Hallucination Questionnaire (LSHS; Launay & Slade 1981), we reported the degree of endorsement of each item. These ranged from 2% ("hearing a conversation in the rear of the car") to 41% ("hearing noises") for the BHQ, with a mean degree of endorsement of 11.8%; and between 4% ("hearing the voice of God") and 76% ("voices in the head") for the LSHS, with a mean degree of endorsement of 35.7%. These data do not detract from the arguments made in the target article, but they certainly suggest that the phenomena under discussion are, by far, not only associated with pathology.

My second point is that it is of paramount importance to consider the *interaction* of trait and context in determining subjective experience (Glicksohn 1987) in general, and in particular, with respect to hallucinatory experience. I single out the trait of *absorption* (for a review, see Roche & McConkey 1990). In a recent paper, we presented data indicative of a common pseudohallucinatory experiential base, and suggested that absorption can serve as the predisposing factor for hallucinatory experience (Glicksohn & Barrett 2003). Absorption might very well be viewed as a *diathesis* for hallucination (for general discussions, see Butler et al. 1996; Monroe & Simons 1991). B&Y have ignored the role of individual differences in developing their model, and yet some authors consider the role of such individual differences to be critical for testing the validity of any model (Underwood 1975). Let me give two examples from the target article. The authors write that "it is doubtful that thoughts, inner speech, verbal images, or retrieved memories can be transformed into experiences with perceptual qualities just by virtue of their misattribution to an external origin" (sect. 2, para. 4), but this is exactly what individuals scoring high on absorption seem to do (Destun & Kuiper 1999). Second, the authors argue that when sensory constraints are weak, "then attentional mechanisms may become the dominant modulatory influence on thalamocortical self-organization and hallucinations may arise" (sect. 1.3, Fig. 2 caption). Yet, this is exactly what distinguishes between individuals scoring high and low on absorption (Crawford et al. 1993a). B&Y might well consider the implications of such individual differences for their model.

Paradoxical sleep and schizophrenia have the same neurobiological support

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Abstract: During the paradoxical dreaming sleep stage, characterized by hallucinations and delusions, as in schizophrenia, the increased subcortical release of dopamine, the presynaptic inhibition of thalamic relay nuclei, and serotonergic disinhibition are in accordance with the model for the mechanism of hallucination-induction.

Behrendt & Young (B&Y) develop a highly interesting model based on powerful arguments. Indeed, the thalamus is a crucial step for treatment of sensory information. Moreover, the thalamocortical loop is strongly involved in electrophysiological activities concerned with normal consciousness, in that the gamma rhythm, which is impaired in Alzheimer's disease (Llinas & Ribary 1993), is recorded, most often synchronized, at both levels. The assumption that hallucinations are able to occur in the activated brain when the constraint of sensory afferents is decreased is, of course, very attractive for a sleep researcher, particularly when one is involved in the paradoxical dreaming sleep stage (PS). Indeed, there are strong functional analogies between dreaming and schizophrenic mind disturbances (principally hallucinations and delusions, cognitive impairment). First, already-established results show that there is thalamic postsynaptic activation, but presynaptic inhibition, in relay nuclei during the eye movement bursts of PS (Gandolfo et al. 1980; Steriade 1970), which are in strong relation to dreaming activity (Aserinsky & Kleitman 1953; Dement & Kleitman 1957). These data are in accordance with the hypothesis of sensory deafferentation for PS hallucinatory activity. More recently, the gamma rhythm was discovered in animals (see Maloney et al. 1997) and humans (Llinas & Ribary 1993; Ribary et al. 1991). It occurs during waking as well as during PS, but there is a specific difference when compared to waking. In addition to the absence of reset by sensory stimulation during PS (Llinas & Ribary 1993), recalled by the authors in the target article, which confirms the sensory deafferentation during this sleep stage, the synchronization over the cortical areas disappears during this sleep stage (Perez-Garci et al. 2001). This is an indication of disconnectivity of central structures, which are also repeatedly mentioned for schizophrenia (Meyer-Lindenberg et al. 2001; Tononi & Edelman 2000; Young et al. 1998). Finally, blood flow shows two important facts: (1) Although the associative visual cortex is activated during PS, the primary one is deactivated (Braun et al. 1998), which is also in accordance with some visual deafferentation, the main sensory modality concerned with hallucinatory dreaming activity. (2) There is a prefrontal dorsolateral deactivation both during dreaming (Maquet et al. 1996) and in schizophrenia (Weinberger et al. 1986).

