Neuroimaging Studies of the Hippocampus in Schizophrenia

Stephan Heckers*

Department of Psychiatry, Massachusetts General Hospital, Charlestown, Massachusetts

ABSTRACT: Three neuroimaging techniques, morphometric neuroimaging, magnetic resonance spectroscopy, and functional neuroimaging, have provided evidence for abnormal hippocampal structure and function in schizophrenia. Hippocampal volume reduction is now one of the most consistent structural abnormalities found in schizophrenia: it is present at the onset of the illness and, to a lesser degree, in first-degree relatives of schizophrenic probands. Decreased levels of N-acetyl-aspartate point towards a cellular basis of such volume changes. Functional neuroimaging studies have demonstrated abnormal levels of hippocampal activity at rest, during the experience of auditory hallucinations, and during the performance of memory retrieval tasks. These results of neuroimaging studies complement evidence from post-mortem and behavioral studies, which have found regionally specific abnormalities of the hippocampus and of memory function in schizophrenia. Hippocampus 2001;11:520–528.

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“. . . there is reason to believe that the hippocampus may be a key structure in which a serious disturbance of activity is critical for the production of psychosis.”

Donald R. Roberts, 1963

INTRODUCTION

Starting with Kraepelin (1896) and Bleuler (1911), psychiatrists and neuroscientists have mapped the complex cognitive, affective, and interpersonal changes associated with schizophrenia to abnormalities in the brain. Based on the first pathological study of dementia praecox (Alzheimer, 1897), Kraepelin (1919) proposed that prefrontal cortex abnormalities play a primary role in the pathogenesis. Since then, the prefrontal cortex theory of schizophrenia has dominated the field of schizophrenia research.

The hippocampus is a late arrival among the brain regions implicated in the pathophysiology of schizophrenia (Dwork, 1997; Heckers, 1997). Initial theories of hippocampal (Roberts, 1963) and limbic-system (Stevens, 1973; Torrey and Peterson, 1974) dysfunction in schizophrenia were built on the idea that the anatomy and behavioral affiliations of the medial temporal lobe are well-suited to explain some of the abnormalities seen in schizophrenia. However, it was not until 1985 that we had the first evidence (Bogerts et al., 1985) for an abnormality of the hippocampus in schizophrenia. Since then, many studies have provided compelling data consistent with the hypothesis that schizophrenia is associated with a disturbance of the structural and functional integrity of the hippocampus.

Neuroimaging techniques provide sufficient spatial and temporal resolution to inform us about abnormal hippocampal structure and function in disease states. Three such techniques, i.e., magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET), have provided much of the evidence for an abnormality of the hippocampus in schizophrenia.

Following the original description of hippocampal volume changes in postmortem specimens of schizophrenic patients, the first neuroimaging studies of the hippocampus in schizophrenia focused on volumetric abnormalities. More recently, these have been complemented by studies of hippocampal shape abnormalities (Csernansky et al., 1998). Comprehensive reviews (McCarley et al., 1999; Nelson et al., 1998) of the morphometric literature have concluded that the hippocampus is smaller in schizophrenia. MRS studies have elucidated the cellular basis of the hippocampal abnormalities in schizophrenia by documenting a decrease of hippocampal N-acetyl-aspartate (NAA) in schizophrenia. Finally, functional neuroimaging studies have provided evidence for abnormalities of the medial temporal lobe during rest, during the retrieval of previously learned words, and during the experience of auditory hallucinations.

Here I will review some aspects of neuroimaging studies of the hippocampus in schizophrenia, to integrate them into a model of hippocampal dysfunction in schizophrenia.

MORPHOMETRIC STUDIES OF THE HIPPOCAMPUS

The ventromedial area of the human temporal lobe contains the amygdala, the hippocampal region, and superficial cortical areas that cover the hippocampal region.
and form the parahippocampal gyrus. (Van Hoesen, 1997) The hippocampal region can be subdivided into three subregions: the dentate gyrus, the cornu Ammonis sectors, and the subiculum. Some authors have defined the hippocampal region and the closely connected entorhinal cortex, located on the anterior aspects of the parahippocampal gyrus, as the hippocampal formation (Amaral and Insausti, 1990).

