic and hypnopompic hallucinations may also be occurring at times of low illumination.

The time of day of hallucination may be consistent within the individual, though most often it is not. In contrast, RCVH tend to occur in the same location, mostly in the house or looking out of the house. As an example, patients with dementia often report visitors who only appear in their living room. Although this may partially be a function of the amount of time spent in each location, it is striking that once the patient moves to a new environment, the hallucinations disappear (Cole 1992). The image usually appears in a contextually correct location – a person who is sitting in a chair rather than floating on the ceiling – and with the correct orientation – an upright rather than inverted face, for example.

Hallucinatory images occur in the focus of the visual field and do not generally disappear when attended to (Kolmel 1993; Manford & Andermann 1998; Santhouse et al. 2000). The hallucinatory image is seen against the background of the existing visual scene more often than is an image of a person and background filling the whole visual field (Barnes & David 2001; Manford & Andermann 1998; Scott et al. 2001). Although these latter, panoramic, hallucinations are described in eye disease (ffytche & Howard 1999; Scott et al. 2001; Teunisse et al. 1995; 1996), they are in the minority. It may be that in a person with no effective vision, there will be no existing visual scene to act as the background to a nonpanoramic hallucination.

5. Requirements for a general model

A good general model should account for who hallucinates, what they see, and when and where they see it. Thus, at a minimum, a general model of RCVH has, in our view, to be applicable to the pathological states of dementia, delirium, schizophrenia, and eye disease. It should also account for the induction and treatment of RCVH by pharmacological manipulations. It needs to predict why nonpathological hallucinations occur on the borders of sleep. It has to explain the associations within disorders with poor vision, disturbed alertness, and intellectual impairment. Finally, it needs to account for the phenomenology of RCVH; for the frequency of hallucinations of people and animals; for their abrupt onset and offset, and their movement; for temporal and situational regularities where they exist; and last, for their extinction with eye closure.

6. Existing models

A number of candidate models have been put forward based upon the pathology in particular disorders in which hallucinations occur. These have mostly been developed in parallel, with the result that there is a degree of overlap. For example, cortical irritation and more modern versions of cortical release both suggest hyperexcitability in visual cortex as a causative mechanism.

Despite each model's undoubted strengths, we feel that each faces considerable challenges when measured against the aforementioned requirements. Because none were developed with these requirements in mind, at the least all would require extension. However, beyond this, we feel that each faces the major hurdles outlined next.

6.1. Illusionary misperceptions and misidentifications

This intuitive explanation suggests that the hallucination is simply the failure to see something correctly – and hence to mistake it for something else. It is not widely supported, even by patients (Nesher et al. 2001). Two areas of evidence count against it. Misperceptions would seem most likely if objects were not at the focus of attention. However, many RCVH occur in the very centre as opposed to the periphery of the visual field (Kolmel 1993; Manford & Andermann 1998; Santhouse et al. 2000). Misperception would also suggest that rather than the experience of an image being superimposed on a background, it should take the place of another perception. The hallucination would not be of a person sitting on a chair, but of a chair turning into a person and back again. This has been reported in eye disease (ffytche & Howard 1999). In these cases, however, it appears to be a separate phenomenon that accompanies RCVH rather explains it. Thus, patients with these experiences also have more purely hallucinatory images.

6.2. Cortical irritation

This model suggests that hallucinations result from intrinsic electrical overactivity in the brain areas that contain specific image memories or representations (Levine & Finklestein 1982; Noda et al. 1993). It was developed initially to account for visual hallucinations in temporal lobe epilepsy and drew on Penfield's work on the effects of stimulation of that area (e.g., Penfield & Perot 1963). As previous reviewers have concluded, however, it has a range of limitations as a general model (Brasic 1998; Manford & Andermann 1998; Schultz & Melzack 1991). Penfield's initial formulation of experiential hallucinations as reactivated

memories is at odds with the unfamiliarity of many hallucinations. Though Horowitz et al.'s later stimulation work activated a wider range of images (Horowitz et al. 1968), many of which are reminiscent of those described by people who hallucinate, this still leaves the problem of the lack of evidence for focal cortical irritation in the majority of people with RCVH (e.g., from stroke; see Anderson & Rizzo 1994; Vaphiades et al. 1996).

6.3. Cortical release and hyperexcitability or unbalanced top-down activation

Au Eong et al. (2001), Anderson and Rizzo (1994), Asaad and Shapiro (1986), Brasic 1998, Burke (2002), Cogan (1973), Fernandez et al. (1997), ffytche and Howard (1999), ffytche et al. (1998), Howard et al. (1997), Lepore (1990), Santhouse et al. (2000), Schultz and Melzack (1991), and West (1962) suggest that, in several disorders, hallucinations result from a lack of sensory input. They suggest that this results in the release of stored images. This initially drew upon what was then thought to be the inhibitory nature of stimulus-driven, bottom-up visual processing with a lack of inhibition-releasing spontaneous activity. More recent conceptualisations (e.g., Burke 2002) suggest that a lack of input leads to chronic hyperexcitability. In a development of these ideas, Manford and Andermann (1998) and Stoerig (2001) brought together a wide range of different causes of visual hallucinations by suggesting that they perturbed diverse aspects of the visual system, although, as with other models in this class, the common result was a hyperexcitability or disinhibition of image-containing cortex.

Approaching this from the other end of visual processing, Grossberg (2000) suggests that, within adaptive resonance theory (ART), hallucinations are caused not by a lack of bottom-up inhibition but by an excess of excitation from top-down attentional processes. In general, these top-down excitations are not enough to spontaneously activate images, unless the person wills it. However, Grossberg argues that, on occasions, they become tonically hyperactive with incorrectly activated images (hallucinations) as the result.

There are strengths in these models that invoke cortical release. They are able to account for the content of RCVH by the cortical areas that are released (ffytche et al. 1998; ffytche & Howard 1999; Santhouse et al. 2000). ART may be able to explain the recurrent features of hallucinations by linking activation of the hallucinatory image to the context in which the prototype image was learnt. However, this class of models struggles particularly in predicting who has complex hallucinations. Dysfunction of visual input (eye disease, occipital lesions, or sensory deprivation) alone (Fig. 1), and isolated failures of attentional regulation due to stroke (Chemerinski & Robinson 2000; Rabins et al. 1991) or frontotemporal dementia (Bathgate et al. 2001) are associated with rates of RCVH in, at most, the 10–15% range. This is well below that seen in some forms of dementia or delirium. As we will show, it may be that both sensory release and top-down activation are necessary, but neither in itself is sufficient to cause high rates of RCVH. Returning to the double dissociation between simple and complex hallucinations and the relatively high rates of simple hallucinations in eye disease and sensory deprivation, it may be that the disinhibitory effect of lack of sensory input more successfully accounts for simple hallucinations.

6.4. Dream intrusion

Dream intrusion suggests that hallucinations are the intrusions of dream images into waking or semi-waking states (Arnulf et al. 2000; Asaad & Shapiro 1986; Manni & Mazzarello 2001; Manni et al. 2002; Nomura et al. 2003; Onofrj et al. 2002; Pappert et al. 1999). It has a long history as an explanation, dating back to L'Hermitte's initial descriptions of peduncular hallucinosis, though there is almost an equally long history of disagreement (for discussions, see Asaad & Shapiro 1986; Risser & Powell 1993).

In support of this as a general explanation, RCVH in dementia and Parkinson's disease have been reported to be associated with periods of sleep or disturbed alertness; fatal familial insomnia, delirium, and narcolepsy are all characterised by primary impairments in alertness or sleep; and virtually all non-pathological hallucinations occur between sleep and full wakefulness.

We see three major challenges to dream intrusion as a general explanation. First, RCVH are less common in some disorders with primary impairments of alertness (narcolepsy without cataplexy and delirium) than in other illnesses in which disordered alertness, though common, is not an invariable feature (dementia with Lewy bodies and vascular dementia; Fig. 1). Second, within specific disorders, there is not an invariable relationship between sleep disturbance and RCVH. Thus, RCVH in narcolepsy is associated more with cataplexy than sleep disorder per se (Aldrich 1996); and within peduncular hallucinosis, a significant minority of patients do not have sleep abnormalities (Risser & Powell 1993). In Parkinson's disease, although sleep disorder and RCVH both occur, they do not necessarily occur in the same patient or at the same point in the illness (Arnulf et al. 2000; Manni et al. 2002; Nomura et al. 2003; Onofrj et al. 2002). Third, dreams and RCVH are phenomenologically distinct. Dreams fill the whole visual field, with the dreamer being a participant in the action. In contrast, visual hallucinations occupy only the centre of the visual field, with the hallucinator being an observer. Even when content is similar (Nomura et al. 2003), people who experience both are well able to tell them apart (Arnulf et al. 2000; Cole 1999).

6.5. Interactive and information-processing models

Asaad and Shapiro (1986), Brasic (1988), Gold and Rabins (1989), and Schultz and Melzack (1991) describe a number of solely psychological theories to account for RCVH. Causal theories are mainly, though not exclusively, psychodynamic and sociological. They argue that visual hallucinations arise from trauma-induced breakdowns in ego boundaries, or a culturally influenced exaggeration of the normal human propensity to hallucinate. On the positive side, their dependence on internally generated images is supported by evidence that spontaneous and volitional images are a normal feature of many people's lives (Horowitz 1967; McKelvie 1994). The emphasis on the role of expectancies and past experience is consistent with evidence that childhood and adult trauma is a risk factor for RCVH (Read et al. 2003) and that vivid daydreaming is associated with visual hallucinations in non-patients (Aleman et al. 1999; 2000; Morrison et al. 2002). Furthermore, flashbacks incorporating visual experiences are characteristic of posttraumatic stress disorder (American Psychiatric Association 1994). Bereavement may be followed by visual hallucinations of the deceased, though more commonly in other modalities

and perhaps not more frequently in the general population of a similarly old age (Grimby 1993; 1998; Rees 1971; Schneck 1990; Wells 1983), and there is some evidence that hallucinations interpreted as hauntings are associated with expectancies congruent with this (Lange et al. 1996). There are also reports of emotionally significant experiences influencing the content or interpretation of, and hence emotional reaction to, some hallucinations (Needham & Taylor 2000; Schultz & Melzack 1993). This is not the case for the majority of hallucinations (Teunisse et al. 1996).

Overall, given the preponderant associations of RCVH with organic disease (Figs. 1 and 2), and that it is so rare in psychologically normal, or clinically anxious or depressed people (outside of sleep-wake transitions), it seems improbable that purely psychological factors cause more than a minority of hallucinations, though they may affect the interpretation and emotional reaction to them (Collerton & Dudley 2004).

In psychosis, difficulties with explanations that rely on a single cause have led to the development of models in which several factors can interact. In a well-developed information-processing model, Bentall and coworkers (Bentall 1990; Slade & Bentall 1988) suggest that visual hallucinations result from mistaking an internally generated image for one based on an external reality as a consequence of an impaired reality monitoring: a model analogous to models of auditory hallucinations that suggest these are misidentified internal speech (e.g., McGuire et al. 1996). This image may be generated without awareness and appear to intrude into consciousness. They suggest this becomes more likely if there is high arousal, a predisposition to confuse reality with imagination, a poor environmental signal-to-noise ratio, a context that encourages hallucinations, and reinforcing changes in arousal associated with the hallucination. Morrison and colleagues (Morrison 2001; Morrison et al. 2002; 2003) have elaborated on this to account for the relationship between with traumatic experience and hallucinations. Extending this to Parkinson's disease, Barnes et al. (2003) suggest that these mistakenly identified images result from a combination of impaired object perception and poor source monitoring in episodic memory.

The suggestion that the primary cognitive error is in the misidentification of an internal image seems to us to conflict with the evidence that about half of the people are aware that they are hallucinating. Granted that the misidentification might be nonconscious, it needs to be demonstrated how it has little apparent relationship to conscious awareness of unreality, especially when volitional images and dreams are readily identified as such, and when there is no other apparent differences between hallucinators with and without awareness. Additionally, although subjective visual vividness is related to reported hallucination proneness, imagery performance is not (Aleman et al. 1999; 2000).

Horowitz's perceptual nidus theory (Horowitz 1975) does not depend upon this mistaken identification. It suggests (as we later do ourselves) that the primary pathology lies in the generation of images rather than their tagging as internal or external. He suggests that hallucinations occur when there is a combination of an ambiguous relationship between an internal image and reality (the perceptual nidus), in combination with a template of expectancy (derived from psychoanalytic drives and other wishes), and an active memory or fantasy image. This shares several central features with our PAD model, though it was only after we developed it that we became aware of Horowitz's work.

Perhaps the greatest problem for these models as they stand at present is in accounting for the variations in the frequency of RCVH across disorders. There seems no a priori reason why images should be generated or mistaken less frequently in, for example, eye disease than in dementia with Lewy bodies, or that the perceptual nidus would systematically vary across disorders.

Recent biological models of psychosis have focussed on the role of the thalamus in coordinating the multiple brain areas that subserve attention and perception (e.g., Behrendt & Young 2004; Lee et al. 2003; Pelaez 2000). They suggest that thalamic dysfunction creates a stable perception that incorporates incorrect elements. Though attractive in that they can reconcile the need for multiple factors interacting, these models are at odds with the lack of relationship between thalamic dysfunction and rates of RCVH across different disorders (Collerton & Perry 2004). Thus, massive but restricted thalamic damage due to infarcts (del Mar Saez de Ocariz et al. 1996) or fatal familial insomnia (Gallassi et al. 1996; Tabernero et al. 2000) is not generally associated with RCVH, though isolated cases have been reported (Noda et al. 1993). Conversely, we show later how thalamic dysfunction need not be present in disorders with high rates of RCVH.

7. The Perception and Attention Deficit (PAD) model

Based on the foregoing analysis, we conclude that the existing models of RCVH have specific strengths, but all have limitations as general models. This led us to develop a new model. We were guided by two features of RCVH: (1) the occurrence of the hallucination at the focus of visual attention in an otherwise unchanged scene, and (2) the cognitive and pathological characteristics of the disorder with the most consistent evidence for the highest levels of RCVH – dementia with Lewy bodies. (The finding that narcolepsy with cataplexy has equally high rates rests upon a single report from Aldrich 1996.) Exploring these led us to propose that most cases of RCVH are a result of combined attentional and visual perceptual impairments interacting with scene representations to produce the activation of incorrect but environmentally expected perceptual proto-objects.

7.1. Normal scene perception

Cognitive psychology models of scene perception (e.g., Biederman 1972; Biederman et al. 1973; 1974; 1982; 1983; Henderson & Hollingworth 1999; 2003a; 2003b; Rensink 2000a; 2000b; 2002) propose that the subjective experience of a consistent, whole visual world is a construction based upon interactions between abstracted top-down attentional, perceptual, and mnemonic processes and bottom-up sensory processes, with the former generally the more influential in subjective perception (Fig. 3). In parallel, neuropsychological models of selective visual attention and frontal lobe function (e.g., Desimone & Duncan 1995; Miller & Cohen 2001), and of the ventral visual stream and object perception (e.g., Grill-Spector 2003; Vecera 2000), have developed similar divisions. They also require abstract, top-down representations – attentional, feature, or

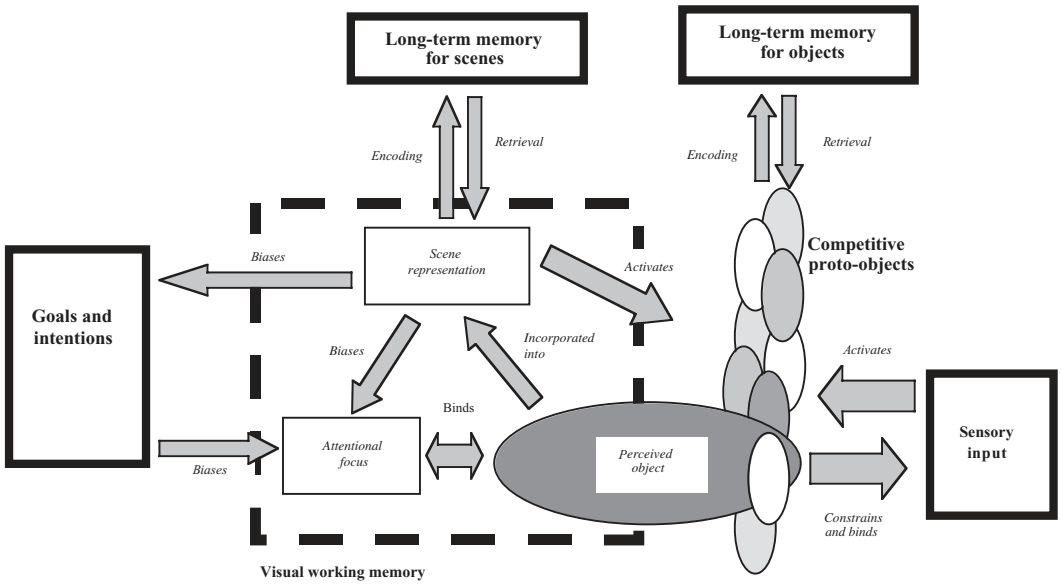


Figure 3. A model of scene perception. This model is the integration of several aspects of the perception of scenes and of objects within those scenes. It draws heavily on Rensink's triadic architecture (Rensink 2000a; 2000b; 2002), Henderson and Hollingworth's visual memory theory (Henderson & Hollingworth 2003a; 2003b), and Desimone and Duncan's biased competition account (Desimone & Duncan 1995; Miller & Cohen 2001; Vecera 2000; Vecera & Behrmann 2001). It is described as if these processes are separable, though this may be more conceptual than real (Peterson & Rhodes 2003; Tarr 2003).

object templates. These are activated by, but also act to bias processing of, sensory and mnemonic information towards specific subjective perceptions. Thus, subjective perception is the result of dynamic reciprocal interactions among external sensory input, internal object and scene representations, and goal-directed attention (Driver et al. 2001; Frith 2001; Scholl 2001; Vecera & Behrmann 2001; Wolfe et al. 2003).

As external sensory input changes, it either activates a number of new, potentially "seen" proto-objects, or modifies those already activated. These proto-objects are not in conscious awareness. They are holistic (Farah et al. 1998) or part-based abstracted object representations (Peterson & Rhodes 2003; Tarr 2003) that are segmented from visual information and act as candidate objects for further processing (Driver et al. 2001; Wolfe et al. 2002). They are equivalent to templates in Desimone and Duncan's biased competition account (Desimone & Duncan 1995; Miller & Cohen 2001; Vecera 2000; Vecera & Behrmann 2001).

These proto-objects are in mutual competition for further processing. Top-down or bottom-up biasing information will influence this competition to allow one to enter conscious awareness and be *seen*. Thus, highly salient physical properties of the visual stimulus created by the object – colour, brightness, contrast, for example – can produce a bottom-up bias that allows unattended objects to enter awareness (Rensink's low level visual System I; Frith 2001; Tarr 2003). Similarly, top-down biasing information from familiarity of the object, individual goals and expectancies, and spatial attention will influence the speed and accuracy of object awareness (reviewed in Vecera 2000).

Top-down activation of a number of proto-objects may come from a mnemonic representation of the visual scene (Biederman's scene schema, Rensink's nonattentional setting System III, Henderson & Hollingworth's Scene Representation). Though exact conceptualisations differ, this is an abstract, relatively stable, relatively sparse, noniconic, nonsensory representation reflecting a specific environment. Elements of this are built up in long-term memory over successive attended perceptions of scenes (Chun & Nakayama 2000; Henderson & Hollingworth 2003a; 2003b; Irwin & Zelinski 2002; Shinoda et al. 2001). It contains gist and semantic information about the scene as a whole, as well as details on object shape and layout (Henderson & Hollingworth 2003a; 2003b; Rensink 2000a; 2000b; 2002). It also has the properties of a template in the sense that it biases sensory processing, though different conceptualisations locate this pre- and post-object recognition: Henderson and Hollingworth suggest there is little influence on object recognition per se, whereas Biederman assigns a direct, and Rensink, a more indirect, role in this.

This scene representation, together with ongoing goals and intentions, also influences dynamic top-down attentional processes (Chun & Nakayama 2000; Clark 2002; Humphreys & Riddoch 2001/2002; O'Regan et al. 2000). Attention is the primary mechanism for biasing competition among proto-objects via an increase in signal to internal noise (Lu & Dosher 1998). This induces further segmentation and attentional binding of object features and a relatively stable "seen" object (Rensink's attentional object binding System II; Delvenne & Bruyer 2004; Driver et al. 2001; Treisman & Gelade 2001; Wheeler & Treisman 2002). Thus, seen objects are behaviourally relevant but temporally limited (Beck & Levin 2003). Once active, object representations both bias lower-level sensory processing (Peterson 1999; Vecera & Behrmann 2001) and are incorporated into the higher level scene representation.

The interplay of these processes is closely, but not exactly, related to visual working memory (de Fockert et al. 2001; Delvenne & Bruyer 2004; Henderson & Hollingworth 2003b; Irwin & Zelinski 2002; Scholl 2001; Wheeler & Treisman 2002).

7.2. The characteristics of dementia with Lewy bodies

In a meta-analysis of the cognitive impairments found in dementia with Lewy bodies (Collerton et al. 2003), we identified a cognitive profile characterised by uniquely severe impairments in both attentional/executive performance and visual object perception. Thus, the disorder with the highest rates of RCVH also has the most severe combination of impairments in two key functions that must interact to produce normal scene perception. Combining this neuropsychological finding with evidence from the pathology of dementia with Lewy bodies and the induction of RCVH by cholinergic manipulations, we formulated a general model for RCVH.

7.3. Summary of the PAD model

We suggest that, within scene perception, a hallucination is experienced when an incorrect proto-object is bound in the attentional focus of a scene. This is generally when the visual system is constrained by a combination of impaired attentional binding and poor sensory activation of the correct proto-object, in conjunction with a relatively intact scene representation that biases perception towards an incorrect image. Either impaired attention or impaired sensory activation alone will rarely produce hallucinations. The relationship between the correct and the incorrect proto-object distinguishes a hallucination from an illusion or a misperception; the more distant the relationship, the more hallucinatory the experience.

From this, we suggest that:

1. The frequency of RCVH varies with the frequency of the coexistence of attentional dysfunction and object perception impairments.[2]

2. The phenomenology of RCVH – what is hallucinated, and where and when – primarily reflects the nature of scene perception, in particular, the role of scene-based expectations in influencing the attentional focus (what), and environmental and temporal cues in triggering a scene representation that biases processing towards a hallucination (where and when).

3. Object-based attention depends primarily upon the function of lateral frontal cortex, and object perception depends primarily upon the ventral visual stream. Thus, disorders associated with high levels of RCVH will have a common end stage of both lateral frontal cortex and ventral stream dysfunction. This may be due to intrinsic or extrinsic pathology.

Sections 7.4 to 7.6 demonstrate how the PAD model is consistent with the evidence that highlights the limitations of previous models.

7.4. The relationship between the frequency of RCVH and the coexistence of attentional and perceptual impairments

7.4.1. Associations of RCVH with disease and other states. If the PAD model is correct, there should be a consistent relationship between the severity of attentional and perceptual impairments and the frequency of RCVH across relevant disorders. Neither attentional nor perceptual impairments alone should be associated with high levels of RCVH.

The strongest test of this postulated relationship would be to directly relate attentional and perceptive impairments within scene perception to the occurrence of RCVH. However, such data are not yet available. As an interim measure, we set out to test whether lower rates of RCVH were related to lesser impairments in broad attentional and perceptual function. We plotted rates of RCVH against the severity of attentional and visual perceptual impairment across those disorders for which we could locate data (Fig. 4). We first did this for the disorders included in our dementia with Lewy bodies meta-analysis, then extended it to include other disorders on which we could find comparable data – vascular dementia and Parkinson's disease dementia. Across these disorders, there is the strong correlation that the PAD model requires. At least two potential objections arise to this finding. It is clear that within this data set, attentional and visual perceptual impairments closely covary in severity as a consequence of averaging data from tasks which are both attentional and visual-perceptual. It could be argued therefore that either alone could be sufficient, with the relationship with the other being correlational rather than causal, or that both are reflections of another shared factor. However, as we noted in section 6.3, neither attentional nor visual impairments alone are associated with high levels of RCVH. Nor are RCHV strongly related to other factors (general verbal as opposed to nonverbal impairment, or overall severity of impairment), suggesting a degree of specificity in these cognitive domains. It might also be that the unusually strong relationship is an artefact of the meta-analysis. For example, dementia with Lewy bodies is diagnosed by both the presence of visual hallucinations and attentional fluctuation. Hence, they might appear to coexist as a reflection of patient selection bias. This cannot be rejected as a partial explanation, but if this bias were to account for the findings in other disorders, this would need to systematically vary across other neurodegenerative disorders. We do not consider this likely, but it needs to be tested by direct assessments of hallucinations and cognitive performance across disorders.

In support of evidence relating the general severity of attentional and visual perceptual impairments to the risk of RCVH across disorders, are the relationships within different neurodegenerative disorders. In dementia with Lewy bodies, RCVH has been separately related to the severity of attentional impairment (McKeith et al. 2004; Wesnes et al. 2001) and the severity of visual perceptual difficulties (Mori et al. 2000; Simard et al. 2003). Furthermore, the characteristic intellectual impairments of this disorder may predate the occurrence of hallucinations (Ferman et al. 2002). Barnes et al. (2003) showed a combination of impaired object perception and poor source monitoring in hallucinating patients with Parkinson's disease. To maintain consistency with the PAD model, this difficulty in source monitoring could result from dysfunctional attentional processes (Henkel et al. 1998).

