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Where will insights into hippocampal activity in schizophrenia lead us?

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"...a better understanding of the relationship between self-referential processing, stress reactivity, hippocampal neurogenesis, cognitive deficits and psychotic symptomatology is a promising avenue in search of new and better pharmacological and psychological therapies [for schizophrenia]..."

Evidence for the morphological, molecular and functional alterations of the hippocampus in schizophrenia is well recognized [1]. With the accumulated knowledge on hippocampal pathology in schizophrenia, we are now in a position to make a further advance by integrating the knowledge from different areas of basic, affective and cognitive neurosciences.

The majority of findings to date suggest that hippocampal pathology is not secondary to the illness [2] or its treatment [3] and has a genetic component [4.5]. It is widely accepted that hippocampal aberrations have a neurodevelopemental rather than a neurodegenerative origin, as there is no evidence of gliosis in schizophrenia [6].

The markers for both inhibitory and excitatory neurons and their synapses in the hippocampus have been shown to be affected [7]. There is empirical support for the involvement of both GABAergic [8] and glutamatergic [9] neurons. Some studies show a preferential involvement of the excitatory synapses [10], but there is some evidence to suggest that the excitatory component of the pathology progresses with age [9]. This finding, however, is not specific to schizophrenia, since bipolar disorder patients also show similar and somewhat more severe abnormality [7]. It is not currently clear whether the early phases of the illness are characterised by a greater or an equal involvement of inhibitory neurons and their synapses. Clarifying these issues has significance for the development of pharmacotherapies as different stages of the illness might require either glutamate or GABA-targeted interventions.

The functional significance of hippocampal pathology in schizophrenia is still unclear. The hippocampi of two hemispheres differ morphologically, cytoarchitectonically and functionally. Determining, therefore, whether the two hemispheres show preferential involvement is important for understanding the etiology and functional significance of the hippocampal pathology. The subfields of the hippocampus are also anatomically and functionally distinct. It is currently a matter of debate as well as rigorous empirical investigations which of the subfields is affected preferentially.

"The functional significance of hippocampal pathology in schizophrenia is still unclear."

Cognitively, the hippocampus is involved in the formation of episodic (context-rich) memories and shown to be abnormally activated in people with schizophrenia during episodic memory tasks [11,12]. The precise mechanism by which the hippocampus performs episodic memory function is yet to be established. In humans, the left hippocampus is involved in verbal memory, whereas the right hippocampus subserves spatial memory, specifically allocentric or viewer-independent memory. The allocentric processing refers to the representation of the environment by mapping the relationship between the objects in relation to the objects themselves, thus constructing a cognitive map [13]. An individual is represented as yet another object in the matrix of other represented objects. The allocentric spatial processing is contrasted with the egocentric (or viewer-dependent) spatial processing, which refers to the representation of the environment in relation to one's own bodily axis. The egocentric frame of spatial references is thought to be subserved by the parietal cortex. Animal research into the hippocampal function has particularly focused on the role of the hippocampus in allocentric spatial memory. In humans, the allocentric, but not egocentric, spatial processing has also been shown to activate the hippocampus using virtual reality analogues of well-researched animal paradigms [14,15], such as the Morris Water Maze.

This egocentric versus allocentric distinction in relation to spatial information processing is not merely a process of constructing a perceptual gestalt of the external environment. It could also be seen as a subjective versus objective perception of reality in psychological terms. Langdon and Coltheart defined these in following terms [16]:

- Allocentric simulation of reality: "reconcil[ing] one's ... first person view of the world with other people's viewpoints and on an equal footing";
- Egocentric simulation of reality: tied to one's own point of view.

The egocentric versus allocentric information processing has been applied to the social research on empathy [17]. The empathy construct in social sciences research is complex. It ranges from emotional contagion to cognitive empathy, or theory of mind. It is well established that people with schizophrenia do not lack the affective empathy; if anything, they are hypersensitive in terms of emotional contagion [18] and tend to project their own emotions onto others (self-other overlap). However, they have difficulties with the cognitive aspects of understanding other people's minds, as demonstrated by numerous studies using theory-of-mind paradigms [19]. This difficulty might be due to the inability of patients affected by schizophrenia to disengage from the subjective (egocentric) perspective.

There are other lines of evidence for the excessive self-referential or egocentric processing in schizophrenia. The recent study by Whitfield-Gabrieli and colleagues reported hyperactivation of the so-called default network [20], which is comprised by the medial parts of the prefrontal and parietal cortices, and associated with the self-referential processing, with its parietal modules involved in the construction of egocentric representations.

"...the recurrent form of schizophrenia illness was associated with a more severe reduction of the left hippocampus compared with other groups."

This hyper self-referencing manifests itself in terms of increased salience of both internal and external stimuli. Trivial things are perceived as deeply meaningful in relation to one's own existence. This is accompanied by the processing of familiar stimuli as being novel. Gray linked psychotic symptoms of schizophrenia with the hippocampal hyperactivity, dopaminergic dysregulation, and increased salience in a coherent model, which is still relevant today [21]. Functional MRI studies support the notion that the anterior hippocampus processes novelty and salience, both perceptual and semantic [22]. This overemphasis on the egocentric mode of information processing in schizophrenia is unlikely to be due to the compromised function of the allocentric processing neural machinery *per se.* The evidence for the structural and functional alterations of the right hippocampi is not as strong as that of the left hippocampi [23]. Furthermore, the allocentric spatial processing relies on the function of the posterior hippocampus, which seems to be relatively unaffected in schizophrenia patients. The anterior subregion of the hippocampus, on the other hand, appears to be compromised, both structurally and functionally [24].

