Thalamus, a theory of everything?

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Abstract: Hallucinations do not originate in a single region of the brain, the thalamus, and cannot be traced back to a single pathological mechanism. They emerge from the complex interaction of several brain regions, and are not necessarily the result of sensory impairment or the effect of a defective filter. In the case of schizophrenia, hallucinations are accessory symptoms, in Bleuler's sense, and are thus not central to this disorder.

In the target article, Behrendt & Young (B&Y) give a detailed survey of the thalamocortical system in its relation to hallucinations in neurological and psychiatric conditions. The thalamus as an "entrance door" to virtually all the sensory channels has always attracted the attention of schizophrenia researchers. This region of the brain alone – so the assumption goes – could be the cause of many distortions in perception and of hallucinations, because if it were damaged it would not be able to fulfill its function of gating or filtering incoming information. Defects in sensory "gating" or filtering of stimuli could therefore lead to "input overload" (McGhie & Chapman 1961), and thus to the difficulty of distinguishing between "self" and "nonself."

This model is based on a false notion, namely, the notion that perception is a passive process. Ever since Gibson's (1966) studies, it has become increasingly clear that perception is generated by means of motor processes (star-nosed mole, Catania 1999; bat, Kuc 1994; and saccades in humans, Ballard et al. 1997). Finally, it has recently been shown that visual pattern recognition is a pattern formation in the cerebral cortex (Kenet et al. 2003).

In the brain, perception arises from the interaction of many regions. For the visual system, for example, Felleman and Van Essen (1991) found a hierarchy of extremely complex and varied connections. Studies on so-called blindsight – where the thalamus remains intact – have shown us that only a few cortical regions of this complex system (e.g., V1) provide conscious perception (Weiskrantz et al. 1995).

Hallucinations are no more passive than perception is. Obviously, pathological activity is generated starting from the visual cortex and is detached from sensory input. This can be clearly seen from the Charles Bonnet Syndrome (CBS). The first person to describe CBS, de Morsier (1936), pointed out in his studies that the presence of an eye disease was not the most important etiological factor in these hallucinations; he thus excluded the theory of visual impairment. Ffytche and Howard (1999) saw a relationship between CBS and eye disease, however they clearly located the disorder in the cerebral cortex. They were able to classify important types of hallucination and to prove, using fMRI, that increases in activity within the specialized visual cortex are the cause of certain types of visual hallucinations. In their view, various factors result in such increases in activity, but the thalamus is of little importance in this context.

Schizophrenics also experience visual hallucinations in the form described by Ffytche and Howard (1999). They experience these distortions not only in hallucinatory but also in perceptual form. The essential difference to CBS is illustrated by the fact that a particular facial contortion, for example, is interpreted by CBS patients as not being real, whereas schizophrenics interpret it as real. The model of visual impairment and underconstrained perception lacks the ability to explain this complexity of hallucinatory events.

Also, the verbal hallucinations frequently observed in schizophrenia indicate the interaction of various regions of the brain. During the second half of the nineteenth century, psychiatrists (Cramer 1889; Séglas 1892) recognized on the basis of clinical observations that verbal hallucinations are closely linked with the process of language production. And Bleuler (1911/1950) argued against Kraepelin that hallucinations could not be only "perceptual" (cf. Kraepelin 1919/1971), for the simple reason that they clearly had intentional contents.

Thus, clinical experience supports the idea that hallucinations in general are not purely "sensory," but instead are motor disorders. It has been possible to show that in most cases, patients developed activities of the speech muscles in hallucinations they claimed to hear (subvocal speech, Bick & Kinsbourne 1987; Gould 1948).

The emergence of imaging procedures has made it possible to show in numerous studies that activations of the motor language region are in fact involved in hallucinations (e.g., McGuire et al. 1993).

B&Y believe that their understanding of the mechanism of hallucination holds the key to understanding schizophrenia. Bleuler (1911/1950) described the hallucinations and abnormal perceptual experiences in schizophrenia as being "accessory" symptoms, whereas he considered the fundamental features of the disorder to be disorganized thinking, affective disturbances, autism, and ambivalence. He emphasized that this illness is distinguished by the simultaneous existence of normal and bizarre behavior and of simultaneous hallucinatory and normal perception. In this case, the nervous system should be overconstrained rather than underconstrained.

