jective experience that in the state of normal wakefulness is merely constrained by external physical reality" (target article, sect. 1, para. 2). Here, Being is a function of knowing. Our perceptions do not mirror reality but are shaped by it: "we do not *see, hear, feel, or smell* physical reality itself; instead physical reality *constrains* the internal and fundamentally subjective process of perception" (sect. 1, para. 3, emphasis in target article).

The difference between normal perception, dreaming imagery, and hallucination is only the degree to which they are constrained by sensory input. Hallucination is "*underconstrained* by sensory input" (sect. 1, para. 2, emphasis in original). The primacy of subjectivity, which is "merely constrained" by external physical reality, is clear. Kant's transcendental idealism is grounded in the subject. This is not Berkeley's solipsistic idealism. Kant's *ding an sich* is a reality that in itself is unknowable, but knowable via our subjective appropriation of it.

B&Y's theory is not necessarily tied to Kantian philosophy, however. In Neisser's *Cognition and Reality* (1976), perception is where cognition and reality meet. Subjectivity (in the form of schemata with conditions of satisfaction) and reality are at parity, but only in the normal case. In the psychopathology of schizophrenia, reality may underwhelm subjectivity, per B&Y. In Neisser, the balance shifts subjectivity from Kantian dominance over external reality to parity with external reality. When the particular schemata's conditions are satisfied, there is perception of a particular world. In schizophrenia, the schemata are underconstrained. So B&Y's theory is consistent with both Kant's transcendental idealism and Neisser's scientific realism.

Yet, another philosophical position quite consistent with B&Y's brain theory is monadological (Globus 1987; 2003; Globus & Bezzubova 2001). (See Nakagomi [2004] for a monadological interpretation of fundamental physics.) Here, world "thrownness" – to use Heidegger's term – rather than perception, is where cognition and reality meet. But the meeting is no longer one in which abstract conditions are satisfied. The meeting is instead a match – a belonging-together – some match between reality and cognitive attunement, which may be repeated across monadological brains. The mechanism is the same here – cognition and reality meet – but the result is no longer reflective perception *of* the world, but finding oneself already amidst it, in parallel with other world thrownnesses. In this view, reality is no longer the ground of the perceivable, but "is" instead a defaulting unknowable abground (more Heidegger; see Globus 2003). So there is no exclusive philosophical connection between Kantian transcendental idealism and B&Y's conception of brain functioning.

B&Y's theory can be clinically more broadly applied. For autistic mental activity, which is exaggerated in schizophrenia but is by no means confined to that condition, the inner life predominates over the external world. Autism, too, can be conceived of as underconstrained by reality. The Freudian unconscious mind is underconstrained by reality during dreaming. So underconstraint by input explains more than hallucination.

The key explanatory brain mechanism exploited by B&Y involves dysregulation in thalamocortical systems, so that reality underconstrains relative to cognition. The difference between normal perception and hallucination is only a matter of degree. In hallucination, "sensory constraints normally imposed on the process of perception" (sect. 2, para. 5) are disrupted. This explanation is restricted, however, leaving out primary pathology of the cognitive processes in schizophrenia. Bleulerian splitting (Bleuler 1968), so characteristic of schizophrenia, is a breakdown of integrative capacity, which disrupts experience, cognition, and action.

So a richer context for B&Y's account of brain functioning in hallucination is called for. Input may be underconstraining in schizophrenic hallucination and underconstrained in post-traumatic stress disorder. The subjective attunement may be overconstraining in obsessive-compulsive disorder and underconstraining in impulse control disorders. There is a variable imbalance in psychiatric disorders between constraints of the internal attunement and constraints from external reality. In the case of bipolar disorder, the shifts in attunement between depression and mania are striking.

We applaud B&Y for bringing in a philosophical framework, which is rare outside the phenomenological tradition in continental psychiatry (e.g., Jaspers 1962), and their approach to the relationship between symptoms and brain functioning is worth pursuing. We suggest that a broader clinical context would be beneficial to the development of their ideas.

Thalamocortical dysfunction and complex visual hallucinations in brain disease – Are the primary disturbances in the cerebral cortex?

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Abstract: Applying Behrendt & Young's (B&Y's) model of thalamocortical synchrony to complex visual hallucinations in neurodegenerative disorders, such as dementia with Lewy bodies and progressive supranuclear palsy, leads us to propose that the primary pathology may be cortical rather than thalamic. Additionally, the extinction of active hallucinations by eye closure challenges their conception of the role of reduced sensory input.