In a run up to the acute psychotic episode and during the acute stage of the illness, patients with schizophrenia show hippocampal hyperactivity, particularly in the CA1 subfield. This has been demonstrated most recently by a brilliant study by Shobel and colleagues [25], who applied a high-resolution variant of functional MRI to measure regional cerebral blood volume (CBV) in patients with schizophrenia, prodromal patients, and healthy controls, with the 2-year follow-up of the prodromal patients. Patients suffering from schizophrenia demonstrated an increased CBV in the CA1 subfield of the hippocampus and the orbitofrontal cortex, together with decreased CBV in dorsolateral prefrontal cortex (PFC), compared with controls. The abnormally increased CBV in CA1 in prodromal patients predicted conversion to psychosis with 71% of positive predictive value and 82% of negative predictive value. Furthermore, the CBV levels in the CA1 subfield differentially correlated with the severity of positive symptoms, particularly delusions.

"...existing studies convincingly demonstrate aberrant hippocampal activity in schizophrenia both during rest and during a range of memory tasks."

One caveat of Shobel *et al.*'s findings is that out of seven patients who progressed to a clinical diagnosis, two were diagnosed with the schizoaffective disorder bipolar type, and one patient received diagnoses of depression with psychotic features. The specificity of hippocampal involvement in schizophrenia is still a matter of controversy. A recent study directly comparing patients with schizophrenia, patients with major depression and healthy controls, observed more severe bilateral reduction of hippocampal volume in schizophrenia patients compared with major depression patients, who, in turn, showed volumetric reductions compared with healthy controls [26]. Furthermore, the recurrent form of schizophrenia illness was associated with a more severe reduction of the left hippocampus compared with other groups.

The significance of determining such specificity could be questioned. In fact, Kraepelin's dichotomy between schizophrenic and affective disorders might potentially be abandoned, since the evidence from genetic epidemiology points to a substantial overlap in the genetic susceptibility across the Kraepelinian charter of clinical entities [27]. In addition, many individuals experience depressive episode before the onset of psychosis [27,28] and depression seems to be a core component of schizophrenia illness [30,31], often coexisting with delusions [32]. However, the hippocampal alterations appear to have different etiologies in schizophrenia and depression. In depression, reduced hippocampal volume is thought to be the result of disrupted hippocampal neurogenesis due to the impact of the psychosocial stress [33]. The etiology of hippocampal alterations in schizophrenia suggests a prenatal origin caused by an aberration in cell migration [1]. According to double-hit hypothesis of schizophrenia, the initial vulnerability of neurodevelopmental origin is then exacerbated by the environmental factors, such as reactivity to personal and psychosocial stress, with adolescence being a particularly vulnerable period. Furthermore, the initial insult to the hippocampal neural development might be disrupting the process of postnatal neurogenesis. The disruption of hippocampal neurogenesis during adolescence in mice has been shown to increase vulnerability to stress [34].

Stress can, in a vicious circle, influence the integrity of the hippocampus–PFC pathway [35], exacerbating existing neurobiological deficits. The anterior hippocampus is intimately connected with the medial PFC. Hippocampal innervation of the PFC is mainly excitatory and originates from the CA1 subfield projecting to the medial orbital prefrontal cortex [36]. This prefronto–limbic neural network is implicated in emotion regulation [37]. Râdulescu and Mujica-Parodi demonstrated the prefronto–limbic dysregulation of emotional arousal in schizophrenia patients relative to healthy controls [38].

Furthermore, stress disrupts hippocampal neurogenesis, apart from having a neurotoxic effect on the existing hippocampal neurons. A number of studies have confirmed a strong connection between stress, high cortisol levels and damage to the hippocampus [39]. The studies also indicate that cells within a damaged hippocampus can regenerate when stress or cortisol is reduced [40]. The interventions directed at stress management,

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such as mindfulness-based stress reduction [41] or mindfulnessbased cognitive therapy [42], might be able to prevent the onset or lessen the severity of schizophrenia, delay relapse in those already ill and reduce overall anxiety [43–47].

In conclusion, existing studies convincingly demonstrate aberrant hippocampal activity in schizophrenia both during rest and during a range of memory tasks. The investigations now need to focus on the significance of hippocampal aberrations for particular symptoms, illness course and effective treatments of schizophrenia. Schizophrenia is known to be highly heterogeneous and has an unquestionable genetic component. Stress vulnerability is probably a causative or mediating factor in at least a proportion of cases of schizophrenia. We believe a better understanding of the relationship between self-referential processing, stress reactivity, hippocampal neurogenesis, cognitive deficits and psychotic symptomatology is a promising avenue to pursue in search of new and better pharmacological and psychological therapies for the management, if not a cure of this devastating illness. Future studies pursuing this avenue would benefit if they also include the regions closely associated with the hippocampus rather than focussing on hippocamapal activity in isolation.

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