Electrophysiological results related to neurochemistry have shown that noradrenergic and serotonergic neurons that innervate the cortex have mainly inhibitory influences (Araneda & Andrade 1991; Krnjevic & Phillis 1963; Manunta & Edeline 1999; Reader et al. 1979), and that these neurons, active during waking, become silent during paradoxical sleep (Hobson et al. 1975; McGinty & Harper 1976), thus inducing cortical disinhibition during PS (Gottesmann 1999; 2000; 2002). It is worth mentioning that clinical results show a deficit of both transmitters in schizophrenia (Linner et al. 2002; Silver et al. 2000). However, there is one monoamine – dopamine – the activity of which persists during PS (Miller et al. 1983; Trulson & Preussler 1984). It was even hypothesized that these neurons could release more dopamine during PS (Gottesmann 2002), because of firing by bursts (Gonon 1988). Indeed, results have already shown a higher variability of neuron firing in tegmental area neurons during PS (Miller et al. 1983), which implies at least some bursts. Finally, the N_{100} component of the test evoked potential in the prepulse inhibition paradigm shows differences during waking in normal subjects and in schizophrenics; in contrast, an identical increase of amplitude appears during REM sleep, which suggests a disinhibition process in both states (Kisley et al. 2003).

The main neurochemical hypothesis concerning schizophrenia disturbances involves an excess of dopamine functioning, as shown by the improvement by dopamine receptor blockers, and a deficit of glutamate, as shown by NMDA antagonists that induce psychotic symptoms (Grace 2000) and, interestingly, vivid dreaming (Reeves et al. 2001). These dysfunctionings could be responsible for the positive symptoms of schizophrenia (hallucinations, delusions), which mainly concern the nucleus accumbens, whereas a deficit of dopamine at the prefrontal cortex level might induce the negative symptoms of this disease: anhedonia, cognitive impairment (Abi-Dargham & Moore 2003). Moreover, hallucinatory activity and loss of reflectiveness are also observed during PS. Therefore, our laboratory studied dopamine and glutamate release in the medial prefrontal cortex and nucleus accumbens of rats by microdialysis and capillary electrophoresis. The results showed a decrease of dopamine during PS in the medial prefrontal cortex when compared to waking (Gottesmann 2004; Léna et al. 2003). This decrease might cause this transmitter to fall outside the limited range of optimal functioning (Abi-Dargham & Moore 2003) and be responsible for the cognitive impairment observed both during dreaming and in schizophrenia. The level of glutamate was unchanged during sleep–waking stages. In contrast, there was a maximal level of dopamine during PS in the nucleus accumbens, a minimal release during slow wave sleep (SWS), and an intermediate level during waking. Moreover,

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glutamate level was maximal during waking and minimal during both slow wave sleep and PS.

Consequently, our results obtained during PS are in close accordance with those postulated for schizophrenia, and this sleep stage seems to offer a good psychological, electrophysiological, and neurochemical model for schizophrenia. In addition, these results could be reconciled with the model of B&Y. First, the increase of dopamine functioning during PS in nucleus accumbens might also occur in thalamic reticular nucleus, inducing decreased GABAergic neuron functioning and indirectly promoting thalamocortical gamma rhythm. Moreover, the silence of serotonergic neurons during PS might create a disinhibition of thalamocortical neurons and also promote the occurrence of gamma rhythm, thereby supporting potential hallucinatory activity because of the presynaptic inhibition of sensory afferents. The silence of noradrenergic neurons probably suppresses some relay nuclei facilitation. However, even if the silences of the two monoamines cancel each other out, the postsynaptic activation would certainly be induced by cholinergic afferents issued from the mesopontine pedonculopontine and tegmental dorsolateral nuclei.

It is fascinating that there are two different kinds of results supporting the same disturbances of schizophrenia – that is, the model presented by B&Y and our neurochemical results. It is possible that new results will soon completely integrate all these convergent, but still slightly different, data and help construct a unitary model.

Hallucinations and antipsychotics: The role of the 5-HT2A receptor

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Abstract: Behrendt & Young's (B&Y's) novel "unifying model" of hallucinations, although comprehensive, fails to incorporate research into the possible role of 5-HT2A receptors in the mode of action of novel "atypical" antipsychotic drugs (which treat hallucinations effectively), and into the role of such receptors, which are located in thalamocortical circuits, in mediating drug-induced hallucinations.

Behrendt & Young (B&Y) have developed a stimulating "unifying model" of hallucinations. This model integrates data from a number of domains; however, it neglects two major interacting research areas related to hallucinations. First, evidence that hallucinogenic drugs act as 5-HT2A receptor agonists; and second, evidence that such receptors may play a key role in the mode of action of many novel "atypical" antipsychotics. Although the authors' model incorporates a number of neurotransmitters, the only reference to serotonergic actions is to inhibitory effects of ascending afferents from the raphé nuclei on actions of thalamocortical circuits. The specific serotonergic receptors involved in such effects are not stated. We suggest that any "unifying model" of hallucinations will have to incorporate the role of 5-HT2A receptors in the actions of hallucinogens and in the mode of action of some novel "atypical" antipsychotics. We briefly review these two areas in turn.