The concepts of the hippocampal region and the hippocampal formation were born in the anatomical laboratory, where exquisite preparations of the monkey and human brain are available to delineate the hippocampus from surrounding areas (amygdala, parahippocampal gyrus, perirhinal cortex, and fusiform/lingual gyrus). Even when the best structural neuroimaging technology is combined with a keen understanding of the anatomy of the human hippocampal formation, these tools do not allow us to reliably delineate these anatomical units in the living human brain. Rather, we have to rely on arbitrary borders that are clearly visible to the human eye without the luxury of a microscope and a staining technique (Pruessner et al., 2000). We have become increasingly more sophisticated in delineating the hippocampal formation from the amygdala, but there are still no good criteria for the lateral border, which is highly variable in the human brain (Hanke, 1997; Heckers et al., 1990).

Despite these technological caveats, most structural neuroimaging studies have found evidence for reduced volume of the hippocampal formation in schizophrenia (Figs. 1, 2). This is remarkable, since many different morphometric protocols were employed to estimate the volume of the various medial temporal lobe structures. Previous reviews (McCarley et al., 1999; Nelson et al., 1998) summarized the findings of the morphometric studies of the hippocampus in schizophrenia. Here I will emphasize some important issues.

First, the volume reduction of the hippocampus in schizophrenia is subtle. The metaanalysis by Nelson et al. (1998) reported that the hippocampus is 4% smaller, on both sides, in schizophrenia when compared to the normal brain (Fig. 1). This is different from the more pronounced volume changes in neurodegenerative diseases of the medial temporal lobe such as Alzheimer’s disease. The subtle nature of the hippocampal volume abnormality in schizophrenia argues against a degenerative neuropathological process, and the pathological studies confirm this (Dwork, 1997).

Second, the volume reduction is often seen early in the disease process (Bogerts et al., 1990; Hirayasu et al., 1998; Velakoulis et al., 1999). This again argues against a degenerative process leading to marked cell loss and subsequent volume changes. However, the finding of a slow progression of hippocampal volume reduction throughout the disease process (Giedd et al., 1999; Velakoulis et al., 1999) can be interpreted as evidence for a deleterious effect of the disease process (e.g., stress) or the treatment on hippocampal structure.

Third, it is not clear which hippocampal region (anterior or posterior) and which of the compartments (principal cell layer, stratum oriens, stratum radiatum/lacunosum/moleculare, or afferent/efferent fiber tracts) contribute to the volume reduction. Some studies have reported that the volume decrease in schizophrenia affects primarily the anterior half of the hippocampus. Considering the distinct afferent and efferent connections (Barbas and Blatt, 1995; Goldman-Rakic et al., 1984) and the recent evidence for a functional segregation of the anterior and posterior hippocampal formation (Lepage et al., 1998; Schacter and Wagner, 1999; Strange et al., 1999), this finding could indicate that some but not all hippocampal functions are impaired in schizophrenia. Furthermore, there is some evidence that the volume differences of the hippocampal formation in schizophrenia are due to white matter

![FIGURE 1. Hippocampal volume reduction in schizophrenia.](image1)

Percentage reduction in hippocampal-amygdala complex (H + A) in patients with schizophrenia. Combined H + A studies do not overlap with other groups. Reprinted with permission from Nelson et al. (1998).

![FIGURE 2. Morphometry of hippocampus in schizophrenia.](image2)

Three-dimensional volume rendering of hippocampal-amygdala complex in a normal subject (A) and an age-matched schizophrenic patient (B). Note smaller hippocampus in the schizophrenic patient, especially on the left (right side of image). Image reconstruction and figure are courtesy of Martha Shenton and Robert McCarley.
abnormalities (Colter et al., 1987; Heckers et al., 1991). This could be interpreted as evidence for a disconnection of either the intrinsic hippocampal fiber pathways or the extrinsic afferent and efferent projections. More advanced neuroimaging studies of hippocampal structure that can identify the hippocampal subsectors and can parcel out gray and white matter compartments will be needed to study these questions (Zeineh et al., 2000).