In relation to the other disorders to which a general model of RCVH has to apply, the evidence, albeit even less direct, is not against PAD as a potential model.

Although the evidence is less systematic, poor performance on tests of attention and visual perception are also the norm in delirium (Hart et al. 1997; Mach et al. 1996; O'Keeffe & Gosney 1997) and in schizophrenia (Bozikas et al. 2002; Cuesta et al. 1998; Davidson et al. 1996; Gabrovska et al. 2002; Gold et al. 1999; Hoff et al. 1996; 1999; Park et al. 2002; Sanfilipo et al. 2002). In direct comparisons between patients with Alzheimer's disease and schizophrenia,

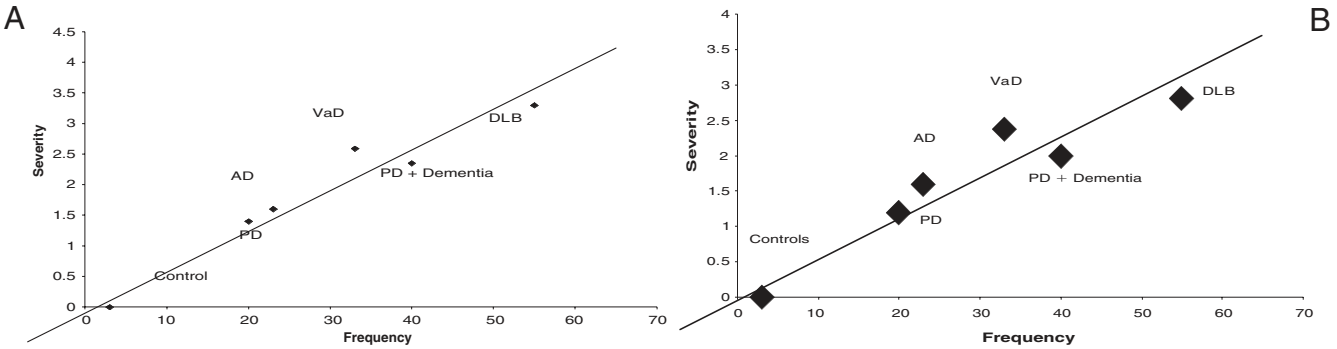


Figure 4. Relationship between frequency of visual hallucinations and severity of (**A**) visual perceptual and (**B**) attentional impairments in neurodegenerative and dementing illnesses. The frequency of RCVH for each disorder is taken from Figure 1. Factor analysis of over 160 tasks used in different neuropsychological studies of these diseases identified four factors: general verbal/nonverbal impairment, attentional/executive impairment, visual perceptual impairment, and verbal memory impairment. The severity of impairment is an inverse variance weighted average of effect sizes on a factor. Full details of the methodology are in Collerton et al. (2003; erratum Collerton et al. 2004). Visual perceptual impairment, $r^2 = 0.92$, $p < 0.01$, and attentional impairment, $r^2 = 0.88$, $p < 0.01$, are both reliably related to the frequency of visual hallucinations. However, overall severity of impairment, $r^2 = 0.52$, $p > 0.1$, general verbal/nonverbal impairment, $r^2 = 0.15$, $p > 0.4$, or severity of verbal memory impairment, $r^2 = 0.63$, $p > 0.05$, were not reliably related to the frequency of hallucinations in this data set. Data for Parkinson's disease (PD, averaged from three studies) and Alzheimer's disease (AD, 10 studies), and dementia with Lewy bodies (DLB, 10 studies) are from Collerton et al. (2003). Data for vascular dementia (VaD) were calculated from five studies referenced in Looi and Sachdev's (1999) systematic review of the cognitive profile of vascular dementia. Data for Parkinson's disease plus dementia were calculated from seven studies identified through Medline and PsycInfo (Ballard et al. 2002; Goldman et al. 1998; Huber et al. 1986; McFadden et al. 1996; Piatt et al. 1999; Soininen et al. 1992, Starkstein et al. 1996).

the patients with schizophrenia had equal attentional and greater visual perceptual impairments (Davidson et al. 1996) consistent with the higher rates of visual hallucinations in the latter illness. The hallucinations that result from deep brain stimulation are also associated with impaired attentional and visual perceptual performances (Saint-Cyr et al. 2000; Trepanier et al. 2000). However, comparisons within these disorders between hallucinators and non-hallucinators need to be made to directly test the model.

In acquired eye disease, poor performance on cognitive tests and the occurrence of stroke disease, both of which might be expected to increase the risk of attentional impairments, are risk factors for RCVH (Table 3). As a corollary, low illumination levels or poor vision (both of which will impair visual recognition) are risk factors for RCVH in dementia. The association with disturbed alertness may reflect the close relationship between this and attention.

The PAD model needs to account for the association of hallucinations with the borders of sleep. The dream intrusion model suggests that some of the features of sleep account for the presence of hallucinations just before or after sleep. However, other possibilities exist that would be consistent with the PAD model. First, it is likely that the transition from sleeping to waking dysregulates the attentional system. Second, sleeping tends to take place at the same time and in the same place each day, often in low illumination. These factors would not only provide the consistent context that we suggest leads to hallucinatory scene representation activation but also impair visual function.

Post-bereavement and other psychologically induced hallucinations may reflect the goal-directed nature of active attentional perception. It may be that difficulties in accepting the loss may potentiate expectations from specific scene representations to engender a purely top-down activation of an image (Schneck 1990). In support of this, the prevalence of post-bereavement hallucinations rises with the length of the relationship with the deceased (Rees 1971), and a better quality of the lost relationship and present loneliness predict hallucinations (Grimby 1993; 1998). These may be some of the uncommon top-down hallucinations. However, given that there is no evidence on risk factors for post-bereavement and other experience-engendered hallucinations, we cannot rule out impairments in sensory or object-perception processes.

7.4.2. Effects of cholinergic manipulations on attention and object perception. There is an extensive literature on the cognitive effects of anticholinergic drugs summarised by Everitt and Robbins (1997) and Ebert and Kirch (1998). Impaired performance on virtually all tests of alertness and attention following reduced cholinergic function is well established (reviewed by Beelke & Sannita 2002; Collerton 1986). Effects of cholinergic antagonism in many aspects of vision have been reported, including visual acuity, tracking performance, stereopsis, and spatial localisation (Caldwell et al. 1992; Fisher 1991; Kobrick et al. 1990; Meador et al. 1993; Mentis et al. 2000; Nobili & Sannita 1997; Penetar et al. 1988). In addition, cholinergic antagonists impair performance on simple and complex visual recognition and visual spatial tasks (Bentley et al. 2004; Dalley et al. 2004; Flicker et al. 1990; Meador et al. 1993; Obonsawin et al. 1998).

Cholinergic projections modulate the signal to noise ratio in cerebral cortex, with the effects of this depending upon the function of specific cortical areas (Everitt & Robbins 1997). In Yu and Dayan's (2002) computational model of cholinergic function, it has a specific role in modulating the interaction between top-down and bottom-up processing. Inhibition of cholinergic input gives a greater chance of incorrect pattern matching (a failure to select the correct proto-object in the PAD model) and allows the intrusion of an incorrect representation. In a similar manner to acetylcholine, dopamine is also considered to mediate a net increase in signal-to-noise ratio in select neuronal assemblies to maintain attentional focus (Dreher & Burnod 2002; Durstewitz & Seamans 2002; O'Donnell 2003). However, given that dopamine receptors are not prevalent in visual

processing areas (whereas muscarinic cholinergic receptors are), and dopaminergic agonists induce RCVH only in conjunction with cholinergic deficits (sect. 3.2), dopamine dysfunction may only be significant when there is existing cholinergically induced dysfunction in perceptual systems.

7.5. The phenomenology of recurrent complex visual hallucinations

7.5.1. Content and phenomenology of hallucinations. We agree with others (Behrendt & Young 2004; ffytche & Howard 1999; ffytche et al. 1998) that the content and character of RCVH primarily reflects the nature of visual processing. However, we particularly stress the interaction of multiple processes within scene perception rather than the activation or release of specific visual areas.

The separation of proto-objects from sensory input (Behrmann et al. 1995; Jankowiak et al. 1992; Servos & Goodale 1995) allows the possibility that top-down biasing can activate a hallucinatory image in the absence of that input in the same manner as Grossberg's (2000) adaptive resonance theory network account suggests. Rensink's proposal that top-down processes create a seen object from a proto-object can account for why hallucinatory images are generally sharply focused and vividly coloured even in patients with poor visual ability (Menon et al. 2003). Because the PAD model suggests the intrusion of an incorrect proto-object into subjective awareness only when the correct object is not attentionally bound, this would account for the rareness of doppelgangers – duplicate but different images of a person who is present. Attentional binding of the correct proto-object would take primacy over that of an incorrect one. Polyopia, seeing multiple instances of the same image of a non-hallucinatory object, is a different phenomenon (Cutting 1997, p. 106).

Selective visual attention within scenes operates at the whole object level, with separations between the representations for, amongst others, living and nonliving objects (Humphreys & Forde 2001). This can account for why whole as opposed to partial objects are generally hallucinated – people, rather than arms or feet, for example – and why these tend to be within a restricted range of categories. It is interesting to note that the only frequently reported hallucinations of separated body parts are of heads (Santhouse et al. 2000), consistent with evidence that faces are perceived as objects in their own right with specific cortical areas specialised for their processing (Farah 2000; Farah et al. 1998; Kanwisher et al. 1997). The focus on activation of individual proto-object may account for why single, as opposed to multiple, images are the commonest hallucination.

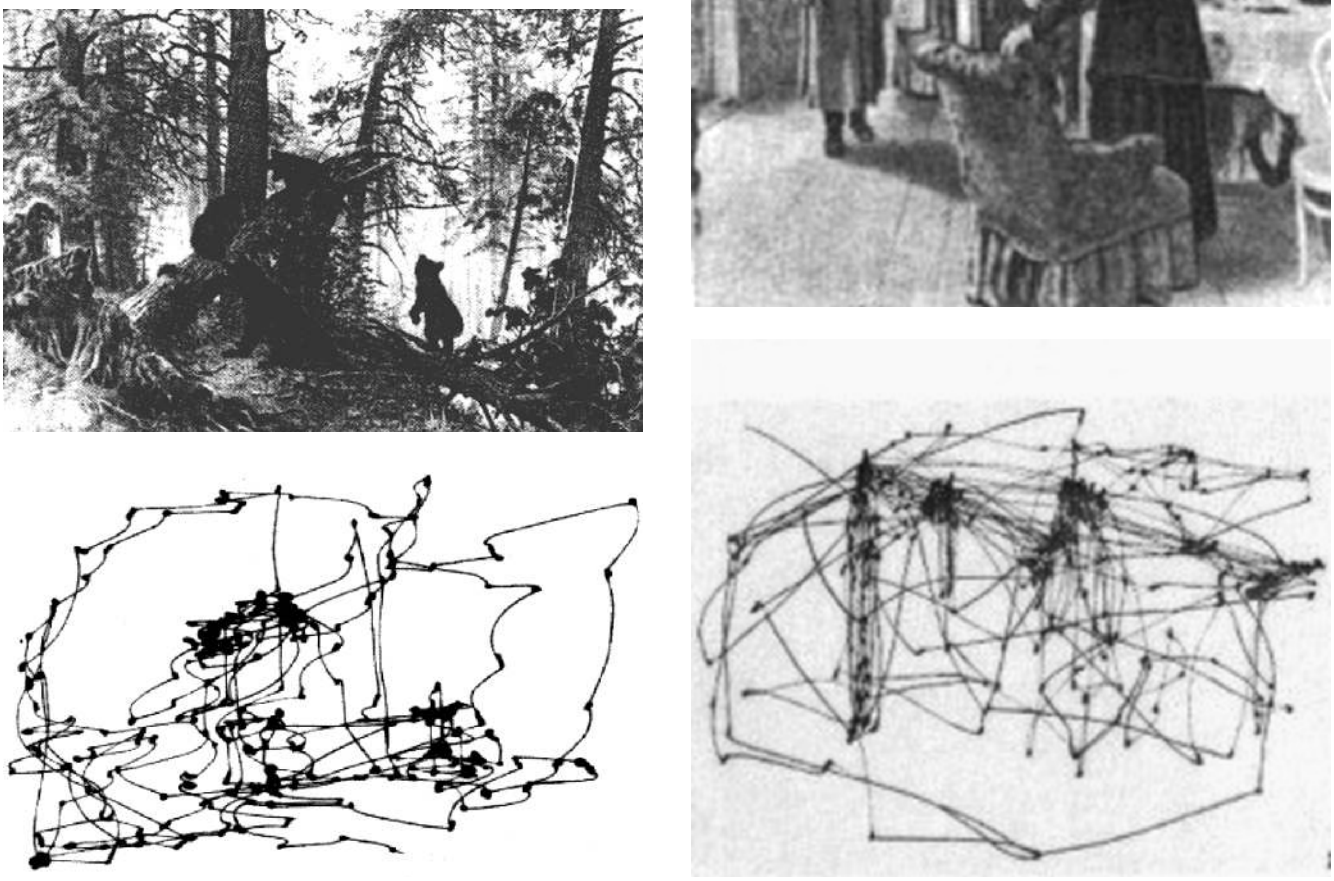


Figure 5. Illustration of eye movements indicating attention being given to animals and people in inspection of a scene. Yarbus (1967, pp. 172–79; reproduced with the permission of Plenum Press).

The immediate behavioural relevance of attentional biasing deriving from scene templates can account for why the content of the hallucination is generally consistent with expectations from the setting in which it is seen. Studies of eye movements in scene perception (e.g., Fig. 5) suggest that attention in complex scenes is more often given to people or animals than to inanimate objects, suggesting a systematic bias towards those stimuli. In addition, specific expectancies may bias subjective perception within scenes (Henderson & Hollingworth 1999). Taken together, these may account for why people and domestic animals are the most common hallucinatory images (Menon et al. 2003), given that most hallucinations occur in the home.

A failure of attentional binding may also account for the nature of hallucinatory distortions when they occur. Those features in faces which are exaggerated are those which are normally most attended to (Fig. 6; Henderson et al. 2001). A face object is also made up of eye, nose, mouth, cheek, forehead, and other objects (Scholl 2001). If these are not bound into a whole face perception, familiarity effects (Vecera 2000) would give greater salience to those objects usually most attended to. Hence, eyes and mouths tend to be exaggerated. We would suggest that distortion might be particularly likely when proto-objects are relatively non-holistic as a consequence of being relatively unfamiliar. This might account for why, to our knowledge, distorted features are not seen on recognised faces.

Abnormally small hallucinations may be a result of the hallucinated image being unintegrated into the scene representation. Thus, as ffytche and Howard (1999) suggested, it may be perceived against an unusually close background – in the same way that a close-up projector gives a small image.

The qualities of proto-objects are not well characterised. There is the danger that we might imbue them with the qualities that are consistent with hallucinated images – though conversely, the qualities of hallucinated images may illuminate those of proto-objects. For example, one of our patients with eye disease remarked that hallucinated buildings remained in the correct perspective as he moved around their exteriors, suggesting that activated image representations are orientation independent. Proto-objects do appear to be highly variable. Generation of an image by activation of a proto-object might explain the mixture of familiar and unfamiliar images, given that it does not suggest the necessary release of specific, pre-existing, visual memories. However, further development of the distinctions within proto-objects and their relationship with episodic memory is needed before we can say this with any confidence.

Once an image is hallucinated, it may become associated with a specific hallucinatory scene representation. This increases the probability of the same image being triggered again and may account for the repetition of specific images. As particular images become part of the scene representation, they will bias perception towards themselves and away from other proto-objects. This may provide a mechanism for the reduction in the range of images with time (Holroyd & Rabins 1996). Finally, the lack of an iconic scene representation may explain why panoramic hallucinations are rare, though it does beg the question as to why they occur at all.

7.5.2. Time and place. Dynamic attentional binding is dependent upon the prefrontal representations (templates, rules, or goals) of Miller and Cohen (2001; see also Vecera 2000). Templates must both be responsive to relevant information in the environment, and resistant to irrelevant information. Thus, a dysfunctional template may fail to respond to relevant environmental information, hence allowing the abrupt activation of the hallucinatory proto-object since the correct proto-object is not bound. Attention is then captured by the hallucination, continuing the exclusion of correcting information – hence the hallucination's persistence over a matter of minutes. This can also relate to how cholinergic function can modulate signal to noise in the cortex, as discussed in section 7.4.2. If this ratio decreases, attentional focus on the correct proto-object will become more difficult.

The necessity for an environmental trigger for a scene representation (a hallucinatory scene template as it were) can account for an otherwise puzzling feature of hallucinations – that they disappear on eye closure or on complete visual loss. Volitional images are as easily evoked with open as with closed eyes (McKelvie 1995). Cortical release and dream-intrusion models would both suggest that hallucinations ought, if anything, to become more pronounced, when sensory input is further reduced. The PAD model suggests that some sensory input is necessary to activate the scene representation that biases perception and attention towards the hallucinatory image. Without a scene representation, there is insufficient top-down bias to activate a perception even with a lack of sensory activation or attentional binding of the correct proto-object.

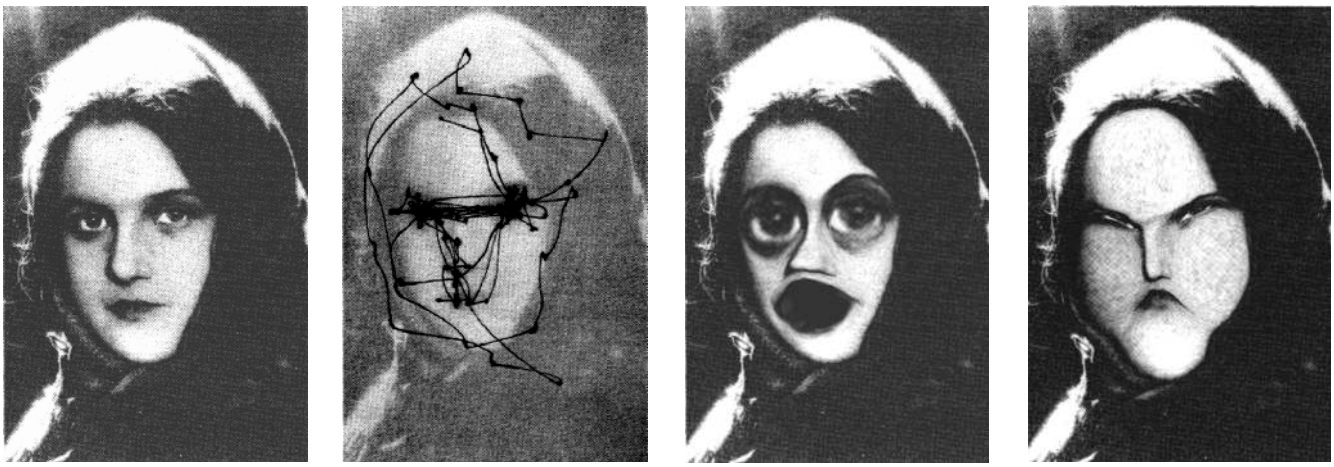
Hallucinations may be most common in dim light since bright light improves the perception of correct proto-objects, while no light removes the cues that activate the scene representation. The extinction of complex visual hallucinations by occipital transcranial magnetic stimulation (Merabet et al. 2003), suggests that strong bottom-up influences can bias perception towards non-hallucinatory images. The reactivation of a hallucinatory template by specific environmental cues may also account for those occasions when there is consistent location or timing of hallucinations.

Since we suggest that attentional processes drive the perception (sect. 7.1), this accounts for the image being at that attentional focus. That the image is perceived within a scene representation, can account for why it does not move with eye movements. Along with Howard et al. (1997), we have located the primary visual dysfunction in the ventral (what) visual stream, allowing the possibility that the dorsal (where) stream functions relatively normally. Thus, hallucinations are generally correctly located in space.

The intrinsic movement of hallucinated images suggests that either proto-objects contain movement information or that, once activated, a perceived image activates other systems for perceiving motion. We cannot distinguish between these possibilities at present.

7.6. Relationship with specific cortical pathologies

7.6.1. Evidence that normal scene perception depends upon the interaction between lateral frontal cortex and the ventral visual stream. There is long-established neuropsychological evidence that locates executive and attentional function in the frontal lobes (Passingham 1995) and object recognition in the ventral visual stream (Farah 2000; Grill-Spector 2003). These are linked by direct and indirect projections (Fig. 7), and functional imaging suggests that



A B C D

E

Figure 6. Effects of distorting images to reflect attentional focus. Figures show the effects of distorting the original picture (Fig. 6**A**) using eye movements as an index of attention (Fig. 6**B**) to emphasize attended features (nose, eyes, and mouth, Fig. 6**C**) or unattended features (cheeks, chin, and forehead, Fig. 6**D**) (Yarbus 1967; reproduced with the permission of Plenum Press, New York). Figure 6**C** best matches descriptions of visual hallucinations. "You have stretched lips, a thick nose, and you are grinning . . . your eyes are stretched and you have big circles under them" (Santhouse et al. 2000). See also the central face (6**E**) from an artist's montage of his own visual hallucinations in Parkinson's disease (Frucht & Bernsohn 2002; reproduced by permission of Lippincott Williams & Wilkins).

the working memory and semantic abilities thought to underlie image perception and retrieval and scene perception depend upon interactions between these frontal and posterior visual areas (e.g., Courtney et al. 1997; Fletcher & Henson 2001; Haxby et al. 2000; Ishai et al. 2000; 2002; Lumer & Rees 1999; Rowe et al. 2000; Vandenberghe et al. 1996; Wilson et al. 1993). More specifically, change blindness in scene perception, the phenomena in which a top-down scene representation overrides a bottom-up perception (Beck et al. 2001), and recognition of repeated real-world objects (Vuilleumier et al. 2002) are both associated with lateral frontal and ventral stream coactivation – among other areas.

As the PAD model demands, top-down attentional factors can bias perceptual processing in the absence of visual stimulation (Kastner & Ungerleider 2001). If frontal attentional systems are stressed by multiple tasks, there is greater activation of inferior temporal cortex and greater intrusions of incorrect information in working memory tasks (de Fockert et al. 2001). Manipulation of cholinergic function by physostigmine in normal people both improves performance on a facial recognition working memory task and decreases blood flow in prefrontal cortex and areas of the ventral visual stream (Furey et al. 2000).

7.6.2. Evidence for simultaneous dysfunction in frontal cortex and ventral visual stream in patients with recurrent complex visual hallucinations

7.6.2.1. Evidence from functional imaging. There is consistent evidence for activation in ventral visual areas in patients who are hallucinating and some, less consistent, evidence of abnormal frontal and ventral stream activation in patients who are prone to hallucinations.

