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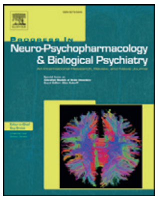

Hallucinatory experience as aberrant event memory formation: Implications for the pathophysiology of schizophrenia

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ABSTRACT

If hallucinations are not fundamentally different from normal wakeful experiences, then the neural basis of hallucinations has to be essentially that of consciousness in general. The additional insight that consciousness reflects the formation (as opposed to consolidation) of event (episodic) memories links the pathophysiology of hallucinations to the hippocampus. Perceptions and misperceptions, insofar as they are consciously experienced, constitute contextualized and unitary phenomena (which are embedded as discrete events in the stream of consciousness); they are experiential manifestations of activity patters that recurrently emerge in the CA3 network of the hippocampus (and that are secondarily consolidated into retrievable and declarable memories). The hippocampus, forming allocentric representations of objects in their world context (event memories), is a point of convergence of neocortical sensory processing streams. Moreover, being extensively modulated by the organism's physiological state, the hippocampus embeds such representations in an emotional context and, through its output to the medial prefrontal cortex, guides decision-making and goal-selection processes. Although sensory and associative processing in the neocortex makes an important contribution to the formation of behaviourally adaptive representations in the hippocampus, it is becoming clearer that pattern formation in the hippocampus is in itself the neural correlate of consciousness and that disruptions in relational memory processing in the hippocampus can give rise to hallucinations. Neurobiological and neuroimaging findings in schizophrenia research can be integrated within the proposed conceptual framework.

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1. Introduction

Common sense would suggest that events and objects that surround us are part of an objective reality that exists independently of our mind. However, according to Kant (1781) and Schopenhauer (1844), objects and events are creations of the mind and conform to rules of the mind. Objects and events that populate our world – and even their apparently objective characteristics – do not exist in themselves; they do not exist without our awareness of them. There is no object without subject (Schopenhauer, 1844). Kant (1781) argued that the mind automatically imposes its 'categories' (concepts) upon sensory data emanating from the physical world (the world 'in itself'). Categories of 'object', 'event', and 'causation' are examples of such 'a priori' knowledge; they are basic to our experience of particular instances of objects, events, and causations. We are prevented from gaining insight into the fundamentally subjective and ultimately dreamlike nature of the perceived world for as long as the phenomena that populate the perceived world are consistent with each other and adaptive to our interaction with the physical world (whereby we need to bear in mind that actual interaction with the physical world takes place beyond the realm of conscious experience).

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The implication of philosophical idealism, as advanced by Kant and Schopenhauer, is that the world experienced in a dream or hallucinatory state is no less real than the world perceived in the state of normal wakefulness. Patients with psychosis typically have no insight into the unreality of their experiences (Jaspers, 1946; Cutting, 1997); but none of us readily gains insight into the subjective and fundamentally private nature of our conscious perceptions. What is often considered to distinguish hallucinations from normal perceptions is that hallucinations, but not normal perceptions, come from within the person's mind (Hamilton, 1974). Hallucinations are thought to derive from 'inner' mental phenomena, such as mental imagery or inner speech, whereby a process of 'external misattribution' has to be postulated, a process that would explain how "non-real mental events (e.g. images, thoughts) somehow become invested with reality" (Cutting, 1997, p. 83). Normal conscious perceptions and hallucinations of external objects or events are experientially identical (Jaspers, 1946; Cutting, 1997), so that their respective mechanisms have to overlap substantially. Conscious experience can, importantly, be underconstrained by changes in the external physical world (and thus maladaptive) – either if neuronal activity patterning that immediately underpins such experience is hyperactive (or less responsive to constraints placed upon it) or if peripheral detection and processing of sensory information, that is, upstream processes that ground conscious experience in external physical reality, are relatively insensitive to changes in physical reality (Behrendt and Young, 2004; Behrendt, 2006).

2. Episodic memory and consciousness

Episodic (declarative) memory is memory for events and objects; and such events and objects are compositions of arrays of *features*, including features of the *contextual* kind. Episodic memory refers to a sequence of events. Event memory is a unitary representation that captures the co-occurrence of multiple features that constitute an event; and a sequence of such events ran be recalled (and declared) as episodic memory. Episodic memory depends on the hippocampus and surrounding medial temporal lobe structures, particularly on the associative (relational) function of the hippocampus, the ability to conjunctively encode (bind) inputs from multiple neocortical regions. Damage to hippocampus and parahippocampal regions (as it occurs progressively in Alzheimer's disease) is known to disrupt the ability to form new episodic memories but is not thought to affect consciousness. However, many complex behaviours operate in the absence of conscious awareness or are followed, rather than preceded, by conscious awareness; so that the nature and extent of the contribution of consciousness to adaptive behaviour remain in question (Chalmers, 1996; Zeman, 2001). While not implicating episodic memory or the hippocampus in consciousness, Crick and Koch (1998) stated that very short-term memory (iconic memory) "seems almost essential for consciousness" (p. 99) and that explicit representations, forming part of consciousness, are 'recorded' (p. 104). Iconic memory is arguably an event memory that has not yet been consolidated or may not be retained; iconic memory is what still needs to be consolidated to become a retrievable event memory (and it would therefore not differ from event memory formation in terms of its critical neural underpinnings).