Fourth, the significance of hippocampal volume reduction in schizophrenia remains unclear. Two important issues, the time course of hippocampal volume changes in the disease process and the relevance of hippocampal volume changes for the expression of cognitive deficits, are particularly important. Do hippocampal abnormalities predict the onset, expression, or course of the hallmark symptoms of schizophrenia (hallucinations and delusions)? If so, can hippocampal volume changes be used to detect patients at risk (Pantelis et al., 2000), and can they be followed over time to stage the disease process? Do hippocampal abnormalities correlate with the degree of cognitive deficits in schizophrenia, especially with abnormalities in explicit memory (Weiss and Heckers, 2001)? Can hippocampal volume changes be used to subtype patients with schizophrenia (e.g., those with and without marked explicit memory deficits)?

Fifth, the generalizability of decreased hippocampal volume to the spectrum of schizophrenia patients and the specificity of decreased hippocampal volume for the diagnosis of schizophrenia are not clearly established. On the one hand, decreased hippocampal volume is not found in all patients with schizophrenia. On the other hand, several other diseases (most notably, unipolar depression (Sheline et al., 1996), bipolar disorder (Hirayasu et al., 1998), posttraumatic stress disorder (PTSD) (Gurvits et al., 1996), and alcoholism (De Bellis et al., 2000)) are also associated with reduced hippocampal volume. Does decreased hippocampal volume tell us something about the pathology unique to schizophrenia? Or is hippocampal volume decrease the final common pathway of several pathological conditions? If the finding of hippocampal volume reduction continues to be extended to other psychiatric disorders, then it will become imperative to study the time course of such volume changes, their relationship to treatment, and their cellular basis in more detail.

Sixth, a recent study has extended the finding of hippocampal volume reduction also to unaffected first-degree relatives of schizophrenic probands (Seidman et al., 1999). If this finding is confirmed in future studies, it may potentially be of great importance in understanding the role of hippocampal dysfunction in schizophrenia. Finding hippocampal volume changes in the same pedigree, unrelated to the expression of abnormal behavior, points to a genetic risk factor and is quite remarkable, since the structure of the hippocampus is very susceptible to environmental influences (Kempermann et al., 1997; Sapolsky, 2000). But if hippocampal abnormalities are indeed confirmed in first-degree relatives (a so-called hippocampal “endophenotype”), then this finding might be helpful in stratifying patients and relatives for genetic studies. Lastly, it raises the question of whether functional hippocampal abnormalities (as discussed below) are also seen in relatives of schizophrenic patients. This would establish hippocampal abnormalities as a susceptibility marker for schizophrenia, but would “uncouple” hippocampal functional abnormalities from the clinical features (e.g., hallucinations, delusions) of schizophrenia.

In summary, reduced hippocampal volume is now established as one of the most robust brain abnormalities in schizophrenia (McCarley et al., 1999). The finding of subtle hippocampal volume loss has been confirmed by postmortem studies and has been linked to abnormalities in interneurons and neuropil (Arnold, 1997, 2000; Benes, 1998). This provides a very strong basis for correlating changes seen in vivo to a potential cellular substrate. The continuing improvement in imaging technology and image analysis tools will allow us to study hippocampal volume changes...
in more detail for early detection, to correlate them to the disease course and the expression of clinical features, and to study treatment effects.

### STUDIES OF HIPPOCAMPAL NEUROCHEMISTRY

The morphometric analysis of the hippocampus in schizophrenia is limited to a gross examination. As documented elsewhere in this issue (Benes and Harrison), the molecular and cellular bases of hippocampal pathology are now being studied with sophisticated techniques in the laboratory. Magnetic resonance spectroscopy (MRS) allows us to test some of the hypotheses generated in the study of postmortem specimens in vivo in patients with schizophrenia.

Proton magnetic resonance spectroscopy (1H-MRS) detects signals from N-acetyl-aspartate (NAA), choline-containing compounds (CHO), and creatine + phosphocreatine (CRE) (Fig. 3). NAA is found predominantly in neurons, serves as a marker of neuronal integrity, and has been associated in degenerative disease states with decreased neuronal density.