We are as dissatisfied as Behrendt & Young (B&Y) with previous models of the genesis of hallucinations. Applying them to complex visual hallucinations (CVH) in neurodegenerative disorders such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), these models struggled to account for who hallucinated, what they saw, and when and where their hallucinations occurred.

We have devised a Perception and Attention Deficit model (PAD; Collerton et al., in press). CVH occur when combined impairments in visual attention and object perception, in the context of a relatively normal scene representation, disturb scene perception. We postulate that these functional impairments result from disturbances in a lateral frontal cortex–ventral stream system. Projections from basal forebrain cholinergic nuclei directly regulate this system, whereas cholinergic projections to the thalamus from the basal forebrain and the brainstem have an indirect influence.

B&Y's emphasis on the primacy of attentional processes in the phenomenology of CVH, and the role of cholinergic regulation, is consistent with PAD. Indeed, as a potential mechanism for synchronizing attention and visual perception, it fills a gap in PAD. Two differences, however, are the role given to the thalamus and the contribution of reduced sensory input to hallucinations.

If hallucinations reflect disruption of thalamocortical synchronized gamma oscillations, then, in principle, the primary locus of dysfunction could be either cortical or thalamic. In support of their thesis, B&Y point to single cases of thalamic lesions with CVH (e.g., Noda et al. 1993; Risser & Powell 1993). However, in group studies, CVH are infrequent in people with massive, but relatively restricted, thalamic damage resulting from infarcts (none reported, del Mar Saez de Ocariz et al. 1996) or fatal familial insomnia (none reported, Gallassi et al. 1996; Tabernero et al. 2000). They are more frequent in AD (average 23%, Ballard et al. 1995; 1999; 2001; Bathgate et al. 2001; Cummings et al. 1987; Holroyd & Sheldon-Keller 1995), Vascular dementia (VaD, average 33%, Ballard et al. 1995; Bathgate et al. 2001; Cummings et al. 1987), DLB (average 55%, Aarsland et al. 2001a; Ballard et al. 1995; 1999; 2001), and Parkinson's disease dementia (PDD, average 40%, Aarsland et al. 2001b; Neimark et al. 1996) – all disorders with more cortical than thalamic pathology. This suggests to us that the primary role that B&Y allocate to thalamic dysfunction cannot be generalized.

Cholinergic function is closely associated with CVH. Pharma-

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cological cholinergic manipulations can both induce and treat hallucinations (Perry & Perry 1995). B&Y relate this to the role of brainstem cholinergic projections to the thalamus. However, there are also wide ranging cholinergic projections to cortical areas. Basal forebrain cholinergic cells in the nucleus basalis of Meynert project to both frontal cortex and the ventral visual stream, as well as directly to thalamic nuclei (Mesulam 1995). Basal forebrain projections to the thalamic reticular nucleus have an additional regulating role in the transfer of corticothalamocortical information (Guillery et al. 1998). We propose that cortical cholinergic projections from the basal forebrain, rather than those to the thalamus, are crucially involved in hallucinations. Thus, loss of cholinergic activity in the temporal and frontal cortex correlates significantly with the prevalence of CVH across AD, DLB, VaD, PDD, Parkinson's disease, and progressive supranuclear palsy (PSP) (Collerton et al., in press). Crucially, in PSP, there is substantial loss of brainstem cholinergic nuclei and concomitant loss of cholinergic function in the thalamus, but no or only minimal involvement of basal forebrain cholinergic nuclei or loss of cortical cholinergic function (Javoy-Agid 1994; Kish et al. 1985; Shinotoh et al. 1999). PSP has low levels of CVH (3%; Aarsland et al. 2001b).

Additionally, in the article cited in the target article on the loss of thalamic reticular nucleus alpha-7 nicotinic receptor in schizophrenia (Court et al. 1999), there was greater loss of this receptor in AD and in DLB. AD has a lower average rate of CVH (23%) than schizophrenia (average 37%, Bracha et al. 1989; Cutting 1997; Howard et al. 1994; Ndetei & Singhe 1983; Zarroug 1975), whereas DLB has a higher rate (55%) – indicative of a lack of obvious relation between thalamic pathology and hallucinations. Because basal forebrain nuclei project to both the cerebral cortex and discrete thalamic nuclei, we would, however, not exclude thalamic dysfunction potentiating the effects of cortical cholinergic loss. Imaging of cholinergic function (e.g., Kuhl et al. 1996) in discrete neocortical, as opposed to thalamic, areas would allow this to be assessed.