B&Y automatically run into difficulties when they try to ascribe the variety of disorders in schizophrenia to a hallucinatory predisposition. Schizophrenia affects such a variety of mental processes, and so many regions of the brain have been described using imaging processes whereby their functions are shown to deviate from those of normal subjects, that to attribute all these changes to the thalamus would mean attributing the entirety of all mental processes to the thalamus.

All in all, the disease seems to be characterized primarily by motor disorders, which are independent of acts of perception in every respect. These include, among others, motivational disorders, which Kraepelin (1919/1971) compared with the frontal lobe syndrome, as well as numerous other motor disorders scarcely discussed in the literature, with perhaps the exception of the impressive catatonic states. In this context, it seems important that the sensory apparatus remains completely intact during these catatonic states, as the minutely detailed descriptions given after such states show.

It does not appear to make much sense to grant one system – the thalamocortical system – a privileged position among the many other systems in the brain. It makes more sense when searching for the origin of perception and hallucination to identify the region in which these perceptions and hallucinations become conscious. Even if it should be the case that the thalamocortical system has a massive influence on the state of the brain, the individual contents of consciousness are generated by very precisely determinable regions in the cerebral cortex.

Deregulation of the balance between data and conceptually driven processing: A shift toward the conceptual

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Abstract: Behrendt & Young (B&Y) propose that a dysfunction in the reticular thalamic nucleus contributes to disinhibition of specific thalamic nuclei, allowing cortical attention mechanisms to engage thalamic relay neurons, causing underconstrained activation of the cortex and hallucinations. The following hypothesis challenges the notion of impaired sensory gating by providing the alternative view that hypofrontality reduces the power of incoming stimuli, causing internal drives to override consciousness, resulting in hallucinations.

https://doi.org/10.1017/S0140525X04360188 Published online by Cambridge University Press

I suggest that a dysfunction in the reticular thalamic nucleus does not explain all the findings in the schizophrenia literature. I propose that a mechanism, which I refer to as "dynamic modulating equilibrium" and which mediates the balance between afferent stimulation and intrinsic activation, is faulty. This dysfunction leads to a shift in the locus of attention toward the conceptual (intrinsic) side of the interaction. This view is consistent with the target article in regard to the basic equality between the waking (data-driven) and dreaming (conceptual) state, except that this position does not view the imbalance as a result of overactivation of thalamic relay cells. Instead, as a consequence of reduced prefrontal activity (Niznikiewicz et al. 2003), modulation or amplification of external input is decreased. This reduced impact of external sensory information shifts the locus of attention on the continuum between the balance of these two states internally. (To elaborate: When daydreaming, attention is focused inward, therefore reducing the impact of the external world on cortical networks. On the other side of the continuum would be, for example, intense focus during batting at a baseball game. During this time, very little inward thought would occur compared to daydreaming.)

According to the target article, intrinsic activation is present and underlying, and external input only constrains the underlying excitation; therefore, any reduction of afferent stimuli should lead to an increase in weighting of internally driven thoughts and stimulus patterns. This shift in weighting causes disproportionate amplification of internally driven thoughts and perceptions, thereby bringing them into awareness as hallucinations. This is consistent with the phenomenology of "thoughts becoming audible" (Alpert & Angrist 2003).

Instead of a deficit in gating resulting in sensory flooding and overactivation of the cortex (Adler et al. 1982), I suggest the opposite – namely, that there is less resolution of afferent stimuli from diminished amplification. The following outlines are evidence for this approach.

The reduced N400 wave to incongruent words at the end of a sentence, found in schizophrenic populations, is interpreted as an overly broad lexical search (Mathalon et al. 2002). These findings lend support for the proposed hypothesis and reflect the signal-to-noise and time-dependent manner of activation in cortical networks. In indirect priming paradigms, priming is facilitated at short Stimulus Onset Asynchrony (SOA) and is reduced at longer intervals for schizophrenic subjects. In contrast, normal subjects' results show that priming is facilitated at longer SOAs and is reduced at shorter SOAs. This has been interpreted as diffuse activation in the semantic maps (semantic loosening), which returns to baseline levels in a shorter time frame in schizophrenics compared with controls (Mathalon et al. 2002; Spitzer 1997).