Wunderlich et al. (2000) reported a case of hallucinations following occipital stroke. Among other areas, dorsolateral frontal and inferior temporal cortices were activated during active hallucinations. Another case reported by Kishi et al. (2000) had occipital cortex hypoactivity. ffytche et al. (1998) showed in patients with eye disease that ventral stream activation was a consistent feature of hallucinators, but frontal

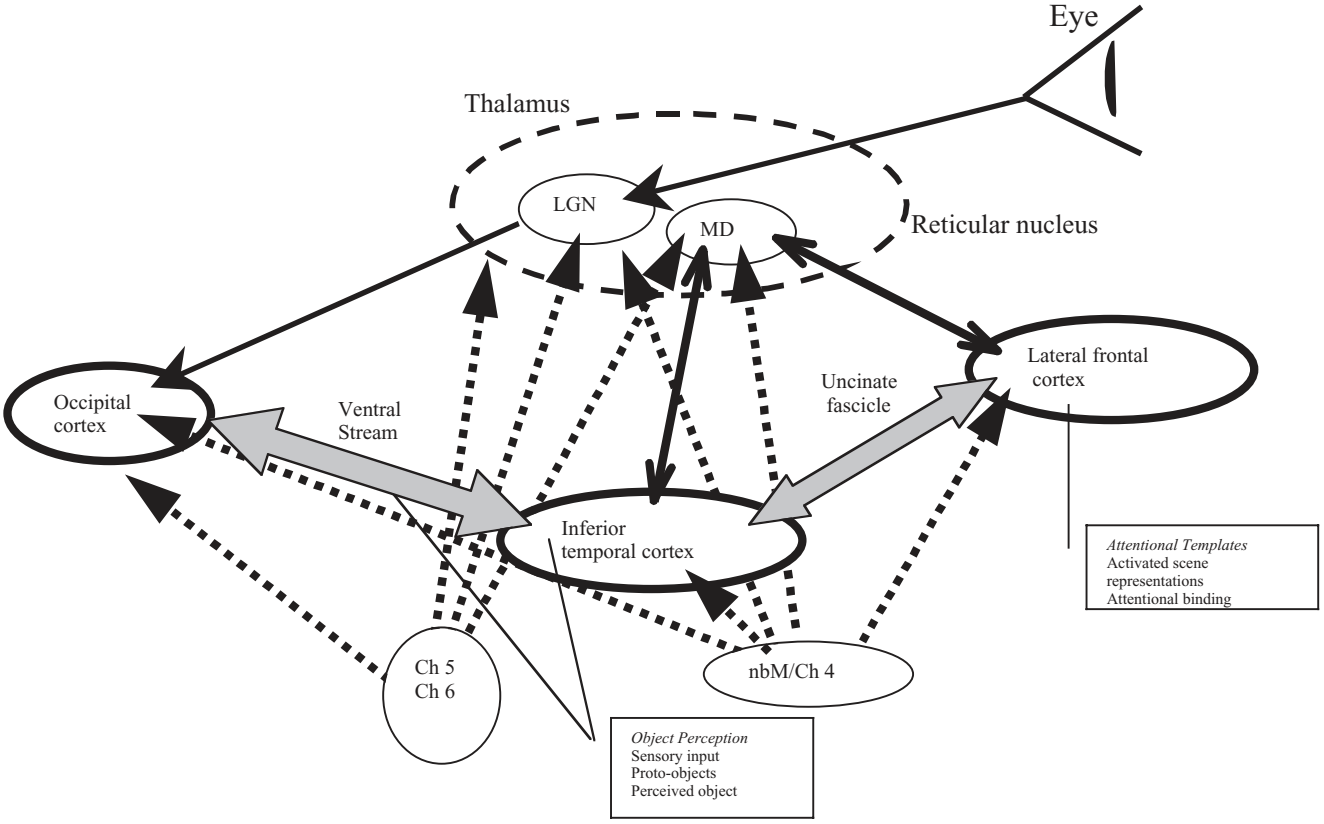


Figure 7. Illustration of the multiple information transfer and regulatory links between cholinergic and thalamic projections and the lateral frontal cortex and ventral stream. Specific thalamic nuclei are intimately involved with visual processing; the lateral geniculate nucleus (LGN) forms the major relay for information from the eye to occipital cortex and thence to the ventral visual stream for object recognition (Sillito & Jones 2002), while the mediodorsal nucleus (MD) maintains active corticothalamocortical loops with the ventral visual stream and, particularly, the frontal cortex (Sherman & Guillery 2002). Basal forebrain cholinergic cells in the nucleus basalis of Meynert (nbM/Ch 4) project to both frontal cortex and the ventral visual stream as well as directly to thalamic nuclei including the reticular, lateral geniculate, and mediodorsal nuclei (Mesulam 1995). Basal forebrain projections to the thalamic reticular formation have an additional regulating role on the transfer of corticothalamocortical information (Guillery et al. 1998). Frontal and inferior temporal cortices are linked by the uncinate fascicle (Ungerleider et al. 1989) and, with other indirect links and nbM cholinergic projections, form a functional visual information processing system (Dudkin et al. 1994; Gaffan et al. 2002; Masuda et al. 1997). Brainstem cholinergic projections from the pedunculopontine nucleus (Ch 5) and laterodorsal tegmental nucleus (Ch 6) also modulate the reticular formation and the mediodorsal nucleus, and, in addition, project to the lateral geniculate and other thalamic nuclei (Mesulam 1995), as well as the occipital cortex (Higo et al. 1996).

activation was more variable. Silbersweig et al. (1995) showed an association with combined active visual and auditory hallucinations in schizophrenia and increased activity in temporal and frontal cortices, among others. Imamura et al. (1999) showed an association with reduced ventral stream activation and relatively preserved temperoparietal activation in patients with dementia with Lewy bodies who were prone to hallucinations. Okada et al. (1999) showed that in Parkinson's disease, propensity to medication-induced hallucinations was associated with lower resting activation in left temporal and temporo-occipital areas, and, less reliably, right temporal and temporo-occipital areas. Adachi et al. (2000) demonstrated hyperperfusion in the lateral temporal cortex, striatum, and thalamus in hallucinating patients with Charles Bonnet syndrome. Howard et al. (1997) demonstrated that, in dementia with Lewy bodies, active hallucinations lead to a decrease in the responsiveness of striate cortex, suggesting a route for synergy in that hallucinations may in themselves reduce visual function.

In the dreaming state, there are changes in both frontal and inferior temporal cortices (reviewed in Braun et al. 1998; Schwartz & Maquet 2002), among others. However, in dreaming, there is underactivity of frontal cortex, suggesting a lack of attentional and scene-based influences. This may account for the different phenomenology of dreaming and argues further against dream intrusion as an explanation for RCVH.

7.6.2.2. Distribution of pathology in patients with high levels of recurrent complex visual hallucinations. With respect to cholinergic neuropathology, it has consistently been observed that there is a more extensive neocortical cholinergic deficit in dementia with Lewy bodies than in Alzheimer's disease (Perry et al. 1993; Tiraboschi et al. 2000; 2002). This raises the question of whether the higher prevalence of RCVH in dementia with Lewy bodies is related to more extensive cholinergic pathology, consistent with the psychopharmacological evidence reviewed in section 3.2. Based on neurochemical findings in autopsy brain tissue from prospectively assessed cohorts of patients with dementia with Lewy bodies, lower levels of choline acetyltransferase and of the nicotinic receptor subtype α7 are associated with visual hallucinations (Ballard et al. 2000; Court et al. 2001). No such relationships have been established for dopaminergic parameters in the cortex (Piggott et al., submitted), nor for cholinergic activities in the thalamus (Ziabreva et al., in preparation). Furthermore, extensive loss of cholinergic innervation of the thalamus in progressive supranuclear palsy (Javoy-Agid 1994; Kish et al. 1985; Shinotoh et al. 1999) as a result of brainstem cholinergic cell loss is not associated with high rates of hallucinations.

There is a striking relationship between levels of choline acetyltransferase in lateral frontal and temporal cortical areas and rates of visual hallucinations within the major dementing disorders (Fig. 8). In contrast, there is no such relationship with levels in the hippocampus, consistent with the lack of a relationship between verbal memory measures and RCVH (see Fig. 4 legend). This would suggest that localised rather than generalised cerebral dysfunction is critical. In vascular dementia, the relatively high prevalence of RCVH is not paralleled by particularly severe cholinergic deficits. Although hallucinations are rare in stroke, Rabins et al. (1991) showed a combination of intrinsic frontal and ventral stream pathology in hallucinators. This suggests that hallucinations in vascular dementia, and perhaps other disorders (e.g., in dementia with Lewy bodies; see Harding et al. 2002), may result from a combination of cholinergic and other pathologies.

Direct or indirect cholinergic modulation of the neocortical areas implicated in our model can also account for the

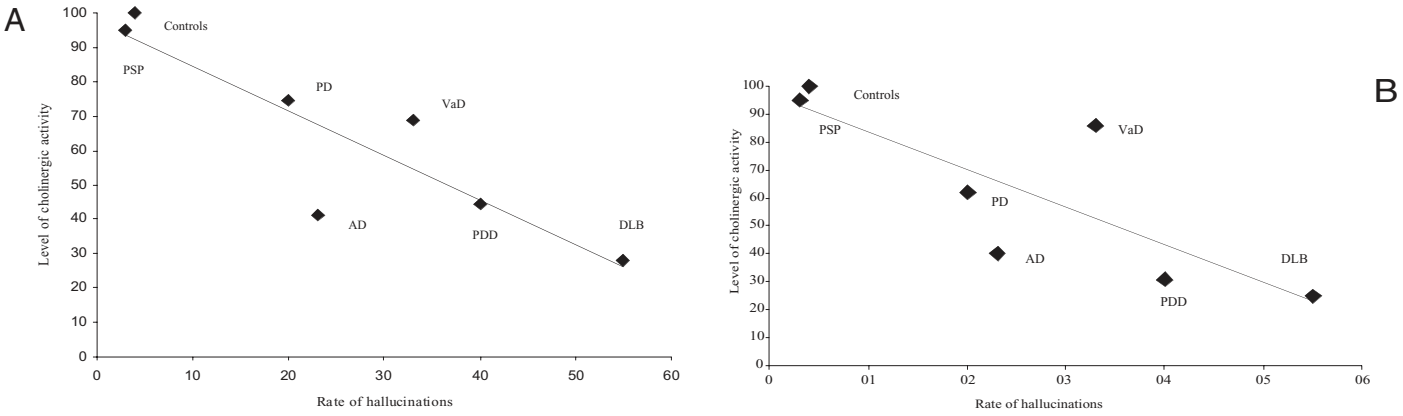


Figure 8. Relationship between cholinergic function and rates of visual hallucinations in dementing and neurodegenerative illnesses in (**A**) inferior temporal cortex (Brodmann Area 20), $r^2 = 0.78$, $p < 0.01$ and (**B**) lateral frontal cortex (Brodmann area 9), $r^2 = 0.65$, $p < 0.05$. Rates of visual hallucinations are taken from Figure 1. Cholinergic function is an averaged percentage of choline acetyltransferase activity of control values. Sources: progressive supranuclear palsy (PSP) (Javoy-Agid 1994; Kish et al. 1985; Shinotoh et al. 1999); Parkinson's disease without dementia (PD) (Perry et al. 1985; Ruberg et al. 1990); Alzheimer's disease (AD) (Bierer et al. 1995; Perry et al. 1977; 1985; 1990; Shaibani & Sabbagh 1998; Tiraboschi et al. 2000; 2002); Parkinson's disease with dementia (PDD) (Perry et al. 1985; Ruberg et al. 1990); dementia with Lewy bodies (DLB) (Perry et al. 1990; Ruberg et al. 1982; Tiraboschi et al. 2002); vascular dementia (VaD) (Perry et al. 1977; Reikkinen et al. 1987; Sakurada et al. 1990; Wallin et al. 1989). Cholinergic function in the hippocampus is not reliably associated with rates of visual hallucinations $r^2 = 0.46$, $p > 0.05$. Sources: AD (Beal et al. 1988; Ikeda et al. 1991; Kuhl et al. 1996; Perry et al. 1977; 1986; 1987; 1992; Sakurada et al. 1990; Smith et al. 1988; Tiraboschi et al. 2000); VaD (Perry et al. 1977; Sakurada et al. 1990); PD (Kuhl et al. 1996; Perry et al. 1986; 1987; Smith et al. 1988); PDD (Beal et al. 1988; Kuhl et al. 1996; Mattila et al. 2001; Perry et al. 1986; 1987; Smith et al. 1988); DLB (Tiraboschi et al. 2000).

induction of visual hallucinations by pharmacologically induced decreases in cholinergic function and their treatment by drugs that counter reduced function (sect. 3.2).

In the context of the PAD model, cholinergic dysfunction in these cortical areas induced by intrinsic anticholinergic factors in delirium could account for RCVH in this disorder. The reduction in function in both brainstem and basal forebrain cholinergic projections as a concomitant of slow-wave sleep (Jones 1993; 2003; Szymusiak et al. 2000; Vazquez & Baghdoyan 2001) may provide a physiological explanation of hypnopompic and hypnagogic hallucinations, with cholinergic hypoactivity occurring on the edges of sleep and loss of consciousness. As hypnagogic/hypnopompic hallucinations (independent of narcolepsy) have been identified as one of the commonest types of RCVH in the population as a whole (Fig. 1), it is clear that understanding the basis of these phenomena would provide insights into RCVH in disease. In narcolepsy, the major deficit of hypocretins (orexins; reviewed in Taheri et al. 2002) that, inter alia, stimulate basal forebrain cholinergic neurons (Eggermann et al. 2001), indicates that RCVH may arise in this disorder as a result of indirect dysfunction of this cholinergic pathway. Although associations between sleep disorder and hallucinations have frequently led to the implication of brainstem cholinergic mechanisms in hallucinations, it is equally plausible that the link between these two phenomena is pathology of the basal forebrain cholinergic system, which plays as important a role in transitions from wakefulness to slow-wave sleep or from non-REM to REM sleep. The hypothesis that hallucinations relate to REM sleep is not consistent with the evidence summarized earlier that hallucinations are associated with decreased cholinergic activity in the cortex, since REM sleep is associated with activity of both brainstem and basal forebrain pathways (in the latter, activity is even higher during REM than during waking; see Vazquez & Baghdoyan 2001).

Eye disease and schizophrenia pose greater challenges to our model, given the lack of established cerebral pathologies in these disorders. Eye disease will clearly result in impaired function in the ventral visual stream, whereas the relationship with cognitive impairment leaves open the question of disruption in frontal attentional function. Despite established neuropsychological impairments (sect. 7.2.1), pathological findings in schizophrenia are highly variable. Recent evidence for thalamic pathology (Jones 1997), together with known corticothalamocortical loops to frontal and ventral steam cortex, suggests one possible biological mechanism (Behrendt & Young 2004). Additional evidence of possible neocortical cholinergic dysfunction is that anticholinergic drugs impair prepulse inhibition of the startle response in schizophrenia (Kumari et al. 2003). Reduced muscarinic receptors have been detected in the cortex and thalamus in unmedicated schizophrenic patients (Raedler et al. 2003), confirming previous autopsy based findings (German et al. 1999; Karson et al. 1993; Powchik et al. 1998). Sherr et al. (2002) have demonstrated that nicotine improves eye tracking in schizophrenic patients, consistent with the long-standing implication of nicotinic receptors in this disease. Very recent reports (Minzenberg et al. 2004) draw attention to the role of the anticholinergic side effects of antipsychotic medication in schizophrenia in inducing cognitive impairment. This suggests a further method by which cholinergic function in schizophrenia may be disturbed.

The clear-cut thalamic dysfunction in deep brain stimulation, thalamic hallucinosis, and fatal familial insomnia can, in contrast, be incorporated in the PAD model, given the strong indirect regulatory pathways via the thalamus to our cortical areas of interest. Unlike other authors, however (Behrendt & Young 2004; Manford & Andermann 1998), we do not assign a central role to thalamic dysfunction in the majority of hallucinations, suggesting instead that this is only one of a number of causative factors.

8. Predictions from the PAD model

As with any multifactor model, falsification can be a challenge. The key concept in PAD is that a hallucination occurs when an incorrect proto-object takes the place of a correct proto-object. We would therefore say that it could be falsified if this were shown not to be so, that is, if an active hallucination could coexist with active perception of a correct image. This might be tested by, for example, combining perceptual tasks with imaging of visual cortex during and outside active hallucinations. Beyond this, we believe that the constraints that the PAD model suggests within visual processing can be tested at several levels.

The PAD model predicts that RCVH will be accompanied by psychological evidence of impaired attention and object perception, resulting in poor scene perception, and by imaging and pathological evidence of frontal and ventral stream dysfunction. The relationships that we have identified among hallucinations, cognitive function, and pathology by averaging disparate data need to be directly tested across at least the major conditions associated with RCVH – dementia, delirium, eye disease, schizophrenia, and the sleep–wake cycle. We would suggest that isolated lesions or impairments only rarely produce RCVH, although other forms of hallucinations or transitory hallucinations may occur. Comparisons across patient groups would allow the necessity for combined impairments to be examined. Thus, we would predict that the 10–20% of blind people who have RCVH also have attentional impairments and pathology that lead to impairments in frontal function.

Beyond these direct tests of existing indirect data, the model makes specific predictions. Thus, scopolamine challenge in normal individuals will induce the same attentional and visual perceptual impairments as seen in patients who hallucinate. The threshold for inducing these will be lower in patient groups prone to hallucinations. Cholinesterase inhibitors will have the opposite effects to those of antimuscarinic drugs. It also suggests that visual hallucinations in schizophrenia will correlate with the antimuscarinic effects of prescribed neuroleptics.

Manipulating the dopaminergic or other systems could assess the specificity of cholinergic dysfunction. We would predict this would only induce visual hallucinations in the context of pre-existing cholinergic dysfunction. Combination of these experiments with in vivo imaging of cholinergic and dopaminergic function in the ventral stream, frontal cortex, and areas thought not to be relevant, would further develop the model. We would predict that neuroimaging of dopaminergic indices such as FPCIT (the dopamine transporter) or D1/D2 receptors will show a weaker relationship with RCVH than would imaging of cholinergic dysfunction by, for example, IBVM.

The model would predict that individuals susceptible to

hypnagogia or hypnopompia have lower cortical cholinergic activity than those unaffected, and tend towards poorer attentional and perceptual performance, particularly when fatigued.

The relationship between scene perception and hallucinations can be investigated. For example, if hallucinatory scene representations are significant, we would predict an interaction between the frequency of repetition of specific images and the range of locations in which they occur – fewer images should be associated with fewer locations. Our suggestion of relative preservation of scene representations in the context of poor visual attention and perception can be assessed across patient and other groups by, for example, investigating change blindness. We predict that hallucinations should be more closely related to attentional and perceptual impairments than to problems in scene representations per se. Hence, change blindness should be relatively preserved. As the properties of proto-objects are defined, we would suggest that hallucinations should map onto these. The relationship we suggest between distorted and holistic perceptions can be tested.

The PAD model also accounts for existing effective treatments and predicts a range of new possibilities. For example, interventions that improve either attentional or perceptual function should reduce the incidence of RCVH. Thus, on the perceptual side, treatment of impaired vision reduces RCVH (Eperjesi & Akbarali 2004; Menon et al. 2003), as should bright lights or removing the cues that trigger the hallucinatory template by changing the environment (Diederich et al. 2003). Pharmacological improvement of alertness (Wesnes et al. 2001) is effective, as should be modifying the hallucinatory scene representation by associating another image with the environment. Attending to a correct image, for example, a photograph of a hallucinated person, should extinguish the hallucination.

9. Conclusions

We have combined and developed earlier models to account for why some people have recurrent visual hallucinations of a particular character, by relating hallucinations to a specific combination of cognitive impairments and particular patterns of brain dysfunction. At present, we have neuropsychological evidence in about a third of cases of RCVH (those in dementia and neurodegenerative disease, and to a lesser extent delirium, and schizophrenia), with evidence of regional cholinergic underactivity in about three-quarters (dementia and neurodegenerative disease, delirium, and hypnagogic and hypnopompic hallucinations). We look forward to the gathering of further evidence to test PAD and other models of hallucinations.

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NOTES

1. The term *Charles Bonnet syndrome* has been variously used to describe isolated complex visual hallucinations and visual hallucinations accompanied by a range of other phenomena (Menon et al. 2003). Because of this range of uses and because there is no evidence that either definition describes a different subjective experience, we will not use it ourselves.

2. We use the term *object perception* in this context to include not only the perception of inanimate and animate objects but also people, faces, and animals.

Open Peer Commentary

Common or distinct deficits for auditory and visual hallucinations?

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Abstract: The dual-deficit model of visual hallucinations (Collerton et al. target article) is compared with the dual-deficit model of auditory hallucinations (Waters et al., in press). Differences in cognitive mechanisms described may be superficial. Similarities between these models may provide the basis for a general model of complex hallucinations extended across disorders and modalities, involving shared (overlapping) cognitive processes.

The Perception and Attention Deficit (PAD) model of Collerton et al. proposes that a combination of deficits in attentional binding and object perception is essential to the occurrence of recurrent complex visual hallucinations (RCVH). We recently described a model of auditory hallucinations (AH) based on a different combination of deficits, specifically, deficits in intentional inhibition and context binding (Badcock et al. 2005; Waters et al., in press). Our model, herein designated the HEAR model (Hallucinatory Experience of Auditory Representations), was developed and tested in patients with schizophrenia and has not been explicitly applied to other disorders or modalities. Aside from the obvious focus on hallucinations in different sensory modalities, these two models also appear to focus on substantially different cognitive processing abnormalities. However, our commentary draws out similarities between the two models, as this may highlight fundamental constraints that produce hallucinations across all modalities and disorders. Overlapping cognitive mechanisms seem likely, for, as Collerton et al. note, individuals with RCVH often experience hallucinations in other sensory modalities.

Accounting for the wide phenomenological variation of hallucinations is a challenge noted by both Collerton et al. in the target article and Waters et al. (in press). According to the HEAR model, AH in schizophrenia arise at least in part from the intrusion of representations in memory for which specific contextual details have been lost. Consistent with this proposal, Waters et al. (2004) showed that patients with schizophrenia exhibit a more fragmentary recollection of contextual details. The key features of AH (including the compelling sense of reality and omnipotence, involuntariness, non-self-attribution, richness of voice features, and non-vocal experiences) can be accounted for by this subtle interplay between inhibition and memory (Badcock et al. 2005; Waters et al., in press).

Both models suggest a critical role of executive dysfunction. This is consistent with evidence of impairments of prefrontal cortex in disorders with high rates of visual (e.g., dementia with Lewy bodies) and auditory (e.g., schizophrenia) hallucinations. Whereas the PAD model suggests that this is an impairment of dynamic attentional binding, the HEAR model has focused on a deficit of intentional inhibition. Each hinges on the executive control of attention; that is, the selection of correct/incorrect proto-objects or relevant/irrelevant representations. According to Collerton and colleagues, hallucinatory experiences generally arise when there is impaired attentional binding together with a poor sensory response to the correct proto-object. Our model, however, emphasizes the heightened activation of an irrelevant, internal representation (incorrect proto-object); that is, hallucinations are related to a failure to inhibit currently irrelevant memory traces. This difference may simply be a matter of relative emphasis, given that dynamic attentional binding also involves resistance to irrelevant information. Indeed, we have suggested that the salience of currently relevant events depends critically on the ability to suppress memories of previous (now irrelevant) events (Badcock et al. 2005). Consequently, despite the difference in terminology, the mechanism of dynamic attentional binding appears to correspond closely to the process of intentional inhibition.

While the HEAR model links executive dysfunction to impaired memory, the PAD model combines attentional dysfunction with object perception impairments. Nevertheless, both are consistent with disturbed connectivity between frontal and temporal cortical circuits, and both attempt to describe sources of bias favoring the activation of the incorrect proto-object/irrelevant memory. For example, Collerton and colleagues suggest that current scene input/expectations are assumed to bias perception of an incorrect image. In contrast, in the HEAR model, the salience of irrelevant representations may derive from previous presentations and associated reward value. In sum, a perception/memory distinction appears to be a major difference between the two models. However, in studies of schizophrenia, a deficit emerges more consistently on higher-level object perception tasks closely related to memory (Gabrovska et al. 2002). Therefore, the overlap between these two models may be greater than it appears.

Collerton et al. stressed that an adequate model should account for the variation in frequency of hallucinations, yet support for the PAD model rests essentially on indirect observation of the overlap of cognitive and pathological impairments in disorders with high rates of RCVH. By contrast, our investigations have provided direct tests at the individual case level of the role of intentional inhibition and context memory in AH. For instance, we have shown that AH frequency in schizophrenia (but not the frequency of other symptoms) is correlated with degree of inhibitory dysfunction (Waters et al. 2003). We argued that this deficit underpins the intrusive nature of AH, a feature not directly addressed by the PAD model. In addition, we have also shown that intrusiveness is a key component of hallucinatory-like experiences in normal individuals (Paulik et al., submitted; Waters et al. 2003), raising the interesting possibility that inhibitory dysfunction may accompany other hallucinatory experiences in healthy individuals (e.g., across the sleep-wake cycle).

Because the HEAR model incorporates a context-binding deficit as well as an inhibitory control deficit, Waters et al. (in press) examined the percentage of patients with schizophrenia who were impaired on both cognitive processes. Almost 90% of schizophrenia patients currently experiencing AH showed the predicted combination of deficits, compared to only 33% of patients without hallucinations, representing approximately a sixfold increase in risk of having AH compared to patients without. Such findings provide compelling, direct support for the notion that these two deficits are significantly associated with the hallucinatory process.

Both models predict that isolated impairments would rarely produce hallucinations. Specifically, the HEAR model predicts that non-hallucinating individuals may exhibit deficits on either intentional inhibition or context memory, but not both. In direct confirmation of this prediction, patients with obsessive compulsive disorder (who, like schizophrenia patients with hallucinations, experience intrusive cognitions, but unlike hallucinators recognize them as self-generated) showed deficits in intentional inhibition but intact context memory (Badcock et al., submitted).

In sum, the possibility that deficient inhibitory control of attention, coupled with impaired memory (including context binding), could underpin both visual and auditory hallucinations merits its direct test, though the sufficiency of two deficits in accounting for these complex phenomena deserves scrutiny (see Waters et al., in press).

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Attentional deficit versus impaired reality testing: What is the role of executive dysfunction in complex visual hallucinations?

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Abstract: A "multifactorial" model should accommodate a psychological perspective, aiming to relate the phenomenology of complex visual hallucinations not only to neurobiological findings but also an understanding of the patient's psychological problems and situation in life. Greater attention needs to be paid to the role of the "lack of insight" patients may have into their hallucinations and its relationship to cognitive impairment.

> *We may . . . define an instinct as an innate disposition which determines the organism to perceive (to pay attention to) any object of a certain class, and to experience in its presence a certain emotional excitement and an impulse to action which find expression in a specific mode of action in relation to that object.*
> —William McDougall (1924, p. 110)

Perception is not a passive reflection of "things that are there" but an active process of unconsciously operating instinctive forces continuously creating a subjective, though usually adaptive, experience of seemingly external things and events (McDougall 1924; Schopenhauer 1844). Animals or people commonly feature in complex visual hallucinations because they meet unconscious affiliative impulses, and therefore it is not surprising that such hallucinations are associated with social isolation (Holroyd et al. 1992; Teunisse et al. 1994). For the same reason, and in response to unconscious social anxieties, patients with schizophrenia tend to hallucinate people's voices (see Behrendt & Young 2004).

Perceptual expectancies, which can be elicited by contextual or situational cues, or one's interests in certain kinds of objects, ultimately reflect, according to McDougall (1924), the working of instinctive impulses. Expectations or interests, which may not be explicitly conscious, are attentional mechanisms that crucially shape the content of subjective experience, although the possibilities are normally restricted by external sensory input. We hallucinate persons in their proper composition and place, rather than "floating on the ceiling" or with an "inverted face," because this is how we expect to see them. Insofar as hallucinations satisfy drives, the content of hallucinations should not surprise the hallucinator.