Several studies have used 1H-MRS to study NAA levels of the hippocampus in schizophrenia (Bertolino et al., 1996, 1998a,c; Deicken et al., 1998; Maier et al., 1995; Nasrallah et al., 1994; Yurgelun-Todd et al., 1996). These studies have reported low NAA signal intensity or concentration in the hippocampus. The decrease of NAA was independent of drug treatment and was also found in young patients with childhood-onset schizophrenia. Taken together, these results have been interpreted as evidence for a developmental lesion of the hippocampus or as evidence for subtle cell loss in schizophrenia. The limited spatial resolution of the published 1H-MRS studies in schizophrenia does not allow us to infer more details about the cellular basis of hippocampal pathology in schizophrenia. In fact, most of the MRS studies have used a 1.5T MRI scanner, which provides limited resolution and low test-retest reliability of the spectra measured (Bertolino et al., 1998b). Future studies, using higher field strength magnets, are needed to test specific hypotheses about the biochemical and molecular basis of hippocampal pathology in schizophrenia. Furthermore, spectroscopic studies combined with morphometric and functional studies will provide more information about the relevance of decreased NAA levels for the structural and functional integrity of the hippocampus.

A recent 1H-MRS study found that unaffected first-degree relatives of patients with schizophrenia show decreased NAA levels in the hippocampus (Callicott et al., 1998). This finding resembles the recent morphometric finding of smaller hippocampal volume in first-degree relatives of schizophrenic probands (see above). It is particularly intriguing that decreased NAA levels were not found in any other brain region of unaffected relatives. This has been interpreted as evidence that genes involved in the development and maintenance of hippocampal circuitry are at fault in schizophrenia (Weinberger, 1999).

### STUDIES OF HIPPOCAMPAL FUNCTION

Normal hippocampal function is necessary for spatial, explicit, and episodic memory. Furthermore, the conjoint operation of the hippocampal system and the neocortex confers awareness about acquired knowledge (Clark and Squire, 1998; Schacter, 1998). The relative contributions of the hippocampus proper vs. the parahippocampal gyrus/perirhinal cortex in the generation of episodic/autobiographic/autonoetic memory (hippocampus-dependent) vs. semantic memory (hippocampus-independent) are still a matter of debate (Mishkin et al., 1998; Squire and Zola, 1998; Tulving and Markowitsch, 1998). Of particular interest for the study of schizophrenia is the role of the hippocampus in the constructive process of memory encoding and retrieval. An intricate balance of hippocampus and frontal lobes ensures that memory encoding and retrieval create accurate representations of experience (McClelland et al., 1995; Schacter et al., 1998). Models of cortical-hippocampal circuitry have therefore been used to explain the abnormal mental representations of schizophrenia. Roberts (1963) suggested that a functional disturbance of the hippocampus could potentially explain “the production of psychosis.” Venables (1992) and Hemsley (1993) introduced a hippocampal model of impaired information processing in schizophrenia to explain their findings of abnormal auditory sensory gating and the inability to ignore irrelevant stimuli in schizophrenic patients.

It is therefore surprising that there are very few functional studies that have linked the hippocampus (or the medial temporal lobe) directly with schizophrenia. This is due, at least in part, to the intricacy of capturing hippocampal activity in the human brain. In contrast to other brain areas, especially the multimodal association cortices in the prefrontal and parietal lobes or the primary sensory areas, the hippocampus has eluded many neuroimaging researchers. Recent reports have linked the human hippocampus to memory functions such as novelty detection (Dolan and Fletcher, 1997), spatial memory (Maguire et al., 1998), and memory retrieval (Schacter et al., 1996). However, the exact anatomic organization and the functional relevance of hippocampal activation patterns seen in such experiments are still largely unknown.

The studies that have linked schizophrenia to a functional abnormality of the medial temporal lobe (MTL) have made three different types of inferences: schizophrenia is associated with 1) abnormal MTL activity at rest, 2) increased MTL activity during the experience of auditory hallucinations, and 3) impaired hippocampal recruitment during the performance of memory tasks.

### Hippocampal Blood Flow/Metabolism at Rest

Several studies have reported lower regional cerebral glucose metabolic rates (rCMRglc) in the hippocampus in schizophrenia (Buchsbaum et al., 1992; Nordahl et al., 1996; Tamminga et al., 1992). Gur et al. (1995) found increased left temporal metabolism in patients with negative symptoms as well as those with severe delusions and hallucinations. These initial studies were interpreted as evidence for hippocampal dysfunction, possibly hypofunction, in schizophrenia.
Several studies of schizophrenic patients at rest have documented an increase of medial temporal lobe regional cerebral blood flow (Friston et al., 1992; Kawasaki et al., 1992, 1996; Liddle et al., 1992). When resting blood flow values were correlated with clinical symptoms, increased left medial temporal lobe blood flow in schizophrenia was associated with more severe psychopathology in general (Friston et al., 1992) or with more prominent positive symptoms (delusions and hallucinations) (Liddle et al., 1992). These studies were interpreted as evidence that hippocampal hypoperactivity (or lack of inhibition) is involved in the pathogenesis of delusions and hallucinations.