Because increased constriction of a semantic concept will increase the time the concept stays activated, the same should hold true for lower-level functioning related to external input. Compatible with this viewpoint, and an alternative interpretation of the reduced P50 ratio found in schizophrenia patients, is that it reflects a loss of short-term sensory memory. I posit that, as a result of the reduced amplification shifting the locus of attention inward, the excitation caused by the first click does not reach a critical activation threshold to sustain its activation pattern across the temporal gap. When the second click is introduced, the reduced P50 ratio reflects the decay of activation and "forgetting" of the previous stimuli, and therefore no inhibition is necessary. The difference found between schizophrenics and normal subjects has been eliminated in two different task manipulations, compared to the standard 500-msec interval approach. The first one varied the time interval and found that at 75 msec (Nagamoto et al. 1989), 750 msec, and 1000 msec (Dolu et al. 2001) no differences were found. For the 75-msec condition, gating occurred, and for the 750-msec and 1000-msec intervals, gating did not occur for patients or controls. In the 75-msec task, the latency was short enough for the stimulus to remain active, whereas for the 750-msec and 1000-msec tasks, the activation of both the controls and patients had already dissipated. The second study found no difference in gating when the click presentation was of 10 msec duration (Guterman & Josiassen 1994), suggesting that the stimulus intensity reached a threshold to remain active for the schizophrenia patients.

The lower amplitude of the P50 wave in schizophrenia patients, compared to first-degree relatives and controls (Freedman et al. 1983), can be interpreted within this hypothesis as being reduced amplification. Studies have shown that the P50's amplitude can be manipulated by stimulus intensity. Ninomiya et al. (2000) report that an increase in decibels (up to 85 db) increases the amplitude, whereas another study found increased amplitude to the human voice from multiple band frequencies to recruit more of the cortex (Chen et al. 1997). These findings reflect the variability related to stimulus intensity and time. Caution should be used when interpreting the reduced P50 ratio in schizophrenia patients as being solely a deficit in gating. Further studies that vary intensity and time intervals are needed to elucidate this variability.

Finally, because a diminished P50 ratio is found in both patients and their first-degree relatives, as well as the relatives who do not have the reduced P50 amplitude (Clementz et al. 1998), this finding can be inferred to indicate a greater shift toward the internal on the continuum of attentional locus during active psychosis, reflecting the vulnerability of the relatives.

Deficits in visual backward-masking (VBM) tasks found in schizophrenia patients are thought to result from an interruption of the first mask because of an overactive transient channel (Butler et al. 2002). Consistent with the target article's view that the first mask failed to engage gamma oscillations is the finding that reduced amplification of the first stimulus results in a more rapidly decaying activation pattern that is more easily interrupted by the mask. Because the effects of VBM can be manipulated by intensity, luminance, and time (Butler et al. 2002), just like the amplitude of the P50, the assumptions that the findings infer gating deficits in schizophrenia have to be questioned.

This novel theory would predict a global reduction in high-frequency gamma waves induced by stimuli. Evidence for this deficit is outlined in Phillips and Silverstein's (2003) theory on impairment in cognitive coordination, which results from NMDA-receptor hypofunctioning reducing gamma-wave synchronization. The main effect of reduced synchronization is contextual ambiguity and thought disorganization.

The target article offers an integrative approach to psychosis and hallucinations, combining findings from psychophysical and behavioral measures. Because the brain works as an integrative system, it seems that psychosis can emerge from a dysfunction of gating, the balance between excitation and inhibition, or structures that play central roles in modulating and integrating information.

Getting real about experience

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Abstract: The idea that experience is essentially subjective rather than of the real world is paradoxical and deeply flawed. The external world is, much more than a mere constraint, essential to meaningfully describe experience and neural activity. This is illustrated by an analysis of the phenomenology of veridical perception and by the study of experience in psychopathology by the Experience Sampling Method (ESM).

Behrendt & Young (B&Y) must be complemented for the well-documented development of their case. It is unfortunate, however, that the philosophical framework that holds together their effort is deeply problematic, even fatally flawed. The idea that experience

https://doi.org/10.1017/S0140525X04360188 Published online by Cambridge University Press