One is often struck in clinical practice to see how patients in

early stages of dementia are not puzzled by the impossibility of their observations of children or deceased relatives regularly visiting their home. Patients may repeatedly set the table for such hallucinated visitors without ever seriously questioning their actions. Less cognitively impaired patients who can show "insight" when describing their hallucinations may not necessarily be aware of the pathological nature of their experiences during the hallucinatory episode. We need to distinguish between insight on subsequent reflection and insight during actual experience. Despite demonstrating the former, patients with complex visual hallucinations may lack the latter, whereas patients with schizophrenia or paraphrenia, in whom hallucinatory experiences are entangled with delusions and persecutory fears, tend to lack both.

Of course, patients with Charles Bonnet syndrome, who have prominent peripheral visual impairment, see bizarre and apparently unexpected things, but in this condition, attentional mechanisms are much less restricted by peripheral sensory input in their effect on perception than is usually the case in dementia or schizophrenia. The question arises, how unexpected or bizarre do complex visual hallucinations really seem to patients with Charles Bonnet syndrome? How much of their insight is gained retrospectively, like the insight we gain into the implausible content of a dream only upon awakening? Indeed, during a dream we are not usually surprised to observe events that completely defy logic and past experience, as they would have been shaped at the time by attentional mechanisms reflecting unconscious desires or simply natural impulses of fear or curiosity.

By default, we accept externalised conscious experience as real, whether it occurs in wakefulness or as part of a dream. The dream intrusion hypothesis of complex visual hallucinations should not be discarded lightly on the basis of a lack of association with sleep disturbance. What should be of interest is that wakeful perception and dreaming are in a fundamental sense functionally equivalent states (Llinas & Pare 1991; Llinas & Ribary 1993) and, indeed, perception in wakefulness may be but an adaptive state of dreaming. Therefore, we could argue that reality testing is not something given to us by default; it relies on intact intellectual functioning accessible only in wakefulness.

It appears that inconsistencies in the perceived world prompt questioning of reality only if the perceiver has sufficient deductive or reflective cognitive capacity. One has to be able to note that an observation defies one's intuitive logic or does not conform to previous experience, while having at the same time access to the rather abstract notion that an experience one is having might not be real. What makes it even more difficult to perform this cognitive step is the fact that what we see in a hallucination or dream is usually expected unconsciously. Alternatively, it may be lack of capacity to interact with the environment in a coordinated and goal-directed fashion that prevents us from questioning the reality of our dream experiences. Cognitive executive impairment may similarly amount to a deficit in one's ability to translate instinctive impulses into sustained action in accordance with hierarchical behavioural strategies, while such impulses continue to manifest themselves in perception. Perception, whether in wakefulness or dreaming, primarily obeys the *pleasure principle*, in Freud's terms, whereas adherence to the *reality principle* can be regarded as higher cognitive performance involving the lateral prefrontal cortex.

It may be impaired reality testing, partly in combination with unconscious desires or fears (Asaad & Shapiro 1986), that converts a hallucinatory predisposition into recurrent complex hallucinations. Lack of insight as a result of cognitive impairment may be central in promoting the gradual development of simple visual hallucinations into recurrent complex visual hallucinations (which would explain the "double dissociation"), which is similar to how simple noises in patients with hearing impairment can develop over time into voices if there is concomitant psychological or cognitive impairment (Gordon 1987; 1995; 1996). For verbal hallucinations to become elaborate and personified in the course of mental illness (Nayani & David 1996), lack of insight can be maintained at the cost of relatively little cognitive impairment (voices can be heard from behind walls). In contrast, for visual hallucinations to acquire prominence in mental illness, the patient presumably will have to be more profoundly impaired in reality testing, which may partly explain the association between visual hallucinations and organic psychosis that is recognised clinically.

Lack of insight as a result of cognitive impairment and attentional pressures due to psychological problems play complementary roles in relation to the biological predisposition to hallucinate, as illustrated by Charles Bonnet syndrome, in which major psychopathology is absent and consciousness is unimpaired yet peripheral sensory impairment is prominent (Gold & Rabins 1989), or by bereavement states, in which yearning for the deceased can maintain complex visual hallucinations despite relatively intact sensory and cognitive functions.

No explanation is given by Collerton et al. in the target article as to precisely how executive dysfunction, frontal hyperactivity (as opposed to hypoactivity), impaired arousal, or cholinergic deficits that have been reported in clinical populations with complex visual hallucinations relate to their notion of "attentional impairment"; and it is not argued convincingly why "binding" of "incorrect proto-objects" into "scene representations" should be a common denominator of such impairments. Predictions regarding circumstances and content of complex visual hallucinations should be made using a model of attention and perception that is based – independently from what is to be predicted – on physiological and neuroanatomical insights, in order to prevent the impression that what is presented as an explanatory model does not go beyond an attempt to rephrase, in a hypothetical language, correlations between hallucinations and cognitive or visual impairments.

Furthermore, a distinction has to be made between sensory processing and perception. In our view, disruption of sensory constraints that are normally imposed on thalamocortical gamma synchronisation underlying conscious perception constitutes an essential biological predisposition to hallucinations – and it is here that we see the role of reticular thalamic nucleus dysfunction (not the "thalamus" as such) – but the extent to which this predisposition is turned into hallucinations and even psychosis crucially depends on personality problems, coping skills, and social stresses faced by the individual (Behrendt & Young 2004), as well as the individual's cognitive capacity for reality testing.

Catatonia is the Rosetta Stone of psychosis

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Abstract: Recurrent complex visual hallucinations (RCVH) represent a form of psychosis. It may be useful to compare RCVH to another form of psychosis, catatonia. Both include a long list of medical illnesses and have been examined using several different hypotheses. Catatonia has a variety of hypotheses, including neurocircuitry, neurochemistry, and an integrated neuropsychiatric hypothesis. This hypothesis for catatonia supports Collerton et al.'s Perception and Attention Deficit model (PAD) for RCVH.

There have been several reviews of catatonia and the ascribed causative illnesses. Two recent books on catatonia provide a variety of hypotheses for this form of psychosis (Caroff et al. 2004; Fink & Taylor 2003). Specifically, there are genetic, neuroanatomical, neurochemical, and neurophysiologic hypotheses to explain why it occurs. The hypothesis of top-down modulation as applied to catatonia (TDMC) shares some similarities with the Perception and Attention Deficit (PAD) model applied by Coller-

ton et al. to recurrent complex visual hallucinations (RCVH) (cf. Northoff 2002). Northoff's top-down modulation model (TDMC) differs from the Collerton et al. top-down modulation hypothesis as applied to visual hallucination (TDMVH) discussed in the target article. Collerton et al. assert that RCVH result from lack of sensory input and/or cortical hyperexcitability. Like TDMC, PAD is supported by brain imaging, electrophysiology, neurochemistry, pharmacology, neuroanatomy, and a review of the phenomenological literature.

Studies of both catatonia and RCVH have included a review of the literature of the phenomenology without limiting the definition to psychosis. Psychosis itself has several definitions: in one, it is defined by impaired reality testing. That is, the patient does not have insight into having hallucinations and believes that these phenomena are genuine. Psychosis includes: hallucinations (of any modality), delusions, bizarre and disorganized behavior, and catatonia. The research on catatonia has focused on motor signs.

The perceptual and attentional deficit in catatonia is anosognosia of the position of rest. In RCVH, the deficit is of the correct proto-object. To apply the terminology of the TDMC model to RCVH, the deficit would be termed dysagnosia of the visual proto-object and/or anosognosia of vision. The neuropsychological concept of anosognosia of the position of rest is used to explain the phenomena of posturing and waxy flexibility. The patient does not know his or her position of rest. Hence, the arm, when placed in a particular position, tends to remain in that position (waxy flexibility).

The neuropsychological concept of anosognosia of the proto-object of rest is useful in RCVH. The patient does not know the correct proto-object. Thus, when the patient views a scene, the incorrect proto-object appears in the scene. The patient continues to "see" the proto-object in multiple settings, and the proto-object may return at times of reduced levels of consciousness. The view of the proto-object of rest is important to address RCVH in schizophrenia and posttraumatic stress disorder (PTSD).

The work of Northoff (2002) has generated a model for catatonia that is analogous to Figure 3 of the target article, "The model of scene perception." Furthermore, Carroll et al. (2005) have documented the neural circuit in a figure that is analogous to Figure 7 in the Collerton et al. PAD model. In catatonia, we have identified the first complete neural circuit of a form of psychosis. Collerton et al. have identified the second complete neural circuit of a form of psychosis. It is important to point out that both hypotheses identify circuits rather than sites.

The PAD model does not specifically address the role of the proto-object in schizophrenia. In patients with schizophrenia, the proto-object may arise from the delusional processes in this disorder. The erroneous proto-objects are formed from areas known to be dysfunctional in schizophrenia, including the inferior temporal cortex and lateral frontal cortex. It is probable that the mediodorsal nucleus of the thalamus is also deficient in schizophrenia.

In PTSD, the phenomenology of RCVH has been described but is not a DSM-IV criterion. It is seen in a minority of patients and usually involves proto-objects that arise from the episode(s) of trauma. For example, in a patient with combat-related PTSD, the proto-object might be the image of someone the patient witnessed in the traumatic event. Very often, these patients consciously "know" that the image is not genuine but still "feel" that it is. The erroneous proto-objects are formed from areas known to be dysfunctional in PTSD, including the inferior temporal cortex and, specifically, the amygdala. Probably the uncinate fascicle is hard wired between the amygdala and the lateral frontal cortex (Schore 1998). The RCVH may be precipitated by sensory triggers. These may be real or perceived objects that the patient associates with the trauma. It is seeing a trigger or perceiving it through another modality that "triggers" the memory of the trauma.

The PAD model also identifies neurochemical etiologies for RCVH. These include cholinergic, dopaminergic modulation; however, the TDMC model proposes that glutamate may play a role at the cortical level. Catatonia may result from low GABAergic activity, low dopaminergic activity, and high glutaminergic activity, or a combination of these (Carroll et al. 2005; Northoff 2002). The role of glutamate, the NMDA (N-methyl-D-aspartate) receptor, and possible excitotoxicity may prove to be important in RCVH.

The study of catatonia has been advanced by the TDMC model. Like RCVH, there are multiple etiologies and hypotheses of catatonia. However, it is these integrated models that identify complete neural circuits that will advance the study of the psychoses.

Neural correlates of visual hallucinatory phenomena: The role of attention

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Abstract: The Perception and Attention Deficit (PAD) model of visual hallucinations is as limited in generality as other models. It does, however, raise an interesting hypothesis on the role of attentional biases among proto-objects. The prediction that neither impaired attention nor impaired sensory activation alone will produce hallucinations should be addressed in future studies by analysing partial correlations between putative causes and hallucinatory effects.

Collerton et al.'s Perception and Attention Deficit (PAD) model proposes an interesting pivotal role for attention processes in generating recurrent complex visual hallucinations (RCVH). Neuroanatomical evidence should, however, be explored in more detail. If the authors' view is correct, then hallucination probability should somehow depend on lesion laterality, because the neglect literature has shown a right-hemisphere bias in attention deficits. In this sense, the hypothesis is well supported by the observation that 11 out of 12 of the patients reported by Bender et al. (1968) had lesions in the right hemisphere. A right-sided massive bias in association with visual hallucinations had also been noted by Teuber et al. (1960, pp. 104–105). In this regard I believe that the authors should also consider an important role for the parietal network, which is involved in imagery and visual attention, in addition to the contribution of prefrontal and ventral pathways.

Attention may indeed represent an important role in the phenomenology of RCVH, but this does not imply that the proposed dual necessity of attentional or perceptual disturbances for hallucinations to occur is true. Accordingly, Lessel (1975) reported that he had never detected any unsuspected brain lesion among his patients with hallucinations related to blindness. We were able to document similar findings in macular degeneration patients, both psychophysically and anatomically. The claim that attention is the primary mechanism for biasing competition among proto-objects is reminiscent of the literature concerning rivalry and multistability (Castelo-Branco et al. 2000; 2002; Fries et al. 2005). Perceptual interpretation may change with constant retinal stimulation, and this effect can also be modulated by attention. It would be interesting to know whether the PAD model envisages pathological perceptual multistability caused by attentional impairment.

The PAD model suggests that an incorrect proto-object intrudes on perception only when the correct object is not attentionally bound. The authors state that the PAD model could be falsified if an active hallucination could coexist with active perception and attention of a correct image. Polyopia may be discarded as a falsification, although it could still be argued that seeing objects that are not present at a given location (even if they are real at others) may be considered true hallucinations. Other visual perseveration phenomena are, however, more problematic. As early as 1968, Bender and colleagues reviewed palinopsia ("visual perseveration in time") and reported that it is often also associated with visual perseveration in space, for example, illusory visual

spread, and that such phenomena usually occur in field areas with decreased acuity (Bender et al. 1968). Areas with low acuity are unlikely to catch attention, and it is therefore again difficult to grasp how attention can be a necessary condition for hallucinations to occur. If attention deficits need to coexist with sensory impairment for hallucinations to occur, then it is surprising that little or no work is reported on coexistence of neglect syndromes superimposed on age-related macular degeneration (AMD). Furthermore, many counterexamples can be found in the context of AMD for the postulate that attention accounts for the content of the hallucination being consistent with expectations from the setting in which it is seen. These violations of the prediction that the image usually appears in a contextually correct location and with the correct orientation do not dismiss the PAD model, but they raise the possibility that it does not generalize to conditions such as AMD. A good example of such exceptions is tesselopsia (perception of brickwork-like geometrical patterns), which may also occur in normal subjects under particular visual stimulation conditions (Tass 1995; 1997) or even be caused by electrical stimulation of the retina. In these cases the role of an attentional mechanism is unlikely.

Concerning the meta-analysis, I do believe that future studies should clarify and discard the possibility of random and systematic biases. The PAD model is based on the severe attentional/object perception deficits in dementia with Lewy bodies. However, because the available evidence is correlative, one should attempt more solid quantification of perceptual and attentional deficits. The data in the target article's Figure 4 suggest that perceptual and attentional factors share a lot of common variance. That is why a partial correlation analysis would be so important to reveal the true contribution of each factor and to assess whether the points correlated with high incidence of RCVH have strong independent correlations with both predictors.

Finally, concerning the role of certain neurotransmitters and implications of the PAD model for prevention and therapy of RCVH, the authors should take into account the fact that dopamine neurotransmission is not only modulating high-level areas. In fact, dopamine receptors are present even in all layers of the retina, in the LGN and V1, as shown by the work of Qu et al. (2000), Zhao et al. (2001; 2002), Bodis-Wollner (1990), and others. It is also proposed that attending to a photograph of a hallucinated person should extinguish the hallucination. This does not work in cases due to AMD or in schizophrenia (in the auditory domain; see Dierks et al. 1999).

In summary, the model is interesting and valid, but it has to be further refined: in particular, in defining whether the role of attention is merely modulatory or, instead, at least partly causal.

A signal-detection-theory representation of normal and hallucinatory perception

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Abstract: Collerton et al.'s Perception and Attention Deficit (PAD) model argues that all recurrent complex visual hallucinations (RCVH) result from maladaptive, deficient sensory and attentional processing. We outline a constructivist-based representation of perception using signal detection theory, in which hallucinations are modeled as false alarms when confirmational perceptual information is lacking. This representation allows for some individuals to have RCVH due to a criterion shift associated with attentional proficiency that results in an increased awareness of the environment.

In the target article, Collerton, Perry, and McKeith (Collerton et al.) rely on cognitive psychology models of normal scene perception as a foundation for their proposed Perception and Attention Deficit (PAD) model of recurrent complex visual hallucinations (RCVH). Such cognitive constructivist models propose that scene perception normally utilizes the sensation or detection of signals available in the environment that are modified by top-down processes, such as memory, expectation, and attentional state (e.g., Rensink 2000a; 2000b). The commonness of illusions (e.g., Post et al. 2003), hallucinations (e.g., Laroi & Van Der Linden 2005), and other forms of misperception of veridical objects confirms the characteristic noisiness of the perceptual construction process. Signal detection theory (SDT) can be used to help disambiguate types of perceptual error that lead to hallucinations (for example, see Ishigaki & Tanno 1999). Specifically, SDT can separate an increase in hallucinations caused by observer inability to discriminate between the presence and absence of objects, from an increase in hallucinations caused by an increased willingness to interpret ambiguous perceptual information. Applying the signal detection theory, we suggest that instances of perception can be classified into four categories: veridical perception (hits), veridical non-perception (correct rejections), lack of awareness (misses), and hallucinations (false alarms).

Collerton et al. provide an impressive array of evidence supporting the PAD explanation, and they rightly point out that many RCVH are associated with systematic neuropathological symptoms. They base much of their thesis on establishing such biological bases, but singularly argue that all RCVH result from a sensory/attentional deficit. A more global consideration of perceptual error not only examines false alarms, but also considers perceptual errors of omission in which healthy observers are unaware of clearly visible stimuli. A signal-detection-theory characterization allows for a criterion variable, which can bias the ratio of errors of hallucination and errors of omission. This approach entails that some individuals with increased instances of RCVH benefit from an accompanying improvement of veridical percepts due to willingness to err more on the side of false positives versus false negatives. In such individuals, occurrences of RCVH may not be pathological, but rather by-products of a shifted and in some respects enhanced attentional mechanism (Aleman et al. 1999).

Figure 1 shows three signal-detection graphs illustrating a constructionist view of perception in which the presence of an object in the real world can be thought of as a signal to perceive that object. When no object is present, there is a "noise only" distribution of how convincing the stimulus is that an object is present. The distribution can be thought of as resulting from factors such as misleading perceptual information, expectation, and varying attentional state. When an object actually exists, the extra sensory/perceptual information or signal is added to create a "signal + noise" distribution. The *noise only* and *signal + noise* distributions are plotted along an axis indicating the vividness of a percept or, in other words, the convincingness that the experienced stimulus is veridically based on a real object. The *criterion line* indicates the observer's threshold for interpreting the stimulus as a real object. Consistent with Collerton et al.'s observation that attention and other top-down cognitive processes mediate perception, we propose that the location of the criterion line depends on an individual's specific attentional parameters, such as the acuity and range of attention. The criterion line divides each of the two distributions into two regions. The region most strongly emphasized by Collerton et al. is the portion from the *noise only* distribution that lies above the criterion line. This region, traditionally thought of as that of false alarms, represents the occurrence of hallucinations, or the perception of objects when none actually exist. Another region that we would like to emphasize is the portion from the *signal + noise* distribution that lies below the criterion line. This region, traditionally thought of as that of misses, represents the occurrence of lack of awareness of real objects, or insensitivity to signals too weak or unexpected to promote construction of a perceptual object.

Figure 1a illustrates a theoretical set of distributions for a normal observer in which there are both perceptual misses and hal-

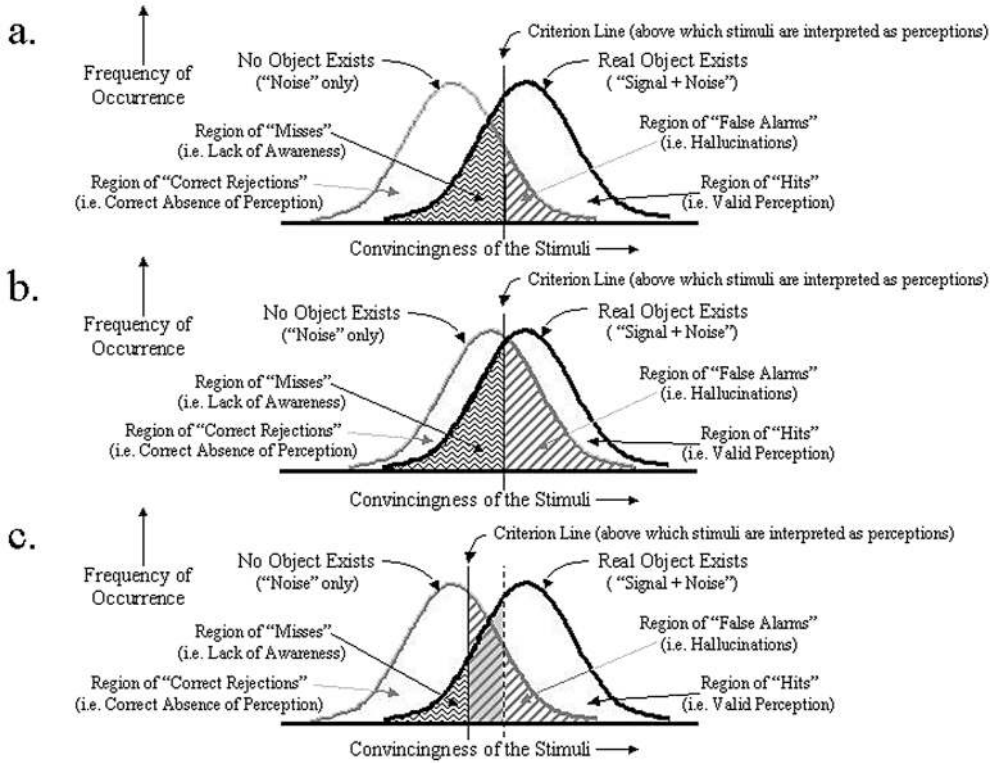

Figure 1 (Dolgov & McBeath). Signal-detection-theory representation of normal and hallucinatory perception. (a) Normal/typical person with low rate of RCVH (false alarms). (b) Person with more frequent RCVH, caused by a deficiency in ability to discriminate, consistent with PAD. (c) Person with normal ability to discriminate but more frequent RCVH, caused by a criterion shift. Such an individual also has enhanced veridical perception (shaded region).

lucinations. Here the observer has a criterion line that produces a balance in which there are notably fewer hallucinations than missed perceptions, presumably because of a higher cost for hallucinating. Figure 1b shows a new set of distributions for a pathologic individual as described by Collerton et al. The *noise only* and *signal + noise* distributions are placed closer together to reflect that persons who suffer from pathologic perceptual disorders have difficulty differentiating veridical reality from hallucinated reality. Here, observers have an enlarged region of hallucinations as a result of perceptual deficiencies that effectively add to the convincingness of stimuli when no object is present. In this representation, the criterion and the distribution when real objects are present is the same as that shown in Figure 1a for normal individuals, so the proportion of veridical perceptions (hits versus misses) remains the same. There is simply less discriminability between the distributions, resulting in more hallucinations.

In Figure 1c we propose a possible alternative representation that produces increased RCVH without requiring perceptual deficiency, instead doing so by having a more liberal criterion for perceiving objects than that of the normal person in Figure 1a. This more liberal location of the criterion line reflects an observer with an attentional mechanism capable of perceiving signals in the more subtle range of available ambient stimuli. Although this criterion shift increases the rate of hallucinations compared to a typical person, it is potentially advantageous in that the region of misses or lack of awareness of real objects is made notably smaller, resulting in a corresponding increase in perception of weakly indicated objects. Thus, there is a new enhanced region of perception within the *signal + noise* distribution, lying between the normal and more liberal criterion lines (shown as shaded in Fig. 1). The importance of clarifying this alternate model for increased hallucinations is that it acknowledges the potential for a population of individuals who experience more frequent RCVH than the typical person, yet who are not only *not* perceptually deficient, but rather individuals who might more accurately be described as perceptually enhanced and more aware of subtle perceptual information. A plausible explanation for such a shift in perception/attention is based on research on the role of attention in visuo-spatial working memory (Pringle et al. 2004). Specifically, attentional processes determine which parts of the immediate environment are stored explicitly or implicitly in memory. We posit that in an individual with a liberal criterion, the explicit-to-implicit ratio is biased toward formation of more explicit memories, thereby resulting in conscious awareness of a larger proportion of the signals in the surrounding environment, as well as enhanced or shifted perception.

The PAD model of RCVH is well thought out and adequately accounts for hallucinations in a pathologic population. However, we suggest the model could be improved by acknowledging that some RCVH may not be pathologic, but rather could be by-products of a more liberal criterion in interpreting weakly indicated stimuli as veridical objects. Furthermore, this liberal criterion can be adaptive[1] in that it reduces perceptual errors of omission of real objects, resulting in an enhanced perception and awareness of subtle real objects and events in the environment.

NOTE

1. The cost of experiencing RCVH must be outweighed by the benefit of an increased number of veridical percepts.

Perception is far from *perfection*: The role of the brain and mind in constructing realities

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Abstract: Dichotomizing perceptions, by those that have an objective reality and those that do not, is rejected. Perceptions are suggested to fall along a multidimensional continuum in which neither end is totally "pure." At the extreme ends, perceptions neither have an objective reality without some subjectivity, nor, at the other end, even as hallucinations, are they totally dissociated from reality.

Higher-level visual cognition is achieved through complex and dynamic interactions, both within the many processing components of the visual system and between the visual system and other brain areas and systems. Before considering the multiplicity of factors that play a role in determining what we see and experience, it is important to pull back and consider one's basic conceptualization and theoretical outlook. Such philosophical issues have (implicitly, if not explicitly) implications for how we approach and conduct research, and even for the very questions we ask and the type of answers we seek (Dror & Dascal 1997; Dror & Thomas 2005).

A naïve view of visual cognition deems that it normally provides perceptions and experiences that have an objective reality. Failures to see things correctly, such as in hallucinations, need to be investigated and explained as system malfunctions. This framework dichotomizes perceptions as either "normal" (i.e., having an objective reality) or as "failures" (i.e., lacking an objective reality). Other perceptual problems, such as illusions, misidentifications, distortions, and misperceptions, may be considered as a subcategory in which perceptions "fail" yet stem from an "objective reality" rather than being totally dissociated from it.

The nature of perception. An alternative view is suggested in which perceptions are seen to fall along a multidimensional continuum. Even at the far extremes of the continuum, perceptions are not entirely "pure." At the one extreme, perceptions never have a full and total "objective reality," and at the other extreme end, hallucinations and delusions are not totally dissociated from reality.