MTL Blood Flow During AH

Recent neuroimaging studies have measured blood flow in schizophrenic patients during the experience of auditory hallucinations (Weiss and Heckers, 1999). While the still-limited number of studies has demonstrated activation of a network of brain regions involved in the processing of auditory information and language, several have also demonstrated an activation of the hippocampal formation. Notably, the studies by Silbersweig et al. (1995) and Dierks et al. (1999) documented activation of the hippocampal formation during the experience of auditory hallucinations. It is unclear whether the hippocampal activation seen in these studies occurs early in the generation of the hallucinatory experience or whether it is involved in the top-down processing of representations generated in the primary and secondary auditory cortices, e.g., to monitor the source of an auditory representation.

Hippocampal Blood Flow During Memory Retrieval

We recently provided the first evidence for abnormal hippocampal recruitment during memory retrieval in schizophrenia (Heckers et al., 1998). While normal subjects activated a right frontal-temporal network to retrieve previously studied words, schizophrenic patients failed to recruit the hippocampus but showed robust and even increased activation of prefrontal regions. Furthermore, patients with and without the deficit syndrome lacked normal hippocampal recruitment but differed in prefrontal cortex activation during memory retrieval (Heckers et al., 1999). Compared to the control group, hippocampal activity was continuously increased in schizophrenia and was not modulated by environmental contingencies (Fig. 4). Increased hippocampal activity at baseline and impaired recruitment during episodic memory retrieval might represent the functional correlate of an abnormal cortico-hippocampal interaction in schizophrenia (Fletcher, 1998). Of interest, Medoff et al. (this issue) also describe increased regional cerebral blood flow values in the hippocampus in schizophrenia. Increased hippocampal rCBF during a tone-recognition task was more pronounced in patients off antipsychotic medication, which confirms previous evidence that antipsychotic drugs normalize hippocampal dysfunction in schizophrenia (Todtenkopf and Benes, 1998).

In summary, functional neuroimaging studies have reported decreased metabolism and increased blood flow in the hippocampus in schizophrenia. Abnormalities of hippocampal function have
been linked to the expression of positive symptoms (delusions and hallucinations) and to abnormal memory retrieval.

These functional abnormalities need to be replicated and extended with more advanced neuroimaging experiments. It is especially important to combine morphometric and functional approaches, and to characterize the relationship of functional abnormalities and clinical features. Several important questions deserve further study: which mechanisms underlie the finding of decreased metabolism and increased blood flow in the hippocampus in schizophrenia? When in the course of the illness do abnormalities of hippocampal function occur? Is hippocampal hyperactivity also linked to the expression of psychotic symptoms in patients beyond the schizophrenia spectrum, e.g., bipolar disorder or neurological syndromes?

**TESTING THE MODEL OF HIPPOCAMPAL DYSFUNCTION IN SCHIZOPHRENIA WITH NEUROIMAGING**

Brain-based models of schizophrenia have associated the abnormal mental states observed or reported by patients to impaired information processing, and have mapped them to structural and functional abnormalities of neural circuitry. Prominent examples of such model building include those that link working memory deficits to prefrontal cortex pathology (Goldman-Rakic and Selemon, 1997), positive symptoms to limbic system pathology (Bogerts, 1997), and cognitive dysmetria (i.e., a disruption in the fluid coordination of mental activity) to cortical, cerebellar, and thalamic abnormalities (Andreasen et al., 1999).