B&Y suggest that all hallucinations, regardless of etiology, arise from one mechanism. Parsimony dictates therefore that any model of hallucinations should also account for drug-induced hallucinations. Indeed, there is a long history of research attempts to understand schizophrenia by analysing hallucinogens. Although such research was popular in the mid-twentieth century, it then went out of favour, but is now showing a resurgence.

Much of our understanding of the mode of action of hallucinogens comes from drug discrimination (DD) studies in animals. In these studies, animals are typically trained to make one of two responses for reward. One response (drug) leads to reward only when drugged, and the alternative response (non-drug) leads to reward only when undrugged. Thus, an animal has to discriminate its internal state to decide which response to make to obtain reward. It is often assumed, although unproven and indeed unprovable, that such states are animal analogs of "subjective" effects of drugs in humans. The DD bioassay has, however, proved to be remarkably specific. When trained to discriminate a hallucinogen, animals typically will only respond on the drug lever when treated with another hallucinogen (Appel et al. 1999). Drug responses can also be blocked by antagonists, and it has been shown that agonist actions at the 5-HT2A receptor mediate the actions of hallucinogens in this model (Winter et al. 1999). Significantly, the ability of risperidone to antagonise LSD in this model played a critical role in the development of the first novel "atypical" antipsychotic to be approved by the FDA (in 1993) for 15 years (see Colpaert 2003 for a review). Furthermore, the actions of hallucinogens in this assay can be blocked by both specific 5-HT2A antagonists and novel antipsychotics (Schreiber et al. 1994). Such data complement findings from other preclinical bioassays that indicate that hallucinogens act as 5-HT2A agonists (e.g., Gresch et al. 2002). Moreover, important studies in humans with psilocybin indicate that its hallucinogenic actions can be blocked by the 5-HT2A antagonist ketanserin (Vollenweider et al. 1998). Collectively, these data suggest that hallucinogens act as 5-HT2A agonists, and that such actions may be valuable in antipsychotic drug development.

5-HT2A receptors are located predominantly on cortical neurons, although some are found on thalamic neurons (see Nichols 2004 for a review). Thus, hallucinogens may act on thalamocortical circuits of the type discussed by the authors. Indeed, Nichols (2004) has suggested specifically (by reference to an earlier article by Behrendt [2003]) that underconstrained perceptions may arise from dual effects of 5-HT2A agonist hallucinogens, involving dysfunction of the reticular thalamic nucleus and concurrent excitation of specific thalamic relay nuclei, leading to marked activation of thalamocortical circuits. Such observations clearly emphasize the need for B&Y's model to include 5-HT2A receptors.

The authors refer to possible actions of novel "atypical" antipsychotics on D4 and GABA receptors, although they do not note that 5-HT2A receptors have been implicated, rather more convincingly, in the mode of action of some of these drugs. Brain imaging studies indicate that some of these drugs occupy 5-HT2A receptors at a high level when used clinically to treat schizophrenia (e.g., Jones et al. 2001; Travis et al. 1998). Importantly, such drugs occupy cortical 5-HT2A receptors at higher levels than striatal D2 receptors (Meltzer 2004), in accord with the hypothesis that a defining feature of "atypical" antipsychotics is that they have higher affinity for 5-HT2A receptors than for D2 receptors (Meltzer 1999). Although this hypothesis is by no means proven as an account of the actions of novel "atypical" agents, it is known that drugs such as clozapine are effective in treating patients who do not respond to other antipsychotics (Meltzer 2004). Significantly, typical agents such as haloperidol do not occupy 5-HT2A receptors (Meltzer 1999), and the enhanced therapeutic actions of agents such as clozapine may result from their ability to block 5-HT2A receptors. This hypothesis is supported by evidence that 5-HT2A systems can modulate the actions of mesolimbic dopamine systems (e.g., Barr et al. 2004), which, it is believed, are hyperactive in patients showing positive symptoms such as hallucinations (Meltzer 2004). A range of preclinical studies designed to detect antipsychotic activity indicate that the selective 5-HT2A antagonist M100907 is effective in reversing behavioural effects associated with hyperdopaminergic states induced by drugs such as amphetamine and cocaine, and by the absence of the dopamine transporter (Barr et al. 2004). Although the precise mechanisms involved in such effects are unclear, they suggest that functional interactions between 5-HT2A and dopamine systems may be of considerable significance in the mode of action of some novel antipsychotics, which may be more efficacious than older agents against symptoms such as hallucinations.

In summary, two related lines of evidence suggest that a "uni-