The underpinning of this framework is not its continuum nature, but that perception is never totally objective to begin with. The lack of objective reality across the plurality of perceptions results in a multidimensional continuum. If one adopts this view, then rather then asking what is wrong or wondering why the system is failing, one tries to understand what factors mediate perception and how they interact. Perhaps the former outlook derives from a more clinical approach and perspective whereby some people are considered "normal" and hence perceive the "objective reality," whereas patients and clinical populations have "disorders" because of system failures to have an "objective reality."

Understanding that *perception* is far from *perfection* provides a contextual framework for examining the visual cognitive system. The mind and the brain are dynamic systems that play active roles in how we perceive and construct realities. Our perceptions depend on a whole range of factors, which I will try to illustrate.

Mental states. Mental states play a critical role in how perceptual information is processed. For example, our hopes, fears, and expectations affect what we perceive. In a recent laboratory experiment, emotional states were shown to affect whether two visual patterns were perceived as the same or as being different (Dror et al. 2005). There are numerous phenomena that can further illustrate how the mind plays an active role in how we perceive and construct reality, such as motivation, wishful thinking, cognitive dissonance, self-fulfilling prophecies, and confirmation bias (e.g., Darley & Gross 1983; Festinger & Carlsmith 1959; Snyder et al. 1977).

Cognitive factors. Visual cognition is a set of complex and interactive processes (e.g., Grill-Spector et al. 1998). No cognitive system works on its very own. Each cognitive system is intertwined and interacts with a range of other cognitive systems. For example, how information is understood, processed, and collected depends on how it compares against information already stored in memory (e.g., Kosslyn et al. 1994). The influence of such processing further depends on how it is represented, available resources, goals of the system, context, and other factors (e.g., Eberhardt et al. 2004; Maier 1930; Reuter-Lorenz 2002; Smith & Dror 2001).

Perceptual mechanisms. Even the lower-level sensory mechanisms, which initially perceive and encode the input to the system, are not passive or isolated from a variety of factors. They try to make (impose) sense and consistency on the world around us, even when the input presents ambiguous or impossible information (e.g., Dror et al. 1997). Among other things, the perceptual mechanisms adjust and change sensitivity thresholds, segment and chunk information in a variety of ways, and perceive colour and lighting based on their own parameters settings (e.g., Land 1964; Prinzmetal 1995). Therefore, much of what we perceive, even at the lower-level mechanisms, is dependent on the perceiver rather than reflecting objective reality.

Bottom-up, top-down, and mental imagery. Perception and cognition, at all their levels, depend on bottom-up, data-driven processes and on top-down, conceptually driven processes (e.g., Humphreys et al. 1997). The top-down processes may be viewed as the source of subjectivity, individualization of perception, and distancing from the "objective reality." However, even the sensory mechanisms in a purely bottom-up mode do not reflect reality as it "really" is.

Mental imagery is a range of phenomena where perception and experience occur without direct perceptual input. Positron emission tomography (PET) and other studies have demonstrated that the same brain substrates are used to process imagined and perceived images, except that in imagery the input comes from other cognitive systems (Kosslyn et al. 1993; 1997). Furthermore, visual mental rotation, for example, shows that imagination follows the laws of physics and rotations in the physical world (e.g., Smith & Dror 2001). Hence, although all the processes involving imagery do not have direct input from the external world, the input and the way it is processed is not dissociated from normal perception.

Summary and conclusions. We are different people, with different experiences, different views, and different brains and sensory mechanisms. This entails that we have different perceptions. Most people share sufficient perceptual commonalities that allow labelling and communication within everyday life activities. Nevertheless, the perceptions across people are far from identical. Furthermore, even if we did perceive the exact same thing, that percept is not necessarily a true and accurate reflection of the "objective reality."

Perceptions fall along a multidimensional continuum and are subjective in nature. This individualization of perception derives from the active nature of cognition and the wide range of factors that affect what and how we perceive.

Two visual hallucinatory syndromes

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Abstract: When viewed from a distance, visual hallucinations fall into one of two symptom patterns, a dichotomy which poses a problem for theoretical models treating them as a single entity. Such models should be broadened to allow for two distinct but overlapping syndromes – one likely to relate to visual de-afferentation, the other to Perception and Attention Deficit (PAD) cholinergic pathology.

Are complex visual hallucinations a single pathophysiological entity? Collerton et al. would have us think so and have produced a

compelling neurocognitive model – Perception and Attention Deficit (PAD) – with which to account for a range of their phenomenological, pathological, and clinical features. Yet the success of the model comes at an expense. For it to succeed, the authors have been forced to make it something of a Procrustean bed, stretching some parts of the visual hallucination evidence and amputating others. This is no more apparent than in their attempt to deal with the hallucinations associated with eye disease, the third-ranking pathological condition in their estimates of population-wide morbid load, exceeded only by delirium and the combined dementias.

As acknowledged by the authors, in eye disease (or, indeed, any visual-pathway lesion), simple hallucinations far outnumber complex ones, an observation which contrasts with core PAD disorders such as Lewy body dementia, Alzheimer's disease, and Parkinson's disease, in which complex hallucinations far outnumber simple ones. For eye and visual-pathway disease, complex hallucinations are only a small part of a much larger clinical picture, their importance needing to be stretched to match core PAD disorders. In fact, even after stretching, the match is an imperfect one. For example, complex hallucinations such as figures in patients with eye disease tend to be bizarre and unfamiliar, often wearing elaborate costumes and hats (Santhouse et al. 2000). In contrast, the figures hallucinated in Parkinson's disease and the dementias tend to be mundane and familiar (Fénelon et al. 2000). Yet, perhaps the most serious objection to including eye-related hallucinations in the PAD model is not the stretched importance of complex hallucinations but the amputation of their simple counterparts. All visual hallucinations, whether simple or complex, relate to phasic increases in activity within visual cortex, the difference between the two categories being the location of the activity increase. For example, activity increase in the human colour centre V4 will result in the hallucination of a "simple" formless coloured blob, whereas activity increase a few centimetres anterior to V4, in object-specialised cortex, will result in the hallucination of a "complex" object (ffytche et al. 1998). An important weakness of the PAD model is that it is forced to make an arbitrary distinction between these different cortical loci and their related hallucinations, amputating from its remit cortical areas underlying the simple hallucinations which typify those found in eye disease.

There are other features of visual hallucinations which require amputation for eye and visual pathway disease to fit the PAD model. In eye and visual-pathway disease, visual hallucinations, whether simple or complex, tend to resolve over time, with 60% of patients with visual hallucinations related to eye disease being hallucination-free at 18 months (Holroyd & Rabins 1996) and almost all patients with visual hallucinations related to visual-pathway infarcts being hallucination free within weeks (Kölmel 1985). Such patients do not develop elaborate delusional explanations for the experiences and typically gain insight into their hallucinatory nature even if, initially, some believe them to be real. These visual hallucinations are invariably silent and are not interspersed with hallucinations in other sense modalities. This overall clinical picture is sufficiently characteristic that exceptions to it point to the presence of other, non-ophthalmic causes for the hallucinations. Contrast this with the clinical picture found in the dementias, Parkinson's disease and schizophrenia. Here the visual hallucinations tend to persist or progress with time (see, for example, Goetz et al. 2001b in the context of Parkinson's disease) and are typically associated with insightless, delusional explanations. The visual hallucinations in these conditions tend to be associated with other sense modalities, either simultaneously (e.g., seeing and hearing the hallucination) or on different occasions (e.g., visual hallucinations interspersed with auditory hallucinations). Indeed, it is something of a psychiatric axiom that visual hallucinations in schizophrenia never occur without auditory hallucinations, either as separate hallucination events or as simultaneous, multimodality hallucinations. The PAD model is forced to ignore these striking clinical differences to allow the visual hallucinations of one set of conditions to sit comfortably with those of another.

Without stretching and amputation, what seems to emerge from the visual hallucination evidence taken as a whole is two distinct, overlapping syndromes.[1] One syndrome consists of predominantly simple hallucinations which resolve with time, occur with insight and without delusions, and are purely visual. The second consists of predominantly complex hallucinations which persist over time, occur with delusions and without insight, and cross sensory modalities. Setting aside those conditions in which the visual cortex is stimulated directly (e.g., migraine and epilepsy), to a first approximation all clinical conditions in which visual hallucinations occur are associated with one or other of these syndromes: eye and visual-pathway disease to the first, core PAD conditions to the second.

The existence of two distinctive syndromes poses a significant challenge to PAD and other models that treat visual hallucinations as a single pathophysiological entity. It seems unlikely that two such very different symptom profiles could emerge from the same disordered mechanism.

Perhaps the time for unitary models of visual hallucinations has passed. If there are two syndromes of visual hallucinations rather than one, we need to broaden our explanatory accounts to allow for this dichotomy. One approach would be to include two distinct but interacting pathophysiological mechanisms into our models, each related to one of the two syndromes. Obvious candidates would be visual de-afferentation as underlying the first syndrome and PAD cholinergic dysfunction the second syndrome (ffytche 2004; 2005). If correct, such expanded, bipartite pathophysiological models have important implications. In the clinic, they suggest, unlike their unitary counterparts, that different types of visual hallucinations need different treatment strategies (ffytche 2004). In the laboratory, and perhaps more significantly, by providing a comprehensive account of the neural mechanisms of disordered conscious vision, such extended models take us a step closer to a neural account of visual consciousness.

NOTES

1. These syndromes are unrelated to those associated with eye disease described in Santhouse et al. (2000), which would be considered sub-syndromes of the first, predominantly simple hallucination syndrome described here.

Hallucinations and perceptual inference

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Abstract: This commentary takes a closer look at how "constructive models of subjective perception," referred to by Collerton et al. (sect. 2), might contribute to the Perception and Attention Deficit (PAD) model. It focuses on the neuronal mechanisms that could mediate hallucinations, or false inference – in particular, the role of cholinergic systems in encoding uncertainty in the context of hierarchical Bayesian models of perceptual inference (Friston 2002b; Yu & Dayan 2002).

Collerton et al. provide a compelling synthesis implicating cholinergic dysfunction in the aetiology of recurrent complex visual hallucinations (RCVH). Furthermore, they observe "that both sensory release and top-down activation are necessary, but neither in itself is sufficient to cause high rates of RCVH" (sect. 6.3, para. 3). This fits very comfortably with models of perceptual inference based on hierarchical Bayes, in which cholinergic mechanisms may balance bottom-up sensory evidence and top-down priors by encoding their relative uncertainty or precision. In short, cholinergic dysfunction may result in a failure to properly integrate sensory information and prior expectations. In what follows, I try to explain how this might happen.

Perceptual inference is the same as statistical inference and

rests on the probability density of the causes of sensory information (i.e., the conditional probability). In classical inference, using, say, *t*-tests, inference is based on two things: (1) an estimate of the effect and (2) the standard error or uncertainty about that estimate. The *t*-statistic is simply the ratio of these two quantities. The basic idea here is that hallucinations can be regarded as false inference that arises not because of impaired estimation (i.e., sensation) but a failure to encode the uncertainty. In the *t*-test example, this might mean the standard error was always too small, leading to false inference based on pathologically large *t*-values. How might this happen in the brain?

Current thinking in computational neuroscience and machine learning points to hierarchical Bayes as the best candidate for understanding perception. I have introduced the notion of empirical Bayes in this context: empirical Bayes using the conditional independence among hierarchical levels to form empirical priors based on the sensory data. This means (almost paradoxically) that cortical hierarchies can construct their own priors, where each level of the hierarchy is subject to constraints or priors from the level above (top-down effects) when accounting for sensory evidence from below (bottom-up effects). There are many issues that attend this theoretical perspective (see Friston 2002b for review). Here I focus on the putative role of cholinergic neurotransmission in the genesis of hallucinations.

Mathematically, neuronal dynamics and synaptic efficacy are considered to minimise something called the *free energy* (F, a concept from statistical physics). The quantities that minimise the free energy are the conditional density $q(\nu)$ of the causes ν of sensory input (e.g., a high-level representation of a face) and some hyperparameters λ encoding the uncertainty or noise. These two quantities correspond loosely to the numerator and denominator of the *t*-statistic above and are updated in two iterated steps: the **E**-step and the **M**-step. This is known as *expectation maximisation* in statistics.

$$\mathbf{E} \quad q(\nu) = \min_{q} F$$

$$\mathbf{M} \quad \lambda = \min_{\lambda} F$$

For a hierarchical model, the **E**- and **M**-steps for the i-th level can be implemented with the following descent scheme, for any generative or constructive causal model $\nu_i = g_i(\nu_{i+1})$ under Gaussian assumptions:

$$\mathbf{E} \quad \frac{\partial \hat{\nu}_i}{\partial t} = -\frac{\partial F}{\partial \nu_i} = -\frac{\partial \xi_{i-1}^T}{\partial \nu_i}\xi_{i-1} - \frac{\partial \xi_i^T}{\partial \nu_i}\xi_i$$
$$\xi_i = \hat{\nu}_i - g_i(\hat{\nu}_{i+1}) - \lambda_i \xi_i$$

$$\mathbf{M} \quad \frac{\partial \dot{\lambda}_i}{\partial t} = -\frac{\partial F}{\partial \lambda_i} = -\left\langle \frac{\partial \xi_i^T}{\partial \lambda_i}\xi \right\rangle - (1+\lambda_i)^{-1}$$

This can be implemented in a simple neuronal architecture of the sort shown in Figure 1. Here the conditional density is represented in terms of its average or expectation $\hat{\nu}_i$ and covariance Σ_i, *i.e.*, $q(\nu_i) = N(\hat{\nu}_i, \Sigma_i)$ where

$$\sum_i^{-1} = \frac{\partial \xi_i^T}{\partial \nu_i}\frac{\partial \xi_i}{\partial \nu_i} + (1+\lambda_i)^2 I$$

which is an implicit function of the hyperparameters. In this scheme, the quantities $\hat{\nu}_i$ and prediction error ζ_i correspond to the activity of two neuronal subpopulations, whereas the hyperparameters λ_i are encoded by the synaptic efficacy of lateral connections.[1] Note that this scheme converges when $\hat{\nu}_i$ cannot further reduce prediction error and $\partial \zeta_i / \partial \nu_i^T \, \zeta_i = 0$. In Friston (2002b) I discuss the potential role of cholinergic neurotransmission in mediating the **M**-step. A related theme, using a different perspective, is discussed in Yu and Dayan (2002). What would happen if the hyperparameters were encoded improperly with cholinergic dysfunction?

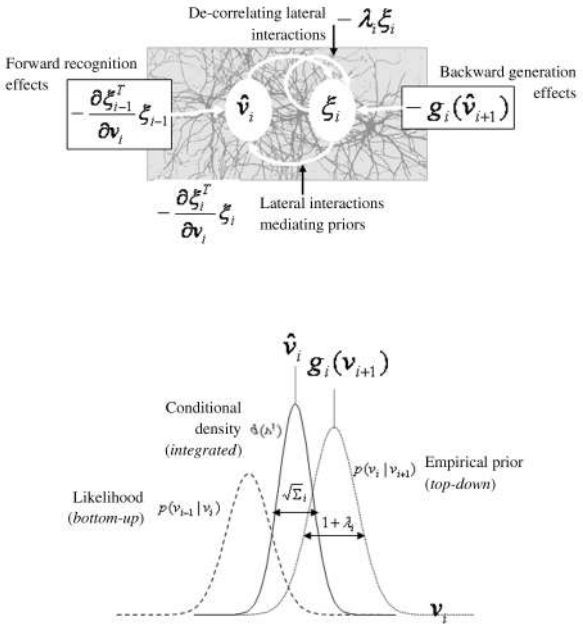

Figure 1 (Friston). The top panel is a schematic showing two neuronal subpopulations representing the conditional expectation of sensory causes for a single cortical level and the influences they are subject to. The bottom panel shows the implicit probability densities encoded by these neuronal activities and synaptic efficacies after convergence. Note that the uncertainty or width of these densities is determined by the hyperparameters. The conditional density, upon which inference is based, is drawn in a solid line.

A failure to optimise the hyperparameters will produce an inappropriate balance between sensory and prior influences on the conditional expectation of what caused any sensation. This is shown schematically in Figure 2. Here, we assume the deficit produces hyperparameters that fail to encode uncertainty in the priors. This means too much weight is afforded to the prior expectation from supraordinate cortical levels, and false inference ensues. Collerton et al. discuss a similar notion from the point of view of a "failure to select the correct proto-object in the PAD model"

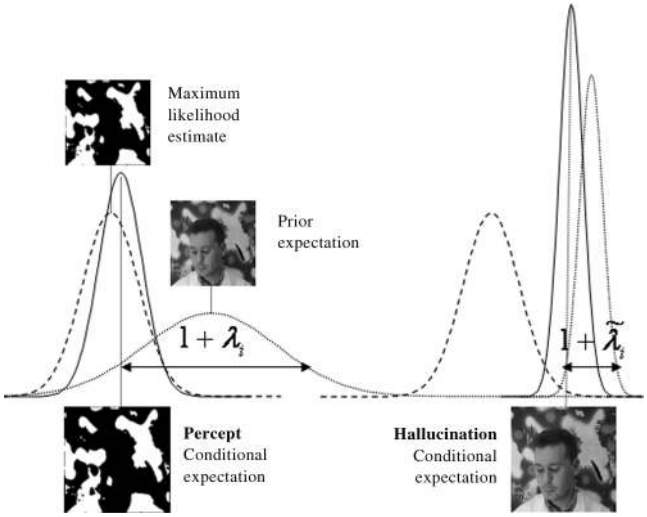

Figure 2 (Friston). A schematic showing one way in which hallucinations could occur. In this example, the hyperparameter encoding prior uncertainty has been made too small $\lambda_i \rightarrow \tilde{\lambda}_i$, resulting in overconfidence in the priors and a false or hallucinatory conditional expectation.

(sect. 7.4.2, para. 2) when cholinergic inhibition leads to incorrect "pattern matching."

The mechanistic understanding afforded by this computational approach can usefully account for many observations made by Collerton et al. For example, "Either impaired attention [i.e., prior expectations] or impaired sensory activation [i.e., evidence] alone will rarely produce hallucinations" (sect. 7.3, para. 1). It is their relationship that defines a hallucination. In this sense, the integration, through the conditional density, is the key mechanism in perception and this integration may depend on the integrity of cholinergic mechanisms. The false learning associated with more enduring changes mediated by the **M**-step may improperly pair sensory contexts with high-level representations leading to "the same image being triggered again and may account for the repetition of specific images" (sect. 7.5.1, last para.). In empirical Bayes the priors are driven by prediction errors from the level below (see Fig. 1). In the absence of sensory input, priors are not induced. This may account for what the target article describes as "an otherwise puzzling feature of hallucinations – that they disappear on eye closure or on complete visual loss" (sect. 7.5.2, para. 2).

In terms of clinical neuroscience, there are remarkable overlaps between the PAD model for hallucinations and the disconnection hypothesis for schizophrenia, a disorder associated with hallucinations. In terms of functional anatomy, Collerton et al. note that "Object-based attention depends primarily on the function of lateral frontal cortex, and object perception depends primarily on the ventral visual stream" (sect. 7.3, point 3). They later cite evidence from functional imaging of patients who are prone to hallucinations. In fact, the disconnection hypothesis was based on early observations of abnormal coupling between left dorsolateral prefrontal cortex and posterior temporal regions, as measured with positron emission tomography in schizophrenics (see Friston 1998 for review).

The disconnection hypothesis posits abnormal functional integration (at the synaptic level) as the primary pathophysiological mechanism in schizophrenia. The premise is that synaptic plasticity is regulated abnormally during emotional and perceptual learning. The abnormal regulation probably involves dopaminergic dysfunction in emotional learning or operant conditioning (i.e., the formation of stimulus-response links) and cholinergic dysfunction in perceptual learning (i.e., the formation of stimulus-stimulus associations). Exactly the same neurotransmitters are implicated by Collerton et al. in RCVH: "pharmacological data so far available indicate a primary role for cholinergic and secondary role for dopaminergic dysfunction in the aetiology of RCVH" (sect. 3.2, last para.). However, they later note "that dopamine receptors are not prevalent in visual processing areas (whereas muscarinic cholinergic receptors are)" (sect. 7.4.2, para. 2). This is consistent with the conclusion of a recent editorial on disconnection and cognitive dysmetria in schizophrenia: "In short, normal interactions between dopamine and the cellular or synaptic mechanisms responsible for plasticity are essential for emotional learning, whereas the interaction between cholinergic neurotransmission and associative plasticity is important for perceptual learning" (Friston 2005). Although Collerton et al. state, "Eye disease and schizophrenia pose greater challenges to our model" (sect. 7.6.2.2, para. 5), there are encouraging and important points of contact between the PAD model and theoretical treatments of cerebral pathology in schizophrenia.

ACKNOWLEDGMENT

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NOTE

1. In this summary I have assumed that the parameters of the generative model of how sensory inputs are caused have already been learned (in the **M**-step). These parameters are encoded by the synaptic efficacy of forward and backward connections linking levels.

Waking hallucinations could correspond to a mild form of dreaming sleep stage hallucinatory activity

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Abstract: There are strong resemblances between the neurobiological characteristics of hallucinations occurring in the particular case of schizophrenia and the hallucinatory activity observed during the rapid-eye-movement (dreaming) sleep stage: the same prefrontal dorsolateral deactivation; forebrain disconnectivity and disinhibition; sensory deprivation; and acetylcholine, monoamine, and glutamate modifications.

To explain the neurobiological deficiencies responsible for hallucinations, the PAD model described by Collerton et al. first highlights attention impairments. These could be related to a prefrontal dorsolateral greater or lesser deactivation also observed in schizophrenia (Bunney & Bunney 2000; Lewis 2000; Weinberger et al. 1986). An analogy can be made with the rapid-eye-movement (REM) dreaming sleep stage, a possible model of schizophrenia (Gottesmann 2002; 2004a; 2004b). During this sleep stage, hallucinatory activity also occurs, as evidenced in cats (Henley & Morrison 1974; Jouvet & Delorme 1965; Jouvet & Mounier 1960; Sastre & Jouvet 1979) and rats (Mirmiran 1983; Mouret & Delorme 1967; Sanford et al. 2001) after experimental suppression of usual muscular atonia, and in normal subjects (Aserinsky & Kleitman 1953) as well as, similarly, in the pathological so-called REM Sleep Behavior Disorder (Mahowald & Schenck 2004), which is the human form of REM sleep without atonia. Indeed, a specific inactivation of the same dorsolateral prefrontal cortex (Braun et al. 1997; Maquet et al. 1996) is observed in this sleep stage. Moreover, whether a cause or a consequence, and during REM sleep as opposed to waking, the frontal cortex seems to be disconnected from other cortical areas, particularly perceptual areas, as the gamma rhythm becomes uncoupled over cortex areas (Perez-Garci et al. 2001). Here, also, there is a strong resemblance with processes occurring in schizophrenia, given that intracerebral disconnections have long been hypothesized to explain the symptoms in this mental illness (Meyer-Lindenberg et al. 2001; Peled et al. 2000; Young et al. 1998).

Therefore, it is of interest that the PAD model also associates this prefrontal cognitive impairment with a decrease in perception processes. This symptom was already described for hallucination development by several authors. More particularly, Behrendt and Young (2004) recently reported a thalamus unconstrained by the usual sensory afferents. Here again, a parallel can be drawn with REM sleep. Indeed, Dement (1958) first identified the increase of arousal threshold by peripheral stimuli, which indicates that this sleep stage corresponds to deep sleep; this was also shown by the difficulty of arousal after central stimulation (Benoit & Bloch 1960). However, more precise experimental arguments have strengthened the notion of perception deficit underlying hallucinations. The sensory de-afferentation hypothesis is strongly supported by the presynaptic inhibition observed during the REM sleep stage in the thalamic relay nuclei of cats (Steriade 1970) and rats (Gandolfo et al. 1980). This failure of sensory afferents during REM sleep is further reinforced at the cortical level. Indeed, while the associative visual areas that lead to the ventral visual stream involved in the PAD model are activated during REM sleep, the primary visual cortex, the target of sensory afferents, is deactivated (Braun et al. 1998).

The neurochemical model of the PAD suggests that hallucination occurrence is based on a decrease of acetylcholine and an excess of dopamine functioning. In our REM sleep neurobiological model of schizophrenia, it has to be emphasized that the cortical release of acetylcholine is lower than during active waking (Marrosu et al. 1995), which could explain a cognitive impairment, although the acetylcholine level is higher in the basal forebrain

(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

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).

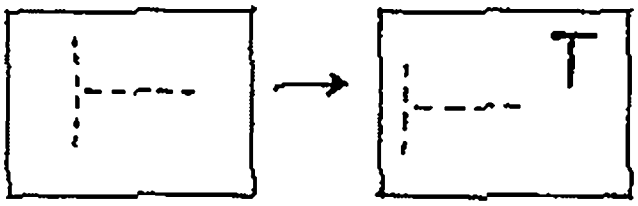

Figure 1 (Ingle). Fixation of a dashed sideward *T* leads to a *visual persistence* (VP) of the unfamiliar pattern. Within 2 or 3 seconds, a *memory image* (MI) of an upright *T* appears on the same index card.

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

concerning the occurrence of visual hallucinations in both non-pathological conditions and a range of psychiatric and neurodegenerative disorders. By combining and developing previous models of visual alertness and its alterations, the PAD model gives an advantageous framework for understanding not only the nature of RCVH, but also the processes underpinning visual consciousness. However, in its attempt to provide a unique schema for RCVH in normal and pathological conditions, the PAD model may meet several limitations.