The hippocampus has not been left out in the effort to explain the neural basis of schizophrenia. Hippocampal theories integrate some of the evidence reviewed above and emphasize either the anatomical (1 and 2, below) or the functional (3 and 4, below) aspects of hippocampal dysfunction in schizophrenia:

1) The hippocampal formation is disconnected from multimodal association cortex in schizophrenia due to abnormal intrinsic and extrinsic hippocampal connections (Roberts, 1963).
2) Perturbation of hippocampal function is due to inefficient, overactive synaptic transmission, leading to an abnormal fronto-hippocampal circuitry, and resulting in cognitive deficits and psychotic symptoms (Friston et al., 1992).
3) Impaired information processing in schizophrenia (e.g., the inability to ignore irrelevant stimuli) and psychotic symptoms (fixed false beliefs) are caused by hippocampal dysfunction or hyperactivity (Adler and Waldo, 1991; Bickford-Wimer et al., 1990; Hemsley, 1993; Kriechaus et al., 1992; Port and Seybold, 1995; Venables, 1992).
4) Decreased hippocampal NMDA glutamate receptor function leads to abnormal hippocampal activity and a disturbance of the cortico-hippocampal network subserving memory (Medoff et al., this issue).

Theoretical frameworks that explain the clinical features of schizophrenia are essential to advance schizophrenia research (Carpenter et al., 1993; Frith, 1992). They provide the basis for experimental hypothesis testing. Based in part on previous theoretical efforts (Friston, 1998; Schacter et al., 1998; Venables, 1992; Wible et al., 1997), I am proposing that delusions and hallucinations originate from an abnormal interaction between the hippocampal formation and the association cortex.

Interactions between the hippocampal formation and association cortex give rise to representations of perceived stimuli, provided either directly by the sensory modules (sensory organs and thalamic relay nuclei) or via imagery and recollection from memory. Such representations provide the basis for conscious awareness of the world and the self. An intricate balance of binding and separation ensures that representations can be distinguished from one another. The core deficit of schizophrenia is an imbalance of hippocampal and cortical contributions to the generation of representations. This leads to an impaired ability to classify representations as internally or externally generated (hallucinations) and to an association of features with each other even in the absence of external dependency (delusions).

Neuroimaging experiments can test several hypotheses derived from the proposed model of hippocampal dysfunction in schizophrenia:

1) The activity of the hippocampus is increased in patients with prominent delusions and hallucinations. This hypothesis can be tested with studies of absolute (PET) or relative (PET and functional MRI) blood flow. Absolute hippocampal blood flow is predicted to be increased, and the hippocampal/whole brain or hippocampal/prefrontal cortex ratio is also predicted to be increased. Furthermore, abnormal recruitment of the hippocampus during task performance is predicted to be linked to increased hippocampal activity at baseline. This hypothesis is consistent with the notion that increased hippocampal activity is also found in patients beyond the schizophrenia spectrum who present with prominent delusions and hallucinations.
2) The structural correlate of hippocampal hyperactivity in schizophrenia is loss of hippocampal volume. This hypothesis can be tested with combined morphometric, functional, and spectroscopic neuroimaging studies. MRS can be employed to study a selective loss of neurons or abnormal synaptic organization, and diffusion-weighted MR imaging may be used to study a disconnection of afferent and efferent fiber pathways.
3) Hippocampal hyperactivity and hippocampal volume loss are correlated with memory deficits and with the degree of psychotic disorganization in schizophrenia. This hypothesis can be tested with functional neuroimaging studies of memory function and with statistical models that predict changes in brain activity by scores from behavioral or cognitive rating scales. Since normal hippocampal function is necessary for several cognitive processes (e.g., spatial, explicit, and episodic memory), it will be important to study hippocampal function in schizophrenia across a spectrum of cognitive processes. If the proposed hippocampal pathology in schizophrenia affects hippocampal-based cognitive processes differentially, then it could provide evidence for abnormalities in selective cortico-hip-
Abnormal hippocampal activity and a disturbance of hippocampal-cortical connections have been proposed to explain the psychotic features (i.e., delusions and hallucinations) of schizophrenia. Neuroimaging studies have provided much of the evidence that schizophrenia is indeed associated with abnormalities of hippocampal structure and function. The most consistent finding is smaller hippocampal volume (possibly as early as at onset of the illness). More recently, increased hippocampal activity and decreased recruitment of the hippocampus during memory retrieval have been reported. We now have the tools to study the onset of hippocampal abnormalities in schizophrenia, their course throughout the disease process, and their response to treatment paradigms. This has moved the hippocampus to the center of schizophrenia research.

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