Unlike B&Y's model, PAD was not developed to account for schizophrenia. However, new evidence of cortical muscarinic receptor abnormalities (German et al. 1999; Karson et al. 1993; Powchik et al. 1998; Raedler et al. 2003), and the effects of neuroleptic agents with antimuscarinic activity, in creating cognitive impairments in schizophrenia (Minzenberg et al. 2004), opens the possibility that intrinsic or iatrogenic cortical cholinergic abnormalities may also be significant in this disorder.

Reduced sensory function is a risk factor for CVH in neurodegenerative illnesses (Ballard et al. 2001; Barnes & David 2001; Chapman et al. 1999; Holroyd & Sheldon-Keller 1995; Holroyd et al. 2001; Murgatroyd & Prettyman 2001), eye disease (Brown & Murphy 1992; Holroyd et al. 1992), schizophrenia (Howard et al. 1994), and the general population (Ohayon 2000; Ohayon et al. 1996). However, further reducing sensory input in hallucinators by closing eyes generally extinguishes, rather than encourages hallucinations (Diederich et al. 2003; Kolmel 1993; Menon et al. 2003; Santhouse et al. 2000; Teunisse et al. 1996). We account for this by suggesting that specific visual environments activate an abstracted scene representation (Henderson & Hollingworth 2003; Rensink 2000) that biases perception toward a specific hallucination. No vision means no activation and hence no hallucination. To our mind, this extinction is inconsistent with B&Y's conceptualization. This would suggest an intensification of the hallucinatory experience when sensory input is reduced further.

Neither model of hallucinations is likely to be wholly correct. Comparisons such as these should stimulate direct tests of their specific predictions.

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Hallucinations and acetylcholine: Signal or noise?

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Abstract: The cholinergic system is a good candidate for the role of determining the relative weight given in cortical information processing to new sensory information versus prior knowledge. We discuss the physiological data supporting this, and suggest that this Bayesian perspective can easily be reconciled with the dynamical framework proposed by Behrendt & Young (B&Y).

Behrendt & Young (B&Y) suggest that the ability of a sensory system to use information from the world to constrain its activity is dependent on the signal-to-noise ratio (SNR) of thalamic processing. Their model accords well with some data on cholinergic actions in thalamus. However, incorporating data on the effects of acetylcholine (ACh) in cortex and refining our understanding of the SNR effects may give a more compelling result.

In engineering terms, SNR is traditionally the ratio between the signal and noise *power* – that is, between the variance in the overall response attributed to signal changes, and that observed when the signal is held fixed, so that fluctuations merely reflect noise. It is noise defined in this way that limits the fidelity of information transmission, and ultimately of sensory performance. In the simple case of a Gaussian channel, SNR is related to the Shannon transmitted information, I, by

$$I = 1/2 \log_2(1 + \mathrm{SNR})$$

Unfortunately, much of the physiological literature (Lena & Changeux 1997; Sato et al. 1987a; Sherman & Guillery 2001; Sillito & Kemp 1983) confuses the issue by, instead, measuring the ratio between signal amplitude and the average level of background activity. The difference between these two measures is illustrated later.

The reason for the confusion is largely historical, and stems from the analysis of situations in which signal detection against a background was the sole requirement. High levels of background activity do not necessarily limit the SNR of transmission. If we think about the receiving neuron's task, average background can simply be subtracted from its input by a thresholding operation set to the level designated "A" in Figure 1. If thalamic relay neurons are so intrinsically active as to swamp evoked input, this is a problem in detection, because subtracting the background will remove the signal as well (i.e., if A = B in Fig. 1). Once the signal exceeds background activity, further changes in background level will not improve the discriminability of responses. If the signal can modulate the thalamic reticular nucleus (TRN) in a stimulus-specific way, as B&Y propose, detection SNR is not at issue. The authors' model does not address discrimination SNR. Additionally, applying a signal/background analysis to sensory processing is problematic because background activity may carry information; that is, it may be a signal.

There are data, however, that suggest ACh can improve the SNR of cortical sensory processing and, from this perspective, the essential elements of B&Y's model still hold. One study has directly examined the trial-to-trial variability (measure "C" in Fig. 1) of neuronal firing under ACh (Sato et al. 1987b) and shows a small decrease in response variability when some cortical neurons are exposed to ACh. Because, without cholinergic modulation, the variance of cortical responses has been shown to increase proportionally to mean firing rate (Tolhurst et al. 1983), this implies that ACh is having a regularizing effect on spiking, such that visually evoked responses are more reliable from trial to trial than would be expected given their magnitude. Unfortunately, in this study

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