Most of these limitations come from research on the neurobiological mechanisms of the highly varying conscious states across the sleep-wake cycle. In particular, the transition from wake to sleep, when hypnagogic hallucinations normally occur, is basically characterized by a lowering of noradrenergic and serotonergic influences to the cortex rather than only by an acetylcholine underactivity, as Collerton et al. propose. Furthermore, during the transition from sleep to wake, when hypnopompic hallucinations are most frequent, there is a substantial enhancement of the activity of each of the noradrenaline, serotonin, and acetylcholine neurotransmitter systems (Gottesmann 1999; 2004a; Hobson et al. 1975; 2000; Pace-Schott & Hobson 2002). The occurrence of visual hallucinatory-like experiences across sleep stages is most frequently observed during rapid-eye-movement sleep (Fosse et al. 2001; 2004; Hobson et al. 2000), and this sleep stage is characterized by excessive acetylcholine overactivity (Gottesmann 1999; Hobson et al. 1975; Pace-Schott & Hobson 2002). Therefore, RCVH that are normally experienced at the borders of sleep may not be simply explained by acetylcholine underactivity only, as stated by Collerton et al. Rather, the role of either monoamines or monoamine-acetylcholine ratio in these types of RCVH is to be considered. Because the hypnagogic and hypnopompic are the most common visual hallucinations in non-pathological conditions, sleep research data and the neurochemical mechanisms of sleep-wake cycling may certainly be accounted for in explaining RCVH in psychiatric and neurodegenerative disorders.

Furthermore, Collerton et al. suggest that the attention deficit is an important contributing factor for RCVH, with the acetylcholine underactivity being the main neurochemical mechanism. However, many experimental (Aalto et al. 2005; Gao & Goldman-Rakic 2003; Nieoullon 2002; O'Donnell 2003) and clinical data concerning attention-deficit/hyperactivity disorder (Castellanos & Tannock 2002; Swanson et al. 1998) strongly point to the critical role of brain dopamine in the processes of attention. Also, Parkinson's disease (PD), where RCVH are frequently observed (Burn & Troster 2004; Poewe 2003), is caused by degeneration of dopaminergic neurons (Blandini et al. 2000; Eriksen et al. 2005; Fedorow et al. 2005; Montague et al. 2004; Nieoullon 2002). Moreover, there are clinical data documenting that the visual hallucinations in PD can be induced by the dopaminergic therapy (Burn & Troster 2004; Goetz et al. 2001b). Dopamine dysfunction is also generally recognized to underpin the phenomenology of schizophrenia (Hirvonen et al. 2005; Montague et al. 2004; Winterer & Weinberger 2004), which, as mentioned by Collerton et al., is one of the conditions associated with RCVH. Dopamine has an important role in controlling signal-to-noise ratio and top-down processes (Aalto et al. 2005; Gao & Goldman-Rakic 2003; Montague et al. 2004; O'Donnell 2003; Winterer & Weinberger 2004), both suggested in the PAD model to be impaired mainly as a result of acetylcholine underactivity. In addition, noradrenaline and serotonin, along with acetylcholine, are also shown to be significantly involved in modulating the signal-to-noise ratio (Gu 2002).

In the PAD model, the authors propose that hypo-functioning of the lateral frontal cortex resulting from a cholinergic deficit is another mechanism involved in RCVH. In this context, it is to be noted that animal-driven (Gao & Goldman-Rakic 2003; Seamans & Yang 2004; Zhou & Hablitz 1999) and human transcranial magnetic stimulation (Moll et al. 2000; 2003) data show that brain dopamine exerts a strong effect on cortical excitability.

In conclusion, the role of brain monoamines, and the role of dopamine in particular, appears very important for understanding the neurobiology of visual alertness and its alterations in normal and pathological conditions. Hence, the nature of RCVH could hardly be explained by acetylcholine underactivity only.

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Mental images: Always present, never there

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Abstract: Recent research on visual mental imagery plays an important role for the study of visual hallucinations. Not only are mental images involved in various cognitive processes, but they also share many processes with visual perception. However, we rarely confuse mental images with percepts, and recent neuroimaging studies shed light on the mechanisms that are differently activated in imagery and perception.

Visual mental images are generated from memory and therefore are of purely cognitive origin. Behavioral (e.g., Mast & Kosslyn 2002) and neuroimaging research (e.g., Ganis et al. 2004) suggests that the mechanisms associated with mental imagery are – at least to some extent – also involved in visual perception, and the functional value of this overlap has been widely discussed (e.g., perceptual anticipation theory; Kosslyn & Thompson 2003). Even though imagery and perception overlap, only rarely do we actually mistake images for percepts (an exception is the Perky-effect). Why is this the case? Despite the fact that images are essentially involved in a variety of cognitive processes, such as object recognition, spatial reasoning, and problem solving, we hardly ever experience mental images as perceptually real. Why are we able to reliably keep apart or separate when images are generated internally and when images are mediated via sensory stimulation? On the one hand, the fact that several mechanisms are shared by imagery and perception makes it even harder to address this question. On the other hand, research on mental imagery can provide helpful guidance on where to look when studying the mechanisms that account for the occurrence of recurrent complex visual hallucinations (RCVH).

Instead of mental imagery, Collerton et al. focus almost exclusively on attention. The question arises whether the mechanisms that underlie attention have enough explanatory value for a better understanding of RCVH. The major problem is that attention itself has no visual quality, even though it is often involved in visual cognition and visual perception. Mental images are not only phenomenologically related to RCVH, but they also share several common visual properties, which reflect the underlying mechanisms. The target article makes no reference to recent research on mental imagery, which renders Collerton et al.'s model of RCVH not only less compelling, but also incomplete. There are at least three separate points that are noteworthy in this context.

First, the spatial properties of RCVH resemble those of mental images. Collerton et al. point out that hallucinations are located in the central part of the visual field and – unlike afterimages – they do not move with eye movements. This description applies just as well to visual mental images. We often need to inspect images in order to retrieve more specific information from them. Neither images nor hallucinations disappear or move when attended to. Attention can be shifted over imagined or hallucinated objects. Thus, mental images and visual hallucinations share widely the same spatial properties.

Second, it has to be noted that the interplay between visual mental imagery and visual perception is an essential component of top-down processing. When objects are seen from a non-canon-

ical perspective or when they appear partially occluded, visual memories are used for the comparison between the input pattern and an already existing representation in memory. Therefore, the mechanisms engaged in object and scene recognition also rely on mental imagery and are partly identical with those mechanisms that enable us to voluntarily generate mental images (e.g., during daydreaming). Even though the approach proposed by Collerton et al. includes a top-down component, no reference is made to visual mental imagery.

Third, a growing amount of recent research revealed that the neural machinery engaged in visual perception is – to some extent – also drawn upon during visual mental imagery. In a recent study, the overlap was more pronounced in parietal and frontal regions, suggesting that at least some sensory processes are activated differently (Ganis et al. 2004). In other studies, however, differences between imagery and perception were found in parietal and prefrontal areas (Ishai et al. 2000). The discussion of these findings is absolutely crucial for a better understanding of RCVH. A more profound knowledge about the neural mechanisms that are engaged differently in mental imagery and perception, is likely to play a key role in the ability allowing for the continuous distinction between internally generated images and perceived images. The findings from recent research on mental imagery offer a more specific approach to investigate visual hallucinations than the failure of attentional binding, which is still a rather speculative explanation for the occurrence of RCVH.

In sum, Collerton et al. leave out major findings on mental imagery, which have a great potential to be useful for a general model of RCVH. There is no doubt that a model has the potential to reveal commonalities across diverse fields of enquiry, but it has to be based on solid grounds, integrating the most important issues relevant to the question.

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Now you see it, now you don't: More data at the cognitive level needed before the PAD model can be accepted

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Abstract: Before a general cognitive model for recurrent complex visual hallucinations (RCVH) is accepted, there must be more research into the neuropsychological and cognitive characteristics of the various disorders in which they occur. Currently available data are insufficient to distinguish whether the similar phenomenology of RCVH across different disorders is in fact produced by a single or by multiple cognitive mechanisms.

Collerton et al. have done a commendable job integrating a large array of clinical and experimental evidence to describe a plausible model for recurrent complex visual hallucinations (RCVH). Although many aspects of the model are congruent with the phenomenology one sees clinically, there are a few significant ways in which the model is incongruent.

The first difficulty is the claim that RCVH are generally appropriate to the scene in which they are observed. While the *category* of image might be considered appropriate (e.g., people and animals rather than, say, demons and cornfields), often the other features are not. For example, hallucinations are often reported as being in inappropriate positions (people/animals on the wall or ceiling, people floating outside the window, children under their bed; Gauntlett-Gilbert & Kuipers 2003; Howard & Levy 1994), inappropriate size (Lilliputian figures, "pixies" running along the window; Holroyd et al. 2001; Howard & Levy 1994), or inappropriate context (people being harmed, birds flying in a hospital; Lipowski 1990).

Even the two studies cited in Table 3 of the target article to support this claim, Asaad and Shapiro (1986) and Teunisse et al. (1996), in fact do not do so. Teunisse et al. (1996) screened elderly people with visual impairment and found that 63 of 505 had RCVH. The authors list some of the hallucinations described and, although the percentage of each type of hallucination is not listed, few could be described as appropriate to context (e.g., "miniature policemen guiding a midget villain"; "a dragon"; "an angel"; "an unfamiliar person"; p. 795). They also judged only 22% of hallucinations as "fitting in well" with the environment. The Asaad and Shapiro (1986) paper is a review of hallucinations in general and lists common features of visual hallucinations in psychosis as "people or animals or events taking place in front of them" without providing data or further detail (p. 1091). The unfamiliarity of hallucinated images in RCVH has also been found in Parkinson's disease (Barnes & David 2001; Holroyd et al. 2001), delirium (Lipowski 1990, pp. 86–87), and eye disease (ffytche & Howard 1999). Therefore, one can say that though the content of RCVH tends to be of people and animals, they are more often unfamiliar and just as often appear in inappropriate positions or contexts as they do in appropriate ones. If the PAD model's prediction is that scene representation bias is responsible for the content of hallucinations, one would expect the images to be at least more familiar, if not appropriate to location and context.

Another vulnerability in the model is the prediction that properly perceived external objects should displace the incorrect proto-object from attention and thus make the hallucination disappear. Clinical experience suggests this is not true. Although some patients may become absorbed in their hallucination and retain it as the focus of attention (as the PAD model predicts), often patients with RCVH actively hallucinate while they are being examined. For example, when looking at the examiner they will report seeing hallucinated images behind the examiner or in their peripheral vision. There is some indirect experimental evidence to suggest this as well. Teunisse et al. (1996) asked their subjects what acts would make the hallucinations stop. As one might expect, the most effective means was keeping eyes closed (38%). Interestingly, "looking/walking away," "putting on a light," and "concentrating on something else" were not effective (e.g., $< 15\%$ effective). Certainly this needs to be tested in more detail experimentally, but this finding would be a significant piece of evidence against the cognitive mechanism that Collerton et al. propose as generating RCVH.

The PAD model proposes a mechanistic *cognitive* theory to account for observations at the *phenomenological* level. Given the above-mentioned problems in accounting for the phenomenology, it would be important to have a more detailed look at how the various disorders with RCVH compare at the cognitive/neuropsychological level. As the authors cite, there are currently limited data in this area. Although the data in Figure 4 of the target article suggest that cognitive measures of "attentional/executive impairment" and "visual perceptual impairment" correspond to the predictions of the PAD model, these categories are quite vague and heavily biased to data from DLB (dementia with Lewy bodies) patients. For example, although Collerton et al. mention that "poor performance on tests of attention and visual perception are . . . the norm in delirium" (sect. 7.4.1, para. 5), the cited references actually evaluated only attention in any detail.

Greater precision at the cognitive level is important for the validity of the model because disorders that might seem similar at the phenomenological level may in fact have different mechanisms at the cognitive level. For example, consistent with findings in auditory and visual hallucinations in schizophrenia, Barnes et al. (2003) found that Parkinson's disease (PD) patients with visual hallucinations had intact visual imagery but poor object perception and deficits consistent with poor source and reality monitor-

ing compared to controls and non-hallucinating PD patients. Poor source monitoring and perceptual processing, combined with intact internal image generating, may lead to visual hallucinations by confusion between images that were imagined with those that were actually seen. Collerton et al. point out that deficits in source monitoring and misidentification of internal images are unlikely to account for all RCVH, as many people with RCVH are aware that they are hallucinating. This is an important observation which serves to highlight the complexity of the processes involved and perhaps the need for a more precise terminology.

In the above case, "reality monitoring" is intact but the online appreciation of source may not be (i.e., is it a memory of an image, or a newly generated one?) and, more crucially, the process of attribution may be suspect. According to some models of reality monitoring, decisions about veridicality follow automatically from phenomenal characteristics. In short, if an image is vivid enough, it will be accepted as real. Such an algorithm may work well in most circumstances but could lead to "loss of insight" and hence false beliefs (see David & Howard 1994) if fairly low-level perceptual factors were enhanced (e.g., by neurotransmitter imbalance) or if supervisory processes were weakened (by general cognitive impairment). It may be that the underlying cognitive mechanisms in schizophrenia and PD psychosis are different from those in Charles Bonnet syndrome or sleep disorders because of such modulating factors.

Complex hallucinations in waking suggest mechanisms of dream construction

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Abstract: Waking hallucinations suggest mechanisms of dream initiation and maintenance. Visual association cortex activation, yielding poorly attended-to, visually ambiguous dream environments, suggests conditions favoring hallucinosis. Attentional and visual systems, coactivated during sleep, may generate imagery that is inserted into virtual environments. Internally consistent dreaming may evolve from successive, contextually evoked images. Fluctuating arousal and context-evoked imagery may help explain dream features.

Collerton et al. describe phenomenological and physiological differences between recurrent complex visual hallucinations (RCVH) and dream imagery. Nonetheless, highly complex visual hallucinations (albeit usually non-repetitive) do occur in dreams, and it is parsimonious to hypothesize some overlap in their mechanisms. Biological models of dreaming (e.g., Hobson et al. 2000) propose neural substrates for a fully expressed dream experience based, in part, upon recent positron emission tomography (PET) studies showing widespread cortical deactivation during sleep with selective reactivation of limbic areas during rapid eye movement (REM) sleep (Braun et al. 1997; 1998; Maquet et al. 1996; 1997; Nofzinger et al. 1997; 2002). Such global reorganization of brain activity differs from the more selective ventral stream and attentional system abnormalities superimposed upon waking activity in the PAD model of Collerton et al. However, when one considers how dreaming might be initiated and maintained, parallels become apparent.

Without retinal input, the dreamer cannot perceive veridical visual contexts that evoke RCVH in waking, according to Collerton et al. However, visual association cortices can be activated in REM (Braun et al. 1998) and NREM (non-rapid eye movement) sleep (Hofle et al. 1997; Kjaer et al. 2002). Ascending signals such as PGO (ponto-geniculo-occipital) waves may activate visual cortex during REM (Callaway et al. 1987) or the NREM-to-REM transition (Steriade 2000b). Visual cortex activation in NREM results from phasic activational processes, "covert REM" (Nielsen 2000), arising perhaps from activity in autonomic and limbic areas (Nofzinger et al. 2002; Rolls et al. 2003).

During sleep, therefore, visual association cortices may support ambiguous visual experiences – one prerequisite for RCVH in the PAD model. Simultaneously, ascending brainstem reticular activation may engage midline attentional structures, such as nonspecific thalamic nuclei and basal forebrain (Dringenberg & Olmstead 2003), and medial prefrontal cortex (Nofzinger et al. 1997), allowing some awareness of this fictive vision. Such partial awareness is deficient compared to normal waking – the other requirement for RCVH in the PAD model. If sufficient activation of visual association and midline attentional systems is achieved in sleep, a rudimentary visual context sufficient to evoke "proto-objects" may arise.

The dream might subsequently emerge by a "boot-strapping" process involving successive, contextually evoked visual images. Fictive "proto-representations" in other modalities (e.g., auditory) may emerge from regional activations of subcortical (e.g., motor), unimodal (e.g., somatosensory), heteromodal (e.g., memory), or limbic (e.g., emotion) areas. An image may elicit congruent representations in other modalities, achieving binding via long-range synchrony of high-frequency electrical activity (Kahn et al. 1997; Llinas & Ribary 1993). Specific memories may become woven into the emerging dream as their cortical representations are activated (Stickgold et al. 2001). Further aspects of dreaming can now be suggested.

Brevity of NREM reports. In sleep, episodic and working memory are deficient (Fell et al. 2003; Fosse et al. 2003; Hobson et al. 2000; Pace-Schott et al. 1997). Without this mnemonic "glue" that ensures continuity of our waking experience across attentional lapses, a developing dream, sustained only by elicitation of successive proto-representations, may be disrupted by any hiatus in conscious awareness. Awareness may, in turn, require continued ascending activation, preventing emergence of the endogenous synchronous thalamocortical and corticocortical oscillations of NREM sleep (Steriade 2000b). Sustained activation is present in REM but may be discontinuous in NREM, leading to brief, relatively unrelated NREM dream episodes. By contrast, the common experience of resuming the same dream following brief arousal is possible because further activation enables sufficient memory to span a semi-waking hiatus. Such continuity may be unavailable when the dream hiatus consists of deepened NREM sleep with resumption of intrinsic oscillatory activity. Forebrain activation may even become insufficient to support consciousness, resulting in cessation of the dream experience.

Internal consistency. The remarkable internal consistency of dream plots may arise because the evolving dream context itself determines which proto-representations will next be evoked. Such self-organization of dreams (Kahn & Hobson 1993), utilizing successively evoked proto-representations, may also explain how coherent plots can emerge despite deficient episodic and working memory (Fosse et al. 2003; Hobson et al. 2000).

Bizarreness. Prototypical forms of dream bizarreness – discontinuities, incongruities, and uncertainties (Hobson 1988) – may arise from interaction between fluctuating arousal and context-generated imagery. Lapses of attention may account for discontinuities such as abrupt scene shifts (Sutton et al. 1994). Dream incongruities may similarly be explained by evocation of contextually semi-congruent but illogical proto-representations. Uncertain recall, to a degree that appears bizarre by waking standards, may be inherent in such ad hoc constructions, especially if context-evoked proto-representations do not fully resolve into fictive percepts before subsequent representations arise. The importance of visual context in spanning attentional lapses is apparent in object transformations – discontinuities that are explicable by visual similarity between the original image and its transform but not by their semantic relatedness (Rittenhouse et al. 1994).

Global dream cessation. Damage to inferior parietal heteromodal association areas (BA 39 and 40) can alone result in global dream cessation (Doricchi & Violani 1992; Solms 1997), caused

by, perhaps, the dreamer's inability to perceive a virtual environment. Maintenance of a dream environment may rely preferentially upon visuo-spatial processing subserved by these areas (Mesulam 2000). Lateralization of visuo-spatial function may account for the greater likelihood of dream cessation following right versus left inferior parietal damage (Solms 1997). Dependency on fictive vision for dreaming may be analogous to cessation of RCVH with total blindness and their dependence on dorsal stream integrity, as proposed by Collerton et al. However, dream cessation following left parietal damage and non-visual dreaming following bilateral extrastriate damage (Solms 1997) suggest that fictive dream environments can be based, at least in part, upon other modalities.

Dream visions and RCVH occur in globally differing brain states and cannot be equated. For example, whereas cholinergic deficits often underlie RCVH (Collerton et al. target article), REM sleep shows cholinergic activity equal to, or greater than, in waking within cholinergic projection neurons (Dringenberg & Olmstead 2003) and their terminal fields in the thalamus (e.g., Williams et al. 1994), basal forebrain (e.g., Vazquez & Baghdoyan 2001), and cortex (e.g., Marrosu et al. 1995). Nonetheless, comparison of dreaming with waking pathologies can provide fresh insights into the neural bases of both conditions (Pace-Schott 2005; Schwartz & Maquet 2002).

Hallucinating objects versus hallucinating subjects

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Abstract: Collerton et al. propose that one and the same mechanism (PAD) underlies recurrent complex visual hallucinations (RCVH) in various disorders, including schizophrenia, dementia, and eye disease. The present commentary offers an alternative account of RCVH and other recurrent complex hallucinations specific to schizophrenia and related disorders only. The proposed account is consistent with the bias of schizophrenic RCVH contents toward animate, socially active entities.

The variety of sensory hallucinatory phenomena is characterized by a dichotomy that may be easy to notice and hard to understand. Considering the visual modality separately, Collerton et al. in the target article point at a double dissociation of recurrent complex visual hallucinations (RCVH) versus simple hallucinations including dots, lines, flashes, amorphous shapes, and panoramic landscapes. If a measure of visual complexity is indeed the best separator of the two dissociated categories, then all RCVH are likely to originate from one general mechanism that is distinct from mechanisms underlying other types of hallucinations. Following this logic, Collerton et al. introduce PAD as a general model of RCVH applicable to all cases in which RCVH are observed, including dementias, delirium, schizophrenia, eye disease, and others.

On the contrary, it may seem reasonable to account for RCVH in schizophrenia and, for example, in eye disease based on different mechanisms, if, instead of complexity, another cognitive dimension specific to schizophrenia underlies the dichotomy. Indeed, most hallucinations in schizophrenic states involve various forms of agents engaged in social interactions with the subject (Frith et al. 1998; Mellors 1970; Silbersweig et al. 1995). This happens regardless of the perceptual modality. For example, the following types of auditory hallucinations are characteristic of schizophrenia (Cahill & Frith 1996): voices arguing, voices commenting on one's action, audible thoughts (voices repeat verbatim or comment on subject's thoughts), and voices that command the subject. On the other hand, auditory hallucinations after deafness may include noises and melodies along with singing or talking voices that do not engage in social interactions (Hammeke et al. 1983). The situation is similar with RCVH in non-schizophrenic cases reviewed by Collerton et al. (reviewed in support of PAD). These include RCVH in visual impairment cases described by Charles Bonnet: faces that never smile (Santhouse et al. 2000), RCVH induced by electrical stimulation of the brain (Penfield & Perot 1963), experienced after stroke, in Parkinson's disease (Manford & Andermann 1998), caused by drugs (Hoffmann 1983; Huxley 1959), and so forth. Generally, all non-schizophrenic hallucinations lack a certain degree of animacy and interactive social activity that are typical for schizophrenic hallucinations.

Therefore: (1) Of the following two statements, (a) one and the same mechanism is responsible for RCVH and recurrent complex auditory hallucinations in schizophrenia, and (b) one and the same mechanism is responsible for RCVH in schizophrenia, in dementia and in eye disease, (a) appears to be more credible than (b). (2) The mechanism underlying recurrent complex hallucinations in schizophrenia probably has to do with the concepts of agency, animacy, social interactions, and more generally, the self and its representation in the brain.

A theory based on the latter idea (2), and supported by analysis of clinical and introspective data, was recently proposed by Samsonovich and Nadel (2005). According to this theory, under normal conditions, discrete instances of the subject's own self (labeled *I-Now, I-Previous, I-Next*, etc.) and of the self of any currently perceived external subject, together with all subjective experiences attributed to those instances, are represented in working memory as separate units (*mental states*) that are processed in parallel and interact with one another, obeying a set of hardwired rules (*self axioms*). From this point of view, schizophrenia is a condition in which identities and normal relations among mental states determined by self axioms become lost or altered (Samsonovich & Nadel 2005). As a result, malfunctioning mental states become independent agents and start creating new memories (delusions), engage in dialogues (voices), independently perform imagery (thereby producing hallucinations), or take control of actions. From this point of view, the visual appearance of a socially active RCVH is secondary with respect to its simulated subject, which is a malfunctioning mental state.

Alternatively, one may assume that in schizophrenic RCVH the step of creating a theory-of-mind (ToM) representation of an imaginary character (i.e., "hallucinating a subject") is secondary with respect to developing a sensory hallucination of a face, a body or a voice ("hallucinating an object"). In this case, it would be difficult to understand the nature of the bias toward animate, socially active RCVH in schizophrenia: starting from this point of view, one should expect an opposite bias, toward inanimate or socially inert RCVH, given that ToM abilities are specifically impaired in schizophrenia (Corcoran et al. 1995; 1997; Doody et al. 1998; Frith & Corcoran 1996; Langdon et al. 1997; Sarfati & Hardy-Baylé 1999). It is not clear why the well-known ToM deficit that is characteristic of schizophrenia in general should be reversed in hallucinatory cognitive activity, unless an opposite assumption is made: that in schizophrenia and related disorders, hallucinating a subject (i.e., having a "lost" or misattributed mental state in working memory) causally underlies the hallucination of the related object (face, body, voice). Stated differently, both well-known attributes of schizophrenia – the general ToM impairment and ToM-biased hallucinations – may have one and the same common origin: malfunctioning of the system of mental states (Samsonovich & Nadel 2005).

The PAD model of Collerton et al. has at least several problems; however, the present commentary is focused on one of them: PAD does not account for the specificity of contents of RCVH in schizophrenia and in fact suggests an opposite specificity, as explained above. Although the combined attentional and visual perceptual impairments interacting with internal scene representations could in principle result in a particular schizophrenic RCVH, it is not clear from the point of view of Collerton et al. why there should be a bias toward elaboration rather than simplification of agency and social activity of hallucinated entities. The above analysis suggests that the

self concept (as it is introduced by Samsonovich & Nadel 2005) could be the key to answering this question and understanding the nature of the dichotomy observed among various types of hallucinations. Finally, incorporating the notion of an imaginary self into the notion of a "proto-object" associated with a living entity may help with further improvements of the PAD model.