Consciousness (awareness) can be dissociated from attention directed toward stimuli (because there are instances of conscious perception without top-down attentional bias; and because top-down attention can operate without giving rise to conscious perception (van Boxtel et al., 2010)), however conscious perception may not be distinguishable from episodic memory formation (Behrendt, 2013a), just as conscious imagery is evidently an integral part of episodic memory retrieval and recombination (Schacter et al., 2007). Indeed, characteristics of consciousness, such as (i) the combination of varied facets of information into a single but complex representation, (ii) availability of this representation for choices among plans of action, and (iii) reportability (Crick and Koch, 1998; van Boxtel et al., 2010), are also attributes of episodic memory. Moreover, proposed functions of consciousness, such as the summation of all relevant information pertaining to the organism's current situation (both environmentally and physiologically) and making this information available for planning, decision making, and setting of goals (Crick and Koch, 1998; van Boxtel et al., 2010) are also functions of episodic memory, functions that are subserved in particular by the pathway from hippocampus and subiculum to medial prefrontal cortex and ventral striatum (reviewed in Behrendt, 2013b). The hippocampus-medial prefrontal cortex axis would ensure that consciousness has the type of direct access to high-level executive systems that was envisaged by Crick and Koch (1998). The relationship between episodic (declarative) memory or consciousness, on the one hand, and the selection of situationally appropriate behaviour modes, on the other, may be an evolutionary extension of the mapping of landmarks to representations of environmental locations (i.e., place memories, which in turn prompt the animal to employ a behaviour mode or strategy that is appropriate in the present location or situation).

Higher level neocortical sensory areas project to the hippocampus via the parahippocampal/perirhinal cortex and entorhinal cortex (see Fig. 1). The entorhinal cortex receives stimulus-related and contextual information processed in parietal and temporal association cortices (Kesner, 2007). The entorhinal cortex (superficial layer 2) projects to CA3 (cornu ammonis subfield 3) both directly and indirectly. The indirect pathway involves the dentate gyrus (whereby the entorhinal cortex projects, via the perforant path, to granule cells in the dentate gyrus, which, in turn, send mossy fibres to CA3). Entorhinal projections to CA3 are characterized by a high degree of convergence (in contrast to the more parallel projections from layer 3 of the entorhinal cortex to CA1). Within CA3, pyramidal (principle) cells are extensively connected to each other via recurrent axon collaterals, thus forming a single 'autoassociation network'. The CA3 autoassociation network is the anatomic substrate for conjunctive encoding and pattern completion processes implicated in episodic memory. This network, being characterized by a high degree of internal connectivity and effective synaptic plasticity, stores 'arbitrary associations' between object and place information (received from neocortical areas via the entorhinal cortex) for durations of seconds to minutes (Kesner, 2007; Rolls, 2007).

The network as a whole settles into attractor state (thereby completing a pattern) (Rolls, 2007), and it does so at each cycle of the θ oscillation observable in local field potentials. Neurons in superficial layers of the entorhinal cortex and their projection targets in the hippocampus discharge synchronously at γ frequencies in relation to the phase of the θ cycle (during exploratory locomotion and paradoxical sleep) (Chrobak and Buzsáki, 1998). Temporal convergence of information-bearing neocortical input to the hippocampus and local θ oscillations (sustained by cholinergic input from the medial septum to the hippocampus) results in the encoding of event (episodic) memories. Synchronous γ firing in subsets of CA3 pyramidal neurons that are tuned to the θ rhythm is necessary for the temporary storage of information. Thus, hippocampal θ oscillations, which are selectively present in behavioural states of exploration and attentiveness (but also in paradoxical sleep), ensure the continuous gathering of information about the environment (Buzsáki, 1996; Vertes, 2005).

The successive states into which the CA3 autoassociation network settles are encoded (although not necessarily consolidated and retained) as event memories (Kesner, 2007; Rolls, 2007); and they may be represented (symbolized) by unitary conscious experiences, which, in their *discrete* succession (VanRullen and Koch, 2003), constitute the stream of consciousness. CA3 would be the 'neural correlate of consciousness' predicted by Crick and Koch (1998). Accepting CA3 as the neural correlate of consciousness would provide an elegant solution to the binding problem, as CA3 is in a position to bind into a single representation information processed in all sensory processing streams (including contextual, object, and emotional information). Subjective conscious experience could then be said to arise from distinct cerebral processes ('the hard problem' (Chalmers, 1996)); conscious experience