The role of acetylcholine in hallucinatory perception

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Abstract: This commentary reviews and extends the target article's treatment of the topic of the role of acetylcholine in hallucinatory experience in health and disease. Particular attention is paid to differentiating muscarinic and nicotinic effects in modulating the use of virtual reality mechanisms by the brain. Then, attention is drawn to the similarities between these aspects of brain function and certain aspects of television digital compression technology.

In the target article, Collerton et al. recognize that normal perception is an amalgam of "down-up" information (*exact inference model* or *I* program) derived from the retinal input (that reports what really is out there) with an "up-down" contribution from stored visual memories (*naïve inference model* or *P* program) as a form of virtual reality (that reports what the brain computes should most probably be out there). An imbalance between these two is associated with repetitive complex hallucinations. The authors then mention the computational model of Yu and Dayan (2002), which modulates this balance. Collerton et al. put this as follows: "Inhibition of cholinergic input gives a greater chance of incorrect pattern matching . . . and allows the intrusion of an incorrect representation" (sect. 7.4.2, para. 2). They suggest that such hallucinations are associated with low cerebral cholinergic activity. As evidence, they mention the hallucinogenic effects of "anticholinergic drugs."

However, the authors do not distinguish clearly between the muscarinic and nicotinic effects of acetylcholine in this situation, which is more complex that appears from their account. The Yu and Dayan model actually states that acetylcholine promotes the retinocortical pathway (essential for the *I* program) by a nicotinic postsynaptic stimulation of cells in layer IV of the cortex, whereas it inhibits corticocortical conductance (essential for the *P* program) by a muscarinic activation of inhibitory presynaptic receptors in cortical layers I/II. This cholinergic activity would promote attention to the environment. The hallucinogenic effects of antimuscarinic agents must therefore depend on a double inhibitory effect on the layer I/II muscarinic system.

In contrast, during a saccade, information from the retina is largely suppressed to be replaced by virtual reality constructed by the brain's *P* processes (Kleiser et al. 2004). A saccade is initiated by a nicotinic signal from the pedunculopontine nucleus (PPN) that initiates the motor corollary of a local increase in *I* activity. Yet, the saccade itself is associated with an increase in *P* activity. It is not known how this is effected, but the following is a possible mechanism. The PPN also has a massive glutamatergic projection to the nucleus basalis. The latter contains many large inhibitory GABAergic interneurons, as well as its cholinergic neurons. It is not known to which of these the PPN projects, but if it is to the former, the GABAergic interneurons, this would supply the necessary mechanism. The projection of the PPN to the superior colliculus would initiate the saccade, and then its indirect projection to the visual cortex via the nucleus basalis would diminish cholinergic activity in that location. The projection from the PPN directly to area 17 mentioned by Collerton et al. is, however, not cholinergic but entirely noradrenergic (Higo et al. 1996).

Most brain structures receive their cholinergic input from only one source. Some, however (such as the intralaminar and medial thalamic nuclei), receive their input from two sources. The superior colliculus belongs to the latter class, as it receives a second cholinergic input from the parabigeminal nucleus, which is part of a midbrain circuit that generates target location information (Cui & Malpeli 2003). The input from the PPN goes to the intermediate layer of the superior colliculus, whereas the input from the parabigeminal nucleus goes to its superficial layer. Here it activates excitatory presynaptic nicotinic receptors on glutamatergic terminals of axons from retinal neurons that synapse on inhibitory GABAergic interneurons. Thus, in this location, the action of acetylcholine is to depress the upward flow of collicular activity (Binns & Salt 2000). The significance of this apparently paradoxical effect is obscure. Incidentally, the only part of the brain that receives no external cholinergic input is the striatum. Here, its cholinergic cells are all involved in local circuits.

The fact that cortical *P* activity is enhanced during a saccade leads one to speculate that one function of the saccades that characterize REM sleep may be to promote the REM state, which is composed of pure, free-wheeling *P* activity (dreams), rather than merely to reflect eye movements directed at dream images, as is supposed at present.

As I have pointed out elsewhere (Smythies 2005), there are interesting parallels between the action of acetylcholine in regulating the *P:I* balance in the cortex and certain aspects of television digital compression technology. Television engineers have discovered that sending every detail of the scene to be televised over the TV channels is very efficient but is also very expensive in terms of computational (and hence financial) cost. This corresponds to our *I* program. So the TV engineers have developed a second (*P*) program that supplements and, in places, replaces the *I* program with material that represents the system's estimate of what should most probably be "out there" based on its memory of the previous outcomes of similar situations. This program is inefficient but cheap in computational cost. This process can involve a third program (the "*P* frame") that records only the differences between successive frames. So the art is finding the best balance between the *P* and *I* programs. The brain seems to follow the same logic. In circumstances when nothing much of interest is happening, the brain can coast along with a $P > I$ ratio. Then, if something of interest occurs, a signal is sent to the nucleus basalis and acetylcholine is released at targeted synapses in the cortex in the manner described above so as to promote activity in areas activated by the new stimulus. This involves changing the ratio to $I > P$ locally or globally. At the same time, the PPN sends a cholinergic (nicotinic) signal to the superior colliculus that initiates a saccade directed towards the computed source of the interesting new stimulus. This is possibly followed by a glutaminergic signal from the PPN to inhibitory neurons in the nucleus basalis that orchestrates the increased $P > I$ ratio that accompanies the saccade itself.

Finally, the authors suggest mechanisms how acetylcholine function could be disturbed in schizophrenia, leading to the hallucinations characteristic of the disease. However, the symptoms of schizophrenia, including the hallucinations, are more probably due to the disturbances of synaptic plasticity, the loss of neuropil and cortical connectivity recently discovered (see Smythies [2004] for details).

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Visual hallucinations, attention, and neural circuitry: Perspectives from schizophrenia research

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Abstract: We tested Collerton et al.'s model of visual hallucinations by re-examining a data set for correlations between visual hallucinations and measures of attentional function in schizophrenia patients. These data did not support their model. We suggest that cortical hyperexcitability plays an important role in hallucinations, and propose an alternative model that links evidence for cortical hyperexcitability with abnormal neural dynamics.

The study of hallucinations can shed light on many aspects of cognitive and brain function in healthy individuals and in individuals with neuropsychiatric disorders. Collerton et al. make a timely contribution to this area of inquiry with their Perception and Attention Deficit (PAD) model of recurrent complex visual hallucinations (RCVH). Collerton et al. have done an admirable job in distilling a unifying model of RCVH from the literatures on RCVH and visual attention. However, research into the neural substrates of schizophrenia has led to views of hallucinations that conflict with the PAD model. Here we discuss the implications of findings from our laboratory and others for the PAD model.

The necessity of attentional involvement in visual hallucinations. A dysfunction in attentional modulation of visual processing is an appealing hypothesis for RCVH. To test this hypothesis, we conducted an exploratory analysis of a data set of ours in which we found relationships between visual hallucinations and electrophysiological measures of visual perception in chronic schizophrenia patients (Spencer et al. 2004). Of the 20 patients in this sample, 7 had some history of visual hallucinations. We looked for relationships between visual hallucinations and attentional impairment by calculating correlations between the visual hallucinations scale of the Scale for the Assessment of Positive Symptoms (Andreasen 1984), the attention scales of the Scale for the Assessment of Negative Symptoms (social inattentiveness, inattentiveness during mental status testing, and global rating of attention) (Andreasen 1983), and the Positive and Negative Syndrome Scale (poor attention) (Kay et al. 1987). None of these correlations approached significance (all $r < 0.2$, $P > 0.42$). Looking further, we tested for relationships between performance measures (error rate and reaction time effects) and visual hallucinations, but found no correlations either (all $r < 0.33$, $P > 0.20$). Subgroup level t-tests (hallucinators vs. non-hallucinators) yielded negative findings also.

These results imply that attentional impairment is not necessarily linked to RCVH. However, we note that the poor impulse control scale of the PANSS did show a significant correlation with visual hallucinations ($r = 0.46$, $P < 0.05$). This finding suggests a possible involvement of deficient executive attention processes in visual hallucinations, rather than the attentional template/biasing processes proposed by Collerton et al.

The role of cortical excitability in hallucinations. We believe that Collerton et al. do not lend enough weight to the relationship between cortical excitability and RCVH, as there is substantial evidence that cortical excitability is related to hallucinations in schizophrenia. The main evidence for increased cortical excitability in schizophrenia comes from studies utilizing transcranial magnetic stimulation (TMS). For example, Hoffman and colleagues (2003) found that slow repetitive TMS, which decreases the excitability of the underlying cortex, reduced the incidence and severity of treatment-resistant auditory hallucinations (when applied to the left temporo-parietal region). Cortical hyperexcitability in schizophrenia would be consistent with the deficits in inhibitory neurotransmission that have been revealed by postmortem cellular studies (Lewis et al. 2005). In addition, there is evidence that N-methyl-D-aspartate (NMDA) antagonist ketamine increases cortical excitability (Di Lazzaro et al. 2003), which links the NMDA receptor hypofunction model of schizophrenia (Tsai & Coyle 2002) with cortical excitability. Finally, there is a report that slow repetitive TMS applied to the occipital lobe eliminated visual hallucinations in a non-schizophrenic patient (Merabet et al. 2003). Hence, we believe that there is in fact substantial evidence to support an important role for hyperexcitability of sensory cortex in hallucinations.

Neural dynamics and hallucinations. From our own research on visual perception and neural dynamics in schizophrenia, we have proposed a different (but not exclusive) account of RCVH. We recently reported that chronic schizophrenia patients show abnormalities in visual gamma-band oscillations (Spencer et al. 2003; 2004). These abnormalities include a response-locked oscillation (RLO) recorded over the occipital lobe, which we hypothesize reflects feature-binding processes in visual cortex. In schizophrenia patients, the degree of phase-locking of the RLO was positively correlated with their visual hallucination symptoms (Spencer et al. 2004). In contrast, the N1 visual evoked potential was reduced in amplitude for patients with visual hallucinations, compared to patients without. We proposed that this dissociation between a putatively endogenous process (increased RLO synchronization) and an exogenous response to sensory stimulation (decreased N1) reflected increased excitability in the visual cortex of schizophrenics with visual hallucinations. A similar pattern of increased endogenous activity and decreased responsiveness to external stimulation in visual hallucinators was found by ffytche et al. (1998).

If the neural substrate of a perceived object is an attractor state in a neural network (such as oscillatory synchronization among cells coding individual features of the object), then RCVH could result from an increased propensity for such a dysfunctional network to go into attractor states independently of other biasing influences, such as external input (sensory stimulation) or an attentional bias signal from prefrontal cortex. The main distinction between our account of hallucinations and the PAD model is that we emphasize dysfunction of the relevant sensory cortex, which is manifested by hyperexcitability. Although it is certainly plausible that attention deficits could exacerbate hallucinations, the lack of correlations between visual hallucinations and measures of attention suggests that attention is not a primary factor, at least in schizophrenia.

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NOTE

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Believing is seeing in schizophrenia: The role of top-down processing

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Abstract: The etiology of visual hallucinations is largely undetermined in schizophrenia. Collerton et al.'s PAD model partly concurs with what we know about neurocognition in schizophrenia, but we need to specify the types of perceptual and attentional abnormalities that are implicated in recurrent complex visual hallucinations (RCVH). Available data suggest that abnormal attentional control and top-down processing play a larger role than the ventral stream deficits.

Hallucinations are core features of schizophrenia. Although cognitive and neuroanatomical origins of auditory hallucinations are beginning to be elucidated (David 1999), the underlying etiology of visual hallucinations remains undetermined. Therefore, Collerton et al.'s PAD model of recurrent complex visual hallucinations (RCVH), which generates testable hypotheses, is both timely and valuable. The broad outline of this model concurs with what is known about neurocognition in schizophrenia. Significant proportions of schizophrenic patients hallucinate, show deficits in a wide variety of attention tasks, and have prefrontal and temporal abnormalities (Mitchell et al. 2001; Shenton et al. 2001). However, to move beyond these surface similarities, we need to specify the types of perceptual and attentional deficits that may result in RCVH and test them empirically.

Attention is a multifaceted concept that can be parsed into distinct multiple systems, implemented by overlapping but separable neural circuits. Schizophrenic patients have problems in orienting, deploying, focusing, shifting, and sustaining attention in space. What aspects of attentional abnormalities in schizophrenia might contribute to RCVH? The PAD model predicts that RCVH are located at the focus of attention and unlikely to be experienced at the periphery of the visual field. Schizophrenic patients have difficulties in shifting spatial attention (Posner et al. 1988), and this deficit is associated with positive symptoms such as hallucinations (Digirolamo & Posner 1996).

Specifically, they show deficits in shifting attention to the right visual field (RVF) but not to the left visual field (LVF). This suggests that they may neglect the RVF. Interestingly, schizophrenic patients tend to experience visual hallucinations more in the LVF (Bracha et al. 1985). A question arises here for the PAD model. If subjects have difficulty shifting focal attention to RVF, they are unlikely to "see things that are not there" in the RVF. Therefore, visual search tasks or Posner's covert orienting task (Posner 1980) may yield a pattern of greater accuracy in the LVF, coupled with greater incidences of RCVH in the LVF. In contrast, the same patients might make more perceptual errors in the RVF. However, it is unclear whether such a relationship has been reliably observed. Following this line of reasoning (i.e., RCVH appear where attention goes), it might be possible to develop strategies for extinguishing RCVH by increasing external visual signals at the location of the RCVH or by redirecting attention.

Control of attention is mediated partly by expectancies or top-down processes. It has been observed that schizophrenic patients give greater weight to top-down expectations on perception than normal controls do (Aleman et al. 2003). This provides a clear test of the PAD model. If top-down expectancies guided by stereotypical scene representation play a stronger role in hallucinators' perception, then, when presented with a familiar scene, they should detect context-congruent objects more quickly and at a lower threshold than non-hallucinators. With unfamiliar scenes, the weight of top-down processing may increase further in hallucinators to make the novel input fit their "theory." Top-down processing may also increase if hallucinators are presented with visually degraded or ambiguous scenes (e.g., blurred, low intensity) to make sense of the visual noise (e.g., seeing faces in the clouds or in Rorschach inkblots). So, unfamiliar or ambiguous scenes may trigger more top-down processing and lead to RCVH. This possibility seems incongruent with the PAD model.

In addition to attentional deficits, the PAD model postulates the existence of concurrent perceptual deficits within the ventral visual processing stream. Schizophrenia patients, indeed, exhibit a variety of visual abnormalities. The majority of reported deficits, however, are confined to the dorsal stream, such as motion perception (Chen at al. 1999) and backward masking (Slaghuis & Bakker 1995). For example, schizophrenia patients are impaired in a visual backward masking task when required to detect target locations, but not when asked to identify masked letters (Cadenhead et al. 1998). These findings are corroborated by visual evoked potentials (VEP) studies that report abnormal P1 component over dorsal visual areas, but normal P1 over ventral regions. The N1 component (generated by early ventral stream structures) is also normal in schizophrenia (Foxe et al. 2001; in press).

Lack of deficits in early ventral processing does not preclude the existence of high-level abnormalities of semantic and object categories. Indeed, evidence of temporal lobe abnormalities with behavioral consequences in schizophrenia is rather striking (Mitchell et al. 2001; Shenton et al. 2001). Although schizophrenic patients show no deficits on simple object perception tasks, they are impaired in higher-level ventral tasks, such as recognition of atypical objects (Gabrovska et al. 2002). But the PAD model does not make an explicit distinction between low- and high-level ventral stream functions; it suggests the deficits are in the generation of proto-objects, which arguably would involve low- to mid-level ventral processes. The PAD model should identify the levels of ventral stream processing involved in RCVH and provide converging evidence for the ventral stream deficits in schizophrenia.

In our opinion, top-down processing seems to be the main driving force behind experiencing hallucinations. Ventral stream deficits may not be necessary for RCVH, at least in schizophrenic subjects, as suggested by the lack of strong evidence for ventral abnormalities. However, perceptual deficits can facilitate generation of RCVH. Generally speaking, all visual defects can be construed as increasing the noise at the expense of "veridical" visual signals. Impoverished visual representations are more susceptible to misinterpretation. Only when combined with abnormal top-down attentional and semantic processes can the misinterpretation of visual input lead to RCVH. Namely, the role of perceptual deficits in RCVH is to simply increase the noise, whereas the actual generation of RCVH lies within faulty higher-level processes. This account of RCVH does not require localization of deficits within the ventral stream, and it is consistent with the increased frequency of RCVH in situations when the visual input is degraded by external factors (e.g., dim lighting). In schizophrenia, widespread dorsal system deficits coupled with structural abnormalities of the primary visual area (Selemon et al. 1995) may be enough to degrade early visual representation, thus making it vulnerable to faulty top-down processes.

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Authors' Response

Still PADing along: Perception and attention remain key factors in understanding complex visual hallucinations

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Abstract: Commentators agree that the Perception and Attention Deficit (PAD) model is a promising model for accounting for recurrent complex visual hallucinations (RCVH) across several disorders, though with varying detailed criticisms. Its central tenets are not modified, but further consideration of generative models of visual processing and the relationship of proto-objects and memory systems allows the PAD model to deal with variations in phenomenology. The commentaries suggest new ways to generate evidence that will test the model.

R1. Introduction

We first developed the Perception and Attention Deficit (PAD) model to understand the constraints in the visual system that led many, but not all, of our patients with dementia with Lewy bodies to experience visual hallucinations of a particular character. It was with some trepidation that we extended its coverage to recurrent complex visual hallucinations (RCVH) in other disorders, and subjected it to peer commentary from colleagues whose expertise in their fields far exceeds our own. We are extremely appreciative of their constructive engagement, challenges, elaborations, developments, and occasional corrections.

We have organised the response to commentaries by the key predictions of the PAD model from section 7.3 of the target article. For ease of reference, Table R1 indicates which commentators have focussed on which areas.

R2. Scope of the PAD model: Is there more than one syndrome of repetitive complex visual hallucinations?

In the target article, we set out to account for "repetitive involuntary images of people, animals, or objects that are experienced as real during the waking state but for which there is no objective reality" (sect. 2, para. 1). We agree with **Castelo-Branco** that it does not apply to phenomena such as polyopia or tesselopsia, although it does apply to palinopsia, given that this is simply a hallucination over a short timescale. However, this leaves the question of whether the PAD model applies to all hallucinations that fit the definition above. In answering this question, it is important to bear in mind that the visual system is, in important ways, probabilistic rather than deterministic (Friston 2002b). There are never certainties to be found. Therefore, the search is for factors that influence the probability of RCVH, not ones that always (or never) cause them. Hence, contrary examples to the PAD model will always be available. It is the balance between consistent and inconsistent evidence that is critical.

Samsonovich makes the point that whether RCVH across disorders are considered the same or different depends upon the basis for the comparison. In his example, social agency groups the visual hallucinations of schizophrenia with the auditory hallucinations of that disorder, not with the visual hallucinations of other disorders.

ffytche similarly uses different bases for comparison to

Table R1. *Themes addressed by commentators*

Commentator	Scope of the PAD model	Cognitive and sensory risk factors	Factors influencing phenomenology	Physiological constraints
Badcock & Maybery		✓		
Behrendt		✓		✓
Carroll & Carroll			✓	
Castelo-Branco	✓	✓	✓	✓
Dolgov & McBeath		✓		
Dror			✓	
ffytche	✓		✓	
Friston		✓		✓
Gottesmann			✓	✓
Halliday		✓		✓
Ingle			✓	
Kirov				✓
Mast			✓	
Morrison & David	✓	✓	✓	
Pace-Schott				✓
Samsonovich	✓	✓		
Smythies	✓			✓
Spencer & McCarley		✓		✓
Tadin et al.		✓		

group together the simple and complex hallucinations in eye disease. He argues for two separate visual hallucination syndromes, with the complex visual hallucinations of eye disease being distinct from those of other disorders, and suggests that we had to do some Procrustean violence to the evidence to make them appear similar. Without wishing to act as Lycomedes to his Theseus,[1] we believe that there are sound grounds for maintaining the original grouping together of all RCVH, at least until more data become available.

To support his view, **ffytche** cites four differences between the hallucinations of eye disease and what he groups as the PAD disorders. Compared to the PAD disorders, hallucinations in eye disease tend to be associated with simple hallucinations, to recover, to be more bizarre, and to not be associated with other psychiatric symptoms.

One major problem with the suggestion that RCVH and other visual hallucinations in eye disease stem from the same cause, namely de-afferentation, is that rates of complex hallucinations in eye disease are much lower than rates of simple hallucinations (Table 1 of the target article). This suggests that de-afferentation alone is an insufficient explanation. In the target article's section 3.1, we argued for two hallucinatory syndromes based on the double dissociation between the rates of simple and complex hallucinations in disorders of visual input and those with more distributed pathology. Double dissociation is the classic, though not infallible, neuropsychological argument for separable mental phenomena, so perhaps the separation of simple from complex hallucinations is not so Procrustean.

Because the people who do have complex hallucinations tend to be more cognitively impaired and prone to fatigue (Table 2 of the target article; but see Menon [2005] for some contrary evidence), consistent with the PAD model, our present inclination is to continue to group them within this, though perhaps in a boundary zone with de-afferentation cases (Fig. R1). If this hypothesis is correct, the overlap group will have both simple and complex hallucinations, as **ffytche** reports.

This leaves the other distinctions that **ffytche** highlights. We have already suggested the progressive visual loss of eye disease as the reason why visual hallucinations become less common as time goes on in those disorders (target article, sect. 7.5.2). We think distorted faces, bizarre figures, and machines are conceptually variations on object representations (as are all other complex hallucinations), rather than variations on simple hallucinations. We will propose later how bizarreness might be accounted for within the PAD framework.

Regarding the association with other symptoms, our present position is that of parsimonious lumpers. Because we believe that, across syndromes, the commonalities of RCVH, as symptoms, outweigh their differences, our position is that they do have a common cause until proven otherwise. Hence, as we discuss in section 5.3, associated symptoms reflect different causes. Circumstances will therefore determine which grouping RCVH are best lumped with. To clinicians in an eye clinic or in mental health services, they may be most helpfully viewed as part of the spectrum of visual abnormalities following de-afferentation or as part of a personally relevant psychosis, but to a researcher trying to understand why they occur in only some people, the PAD model may have more to offer.

As **Morrison & David** say, evidence from direct comparisons across disorders is needed.

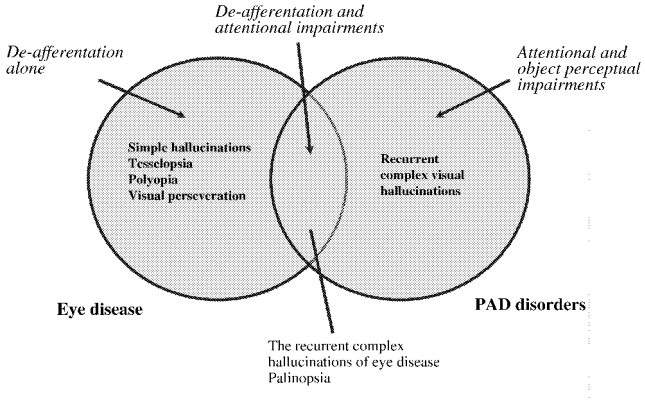

Figure R1. Relationship between the phenomenology of hallucinations in PAD and de-afferentation disorders.

R3. Cognitive and perceptual constraints that increase the risk of RCVH

We predicted that the frequency of RCVH varies with the frequency of the coexistence of attentional dysfunction and object perception impairments.

Commentators **Badcock & Maybery**, **Dolgov & McBeath**, **Friston**, **Halliday**, **Morrison & David**, and **Spencer & McCarley** share our focus on attentional and perceptual factors, though there is variation in the significance attached to these.

R3.1. The role of attentional factors

Spencer & McCarley present data from a reanalysis of their 2004 study on hallucinations in schizophrenia (Spencer et al. 2004). They report a lack of relationship with the presence of visual hallucinations (VH) and clinical ratings of attentional function (except poor impulse control), or with reaction time or error rates on a visual task that involved responding or not responding to a stimulus that was, or was not, a gestalt square. In contrast, there was a clear relationship between occipital gamma band oscillations and visual hallucinations. Spencer & McCarley conclude that this argues against the application of the PAD model to schizophrenia.

However, before attaching high weight to this evidence, we would like to enter several caveats. First, we suggest that attentional impairment alone will not be associated with RCVH (sect. 7.4.1 of the target article). It is clear from Figure 1 in Spencer et al.'s (2004) paper that all of the people with schizophrenia have impaired attentional performance. In order to reject the PAD model, they would need to show that poor perceptual performance in the context of this generally poor attentional performance did not distinguish between the hallucinators and non-hallucinators. Furthermore, Figure R2 shows the results from a small pilot study of ours looking at visual and attentional performance in hallucinating and non-hallucinating patients with dementia. Impaired performance is seen only on some visual tasks – those testing higher-order object recognition. Whether the gestalt recognition of a square would be that type of task, or whether it has more in common with simple visual recognition tasks where there is less difference between hallucinating and non-hallucinating groups, is not clear to us.

Morrison & David and **Tadin**, **Wong**, **Mebane**, **Berkowitz**, **Trott & Park** (**Tadin et al.**) ask for greater

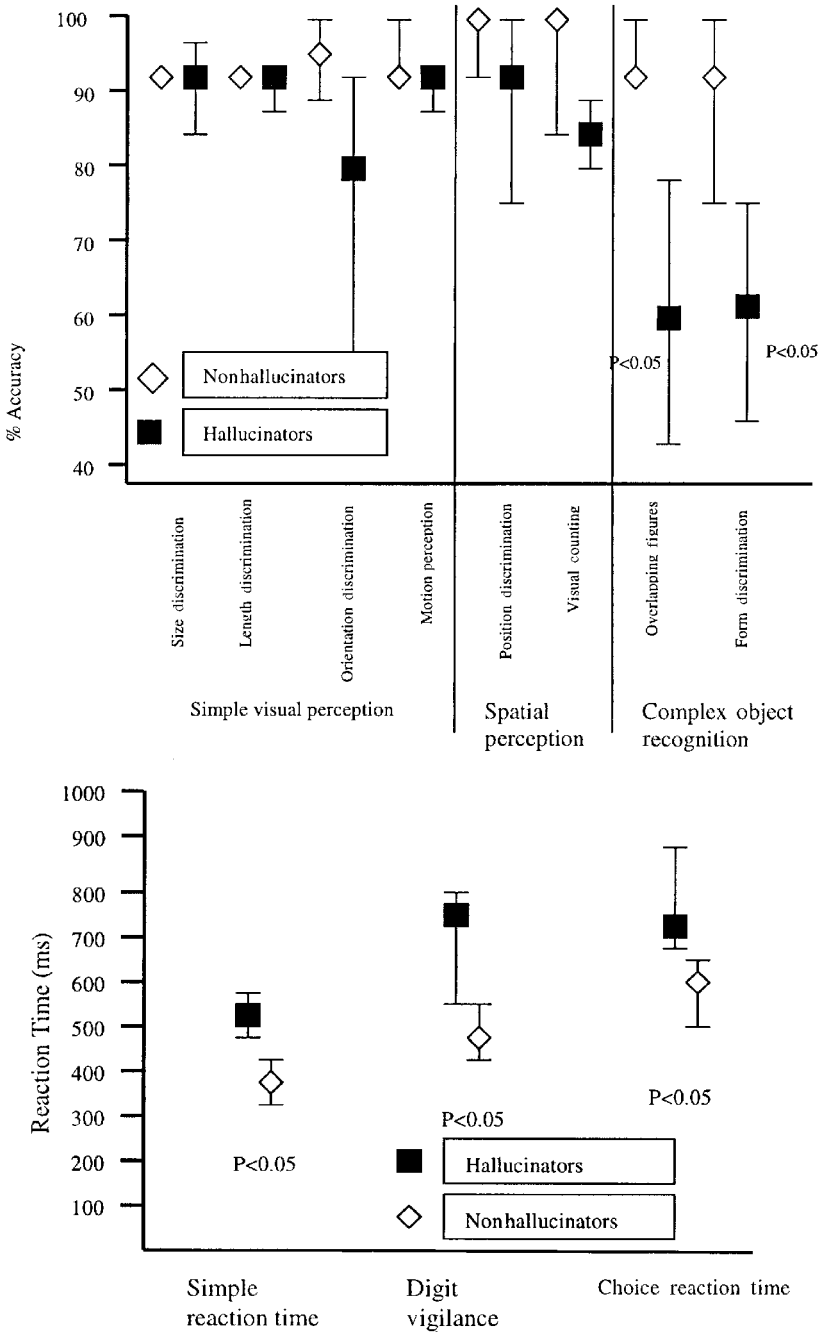

Figure R2. Data from a pilot study comparing hallucinating (N = 7) and non-hallucinating (N = 13) patients with dementia on a range of attentional and visual perceptual tasks. Median scores and interquartile ranges are shown (Bowen, McKeith, Mosimann & Collerton, unpublished data).

specificity in which particular aspects of attention are impaired. This perfectly reasonable request points out the very variable present data. The studies that we featured in the target article's Figure 4 used well over 160 separate measures, very few of them more than once. Additionally, many patient groups with high levels of RCVH do poorly on all attentional tasks. Thus, there is not the experimental evidence to support any specific area of attentional impairment, though we argue on theoretical grounds for impaired dynamic binding. We agree that gathering more specific data is a necessary task.

Morrison & David and **Castelo-Branco** also question the attentional focus that we suggest is important for the perception of the hallucination. As counter-evidence, Morrison & David cite patient reports of seeing hallucinations while doing other activities, and the lack of effect of attending to other things on eradicating active hallucinations. (Menon [2005] similarly reports that this is an infrequently used strategy.) Castelo-Branco additionally queries why hallucinations should be more frequent in areas of the visual field where vision is impaired.

Both of these possibilities need further exploration, particularly because the evidence is not consistent – most reports suggest that hallucinations are seen in the centre of the visual field regardless of aetiology (target article, sect. 4.1.2). However, neither is yet a fatal objection in our eyes.

There is a well-established distinction between being apparently aware of an object in the visual environment and attending to it (see, e.g., Rensink 2002). The models of scene perception that we draw upon (target article, sect. 7.1, Fig. 3) are based upon the extensive evidence of change blindness and other phenomena that highlight this distinction. Since a key feature of the model is that hallucinations are incorporated into the abstracted scene perception (sect. 7.3), it would actually run counter to our hypothesis if patients did not sometimes appear to be aware of them when attending to something else. Data on attentional function during hallucinations is needed to resolve this issue.

Turning to the patients' lack of use of the coping mechanism of attending to something else, we think that it is equally plausible that they fail to do this because it is hard to attend to something else when hallucinating – the opposite of **Morrison & David**'s interpretation, but entirely in keeping with the PAD model. Further evidence is needed.

R3.2. The role of object perception

Tadin et al. ask that we specify the level at which the primary impairment of the visual system lies. It seems probable that, given the highly interactive nature of visual processing with significant forwards, backwards, and lateral connectivity, there is no single locus of abnormality. However, we would locate functional impairments both upstream and downstream of image generating areas. If dysfunction extends into the image generating areas – for example, central loss of colour vision – hallucinations will reflect this. Loss of the ability to generate images would also abolish hallucinations.

Morrison & David stress the thinness of the evidence for object perception impairments compared to attentional impairments in delirium in our citations. However, Mach et al. (1996) showed specific impairments in Object Assembly and Visual Reproduction in patients who were matched for scores on the Mini Mental Status Examination (MMSE), suggesting that the evidence is not entirely lacking. We agree that delirium has many potential advantages as a disorder to study, though there are some practical difficulties with cooperation and consent. Looking at the existing literature, Inouye et al. (1993) showed in a proportional hazards analysis that, out of 15 potential risk factors for the development of delirium, the only significant ones were severe illness (relative risk [RR] 3.5), high blood urea nitrogen/creatinine ratio (a marker for dehydration, RR 2.0), and *cognitive* (RR 2.8) and *visual* (RR 3.5) impairments. In the absence of the PAD model, it would be difficult to explain *a priori* why these two latter risks should stand out.

R3.3. The need for combined impairments

Castelo-Branco echoes our comments that attentional and perceptual impairments co-vary in Figure 4 of the target article (sect. 7.4.1), and that direct rather than meta-analytic tests would be preferable. Covariation of impairments reflects the nature of dementing illnesses, in which the severity of specific cognitive impairments correlates almost by definition. Rather than using analysis of covariance to control for this, as he suggests, a more powerful test is to look at the rates of RCVH in patients with either attentional or perceptual impairments. Section 6.3 of the target article indicates that the rates are low in both these groups.

The need for combined impairments is supported by analogy with **Badcock & Maybery**'s HEAR model for auditory hallucinations in schizophrenia. In slightly different language, this also posits the need for a combination of attentional binding (intentional inhibition) and sensory impairments (context binding of auditory sensation). In contrast to the PAD model, it has directly supporting data (Waters et al., in press). Badcock & Maybery suggest, and we agree, that consistent attentional impairments coupled with different modally specific perceptual impairments could account for the propensity within some disorders (e.g., schizophrenia, delirium, and dementia with Lewy bodies) for hallucinations in more than one modality. Consistent with this, all these disorders have pathology that is, to varying degrees, distributed across several perceptual systems. Functional imaging combined with tests of specific cognitive areas would allow this to be tested.

Friston uses empirical Bayesian modelling of visual perception to demonstrate the need for interactive impairments in top-down priors (proto-objects, as we have called them) and bottom-up sensory processes to produce hallucinatory perceptions. Though these models do not address attention per se, since attention acts to increase top-down activation of a specific prior, an attentional impairment will cause lesser activation of the correct prior. Bayesian approaches also explicitly model the effects of context – the scene representation – on perception. Given that the PAD model couples lesser activation of the correct prior with normal or, over time, excessive activation of a specific incorrect prior, it can provide an account of how excessive top-down weight may interact with sensory impairments, as hypothesized by **Tadin et al**.

Staying with mathematical models, **Dolgov & McBeath** use signal detection theory to show that hallucinatory perceptions need not always be associated with relatively poorer perception. This is a striking reminder of the multiplicity of ways in which a complex, dynamic set of systems may produce an erroneous result and usefully broadens our perspective to include not just deficit models. However, this specific relationship is mainly likely when the noise and true distributions are highly overlapping (their Fig. 1). Both erroneous "hits" and "misses" are improbable in normal sensory function; otherwise, we would not have functional sensory systems. We therefore suspect that these distributions are usually highly separated. They do overlap when perception is impaired, hence the association within the PAD model of perceptual impairments and hallucinations. In this case, higher rates of hallucinations may be a trade-off to reduce agnosia. This is a fascinating possibility that merits further investigation.

Such statistical models may provide the answer to **Behrendt**'s wish for us to explain *precisely* how top-down and bottom-up processes interact within PAD. Static words and diagrams, no matter how eloquent or how carefully drawn, cannot convey the realities of the intensely dynamic systems of the brain. However, given the highly nonlinear properties of these systems, clarifying their interaction is not trivial. It is not clear that, for example, an increase in the severity of object perceptual impairment for a given severity of attentional impairment, or vice versa, will necessarily lead to an increase in the frequency of hallucinations in an individual case. The striking linear relationship in the target article's Figure 4 may simply reflect a group average rather than each individual case.

Halliday draws attention to Diederich et al.'s (2005) model for visual hallucinations in Parkinson's disease. This model envisages recurrent hallucinations resulting from a disturbance in a conceptual space defined within Hobson's AIM (Activation, Input, and Modulation) model of consciousness (Hobson et al. 2000). Hobson sees conscious experience as modulated by *activation* (speed of information processing), *input* (the balance between external and internal stimuli), and *modulation* (the dynamic integration of these over time). Diederich and co-authors suggest that hallucinations are most likely when the balance of input is disturbed, with activation and modulation acting as influences. Consistent with the PAD model, the key focus is on the interactivity of the visual system, though the PAD model gives a somewhat more elaborate account of the nature of the impaired interactivity.

R3.4. Summary of cognitive and perceptual risk factors

In our estimation, the balance of the evidence continues to point towards a dysfunctional interaction between top-down and bottom-up visual processes as the genesis of visual hallucinations. Though the exact contribution of each of these may vary from person to person, and there may be occasions when either alone may produce hallucinations, we would maintain that, in practice, such a dysfunction is much more likely when there are impairments in both.

R4. The phenomenology of RCVH – What is hallucinated, and where and when

We hypothesized that the phenomenology of RCVH primarily reflects the nature of scene perception: in particular, the role of scene-based expectations in influencing the attentional focus (what), and environmental and temporal cues in triggering a scene representation that biases processing towards a hallucination (where and when).

Dror, **Carroll & Carroll**, **Friston**, and **Smythies** agree that we are right to place the experience of hallucinations within a dynamic system that actively seeks to reconcile top down representations and bottom-up sensory input within the context provided by the visual environment and its history.

R4.1. Bizarreness and relationship to the environment

Castelo-Branco, **ffytche**, **Morrison & David**, and **Samsonovich** question our characterisations of RCVH as generally in keeping with the environment (though see Merabet et al. 2004 for some examples in which there are very clear links). Even accepting Morrison & David's factual correction, the safest summary of the evidence is that some are in keeping and some are not. Section 1 and Table 3 of the target article show that there are sizable numbers of exceptions to all of the common features of hallucinations. We used the consistencies with the environment to guide us in developing the PAD model. Can the same framework also account for bizarre hallucinations that apparently lack a relationship? We believe that it can if it takes account of the specific effects of eye disease on visual context and visual input.

Empirical Bayesian models of visual processing, described by **Friston** as most consistent with the PAD model, see perception as the least erroneous match between the actual state of visual inputs and a prediction of those visual inputs deriving from an internal model of the visual environment. In eye disease, visual input is necessarily distorted. Hence, the least bad match may be an internally generated visual environment, which, even though bizarre, is still the best reconciliation with actual activity in occipital cortex. In contrast, visual abnormalities in dementia and other illnesses stem from pathology in higher association cortices. This suggests that occipital function is relatively undisturbed and the least erroneous match will be prosaic. One might add to this the role of the scene representation, or contextual information in generative terms. If this is reduced in eye disease, as we suggested in the target article's section 4.1.2 to account for the relatively high prevalence of panoramic hallucinations, this may also place less constraint on bizarre visual experiences. Thus, the PAD model may not be falsified by variations in bizarreness.

R4.2. Individual differences

Behrendt, **Carroll & Carroll**, **Dror**, and **Samsonovich** stress that phenomenology not only depends upon general expectancies from the environment, but also needs to take account of individual goals, desires, and wishes. Although we did acknowledge this area within the PAD model (see the extreme left box of Fig. 3 and sect. 7.4.1 in the target article), our primary focus was on commonalities of experiences. We are therefore grateful for their proposals.

Carroll & Carroll introduce the idea of the proto-object of rest from catatonia, suggesting that one proto-object may, over time, become the default perception when others are not active. **Behrendt** argues eloquently for an understanding of the person's central concerns and wishes, and their potential link to the development of visual hallucinations and further symptoms. Consistent with these roles of top-down processes in the generation of personally relevant hallucinations, ffytche et al. (2004) have reported a fascinating case of a woman with alexia who knew the meanings of text hallucinations which she could not read.

Samsonovich argues that the generation of visual hallucinations in schizophrenia stems from the same roots as auditory hallucinations in a failure of integration of representations of self and others in the mind. He suggests that abnormalities in theory of mind in schizophrenia in conjunction with the PAD model would suggest asocial rather than all too personally relevant hallucinations. We are not altogether convinced of this. It seems equally plausible that aberrant theory of mind would lead people to imbue non-socially relevant stimuli with social relevance, as the other way around. Reasoning only from people with schizophrenia, or indeed any single hallucinatory syndrome, seems to us risky. People with schizophrenia receive that diagnosis in part because of their interpretations of their hallucinations. To argue that these interpretations are causal may prove to be circular. As with so many of these questions, we need more evidence before we can choose between these alternatives.

We fully accept that individual factors are critical in understanding the personal experience of visual hallucinations, though within these we place a high premium on the person's post hoc interpretations (Collerton & Dudley 2004). Gauntlett-Gilbert and Kuipers (2005) and Menon (2005) have shown that distress is not so much due to the phenomenology of the hallucination, but to what the hallu-

cinator thinks will be the personal consequences of having hallucinations – going mad, for example.

Mast draws attention to the similarities between internally generated images and visual hallucinations. Individual differences in images may provide a route for investigating variations in hallucinations. For example, patients with distorted hallucinations might also have distortions in volitional images.

R4.3. Relationship to memory systems

As **Halliday** and **Ingle** point out, one area that needs further development is the proto-object. As this is conceptualised, it is a potential rather than a real thing, corresponding to potential brain states rather than actual ones. Although interference experiments can clarify this in psychological terms, this unreality has serious implications for the physiological testability that Halliday asks for. It highlights the gap between psychological concepts and the limited temporal, spatial, and neurochemical and neuroanatomical resolution of the techniques that we presently have.

However, we can speculate on which systems hold these potentials. Several commentators produce evidence that procedural rather than episodic memory systems are primarily related to visual hallucinations. **Ingle** uses the qualities of hypnagogic hallucinations, hallucinations induced by blindfolding, and visual persistences to argue that these are canonical representations. He points out that hypnagogic hallucinations are not diminished in people with severe episodic memory impairments, suggesting these are stored in procedural rather than declarative memory systems. This may answer **Morrison & David**'s query why hallucinations are not always familiar if they are biased by the environment. If the activated representation is procedural, its familiarity will depend upon the level of abstraction that it is based on.

This distinguishes hallucinations from the episodic memories replayed by stimulation of the medial temporal lobes, and supports **Carroll & Carroll**'s points that, in posttraumatic stress disorder, flashbacks are episodic memories, and that patients may know that images are not genuine but feel that they are. We have argued (sect. 6.5) that flashbacks are not the same as hallucinations.

If hallucinatory images are generated from procedural rather than episodic memories, this might argue against models that see a causal link between lack of insight or source misattribution. These are features of all procedural memories, and, as **Mast** says, images are rarely confused with percepts. Further grounds for caution come from the consideration of bizarreness and insight in eye disease. If we accept that hallucinations in eye disease are generally bizarre, then there should be more likelihood of recognition of these as hallucinations from the start. In reality, though, insight seems to develop gradually (Menon 2005).

R4.4. Hallucinations and the phenomenology of dreams

Gottesmann, **Pace-Schott**, and **Smythies** draw attention to the overlap between the phenomenology of dreams and visual hallucinations. For the reasons that we outline in section 6.4 of the target article, we do not think that hallucinations are simply waking dreams, even in an attenuated form as Gottesmann suggests. We agree with Pace-Schott, however, that there is much to be learnt from the similarities between the two in the constraints that they place on the visual system. His proposal of "boot strapping" self-organisation within dreams is very appealing and may provide a means of further investigating individual variation in hallucinations. It strikes us that, phenomenologically, the visual experience of dreams is most like the hallucinations of eye disease (bizarreness, full field), despite the different physiology. As with eye disease, there is an impoverishment of the visual environment in the case of dreams by eye closure and low light. Dreams and visual hallucinations produced by blindfolding (**Ingle**) may therefore allow a closer investigation of the effects of contextual scene representations on hallucinatory content.

R4.5. Summary of phenomenology

The PAD model was developed to account for the phenomenology of visual hallucinations at the group level, not to predict the experiences of specific individuals. However, it does provide a framework that can be extended to account for variations, as we have illustrated with bizarreness. Still, before proceeding too far along this road, we do need more evidence to support its core propositions, though there is a degree of support from commentators for them.

R5. Physiological constraints that lead to complex visual hallucinations

The PAD model proposed that because object-based attention depends primarily upon the function of lateral frontal cortex, and because object perception depends primarily upon the ventral visual stream, disorders associated with high levels of RCVH will have a common end stage of both lateral frontal cortex and ventral stream dysfunction. This might be due to intrinsic or extrinsic pathology.

R5.1. Location of abnormalities in the visual network

Behrendt, **Carroll & Carroll**, **Friston**, **Halliday**, and **Smythies** agree that disturbances in a distributed brain network underlie the generation of visual hallucinations. Although most commentators recognise that we have identified the correct ventral system, several suggest that the primary causes of dysfunction lie elsewhere: Behrendt, in the coordinating thalamic reticular system; **Spencer & McCarley**, in hyper-excitability of sensory cortex; and Smythies, in general abnormalities of synaptic connectivity. However, as we argued in the target article, these may well be secondary to abnormalities in our areas of interest or, as Friston suggests, have their functional effect in these areas. Nor are they necessarily exclusive. Careful imaging and other studies will produce the data to distinguish between these possibilities.

Halliday rightly points out the overlap between some of the common physiological factors that we have identified, and those of Diederich et al. (2005). However, with the wider range of disorders that we have considered, we would regard some that they proposed (abnormalities in the ponto-geniculo-occipital system, fluctuating vigilance, intrusion of REM dreaming imagery, and overactivity of the mesolimbic systems) as neither necessary nor sufficient – if there are perceptual and attentional impairments and their underpinning biological dysfunctions.

R5.2. The role of cholinergic function

Friston and **Smythies** both agree that the role we assign to cholinergic dysfunction in modulating the uncertainty in top-down activity is predictable from models of normal cholinergic function, with the proviso from Smythies that this can be more closely specified as more is understood about the contributions of muscarinic and nicotinic receptors. We accept also that only a proportion of projections from the laterodorsal tegmental nuclei are cholinergic, though this does not greatly weaken the overall point that cholinergic function is intimately connected with many aspects of the visual system.

To resolve the question of how broad-spectrum muscarinic antagonists induce visual hallucinations, we need subtype selective drugs. Receptor knockout animals that can be subjected to appropriate tests of visual processing may also be useful. From the limited knowledge available on the distribution and function of different muscarinic receptor subtypes in mammalian brain, M4 antagonist activity may be most relevant to the induction of hallucinations. m4 receptor proteins are concentrated in visual cortex (Tigges at al. 1997), and M4 (and M2) binding is increased in the cingulate cortex of patients with dementia with Lewy bodies and hallucinations (Teaktong et al. 2005). Additionally, in vivo imaging of muscarinic receptors in schizophrenia has shown widespread reductions in availability, as we summarised in section 7.6.2.2. M4 receptors also modulate dopaminergic transmission (Tzavara et al. 2004), providing a link with the secondary role that we assign to dopaminergic function.

Smythies provides some fascinating new ideas on the role of cholinergic function in balancing top-down and bottom-up representation, particularly during saccades. During a saccade, information from the retina is suppressed in favour of the top-down model of the visual environment (Kleiser et al. 2004). Smythies goes on to argue that saccades during REM sleep are not in response to visual images but may actually be responsible for them and for promoting the dream state of "free wheeling." If verified, this concept could be highly relevant in visual hallucinations in the waking state, although in dementia with Lewy bodies, no relation between saccade execution and hallucinations has been noted (Mosimann et al. 2005).

Gottesmann, **Kirov**, and **Pace-Schott** highlight that cholinergic function is *increased* during REM sleep. This poses some problems if hallucinations are equivalent to the dreams experienced during REM sleep; particularly since serotonergic and noradrenergic changes during sleep also diverge from those seen in hallucinatory syndromes. However, as dreams are not invariably associated with REM sleep (Solms 2000), and as we have suggested that hypnopompic and hypnagogic hallucinations occur in the transition between waking and non-REM sleep, this is less problematic for the PAD model. So long as transitions between sleep and waking and changes in cholinergic function are not fully synchronised, the hallucinator could experience low cholinergic function while partially awake.

R5.3. Other neurochemical abnormalities

Kirov and **Morrison & David** support the argument in sections 3.2 and 7.4.2 for an additional role for dopaminergic hyperactivity based on pharmacology and the changes seen during sleep. Despite their arguments, we see this as having a role mainly in the context of cholinergic dysfunction; the difference in the effects of dopaminergic and cholinergic manipulations on the induction and treatment of hallucinations, and the neurochemical findings from patients with visual hallucinations, do not seem to us to admit to another interpretation.

Consideration of the functional roles of dopaminergic transmission can clarify why dopamine has only a contributory role. Dopamine has a functional role in attention but contributes much less to visual object perception (Nieoullon 2002). Therefore, it could be significant only if there was another cause of impaired visual function. Additionally, as **Friston** suggests, dopamine may also have a role in emotional learning, perhaps accounting for why people with schizophrenia develop distress in the context of their hallucinations but people with eye disease develop insight.

R5.4. Dorsal function and the PAD model

The PAD model gave only passing mention to the role of the dorsal, spatial visual stream, seeing this as normal. This probably underplays its importance.

Pace-Schott's assignment of dorsal function to the integration of hallucinatory objects produced by ventral dysfunction into a whole visual environment (the PAD hallucinatory scene representation) is appealing and might account for some of the differences in the subjective experiences of dreams and hallucinations, and for the laterality effects noted by **Castelo-Branco**. **Tadin et al**. additionally suggest some intriguing methods for testing the relationship within visual hemifields, although we caution that spatial and object attention will need to be separately addressed. Tadin et al. argue as well for greater abnormality in the dorsal, spatial stream of the visual system of people with schizophrenia, citing normal N1 visual evoked potentials (VEPs) in support. However, **Spencer & McCarley** cite abnormal N1 VEPs to bolster their argument of sensory cortex hyperactivity in the same disorder. Not being experts in this field, we will await a consensus on the experimental findings before being able to assess their implications for the PAD model.

R5.5. Summary of physiological constraints

Commentators have reinforced the centrality of cholinergic function for many disorders associated with RCVH. However, it is clear that other neurochemical and functional systems may also play modulatory or constraining roles, although none appear necessary or sufficient in themselves.

R6. Future directions

One indication of a useful model is that it is testable. By that standard, PAD has succeeded. Specific tests have been suggested by **Badcock & Maybery** (multimodal hallucinations), **Dolgov & McBeath** (trade-offs in visual processing), **Ingle** (visual persistences), **Mast** (volitional images), **Morrison & David** (delirium), **Spencer & McCarley** (attentional function), and **Tadin et al**. (visual hemifields).

R7. Conclusions

Winston Churchill (1947) famously described democracy as the worst form of government – except for all those others that had been tried from time to time. This remark neatly makes the point that it is not just the imperfections in a model that matter, but also how the model measures up against the alternatives.

Our view is that the PAD model remains more potentially predictive than the alternatives. There are still many questions that need new, reliable, unambiguous data in order to be answered. However, no commentator has advanced an alternative model that meets the requirements that we set out in section 5 of the target article. If there can be a grand unified theory of recurrent complex visual hallucinations, we conclude that PAD, despite its many limitations, best fits the present data. Many commentators have proposed specific tests of aspects of it. If we achieve nothing other than to stimulate these tests and the development of a better model, we will be satisfied.

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NOTES

1. For those unfamiliar with Greek mythology, it was Theseus who slew the wicked Procrustes, and Lycomedes who, in some versions of the tale, ultimately threw Theseus to his doom off a cliff.

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Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.

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