



Reality Is in the Posterior Hippocampus: Who Knew?

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Bilateral Volume Reduction in Posterior Hippocampus in Psychosis of Epilepsy

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Objective: Psychosis of epilepsy (POE) occurs more frequently in temporal lobe epilepsy, raising the question as to whether abnormalities of the hippocampus are etiologically important. Despite decades of investigation, it is unclear whether hippocampal volume is reduced in POE, perhaps due to small sample sizes and methodological limitations of past research. **Methods:** In this study, we examined the volume of the total hippocampus, and the hippocampal head, body, and tail, in a large cohort of patients with POE and patients with epilepsy without psychosis (EC). One hundred adults participated: 50 with POE and 50 EC. Total and subregional hippocampal volumes were manually traced and compared between (1) POE and EC; (2) POE with temporal lobe epilepsy, extratemporal lobe epilepsy, and generalized epilepsy; and (3) patients with POE with postictal psychosis (PIP) and interictal psychosis (IP). **Results:** Compared to EC, the POE group had smaller total left hippocampus volume (13.5% decrease, $P < .001$), and smaller left hippocampal body (13.3% decrease, $P = .002$), and left (41.5% decrease, $P < .001$) and right (36.4% decrease, $P < .001$) hippocampal tail volumes. Hippocampal head volumes did not differ between groups. **Conclusion:** Posterior hippocampal volumes are bilaterally reduced in POE. Volume loss was observed on a posteroanterior gradient, with severe decreases in the tail and moderate volume decreases in the body, with no difference in the hippocampal head. Posterior hippocampal atrophy is evident to a similar degree in PIP and IP. Our findings converge with those reported for the paradigmatic psychotic disorder and schizophrenia and suggest that posterior hippocampal atrophy may serve as a biomarker of the risk for psychosis, including in patients with epilepsy.

Commentary

Ever since the classic report from Flor-Henry in 1969, the temporal lobe has presented particular intrigue for epilepsy and psychosis. Flor-Henry et al also compared psychosis in epilepsy to epilepsy without psychosis and found an increased association of psychosis with temporal lobe epilepsy in the dominant hemisphere.¹ That finding has not been convincingly replicated, but the overlap of the two conditions was noteworthy. During that era, the role of the hippocampus was thought to be primarily related to memory function. The relationships of epilepsy to psychosis and psychosis to the hippocampus were not well understood.

Today, the hippocampus is especially meaningful, not only because it is a common location for seizure foci but also because it plays an important role in anchoring humans to reality. Investigations of psychosis have still consistently implicated the temporal lobe, especially the hippocampus, as a source for hallucinogenic phenomena.² Some theories have suggested volume loss leading to inconsistent sequencing of thought processing. In other words, information may be

perceived out of sequence from other stimuli and thus lead to misperceptions of phenomena as hallucinogenic. In that sense, timing of information flow may be critical for the emergence of psychotic symptoms.

It is well known that the co-occurrence of psychosis and epilepsy is more common than expected. Most scholars have attempted to isolate postictal psychotic phenomena from interictal phenomena by arbitrary criteria regarding timing of symptoms in relation to seizure activity. Unfortunately, the etiology of psychosis in epilepsy is not better understood by these efforts. However, the recent report by Abilene et al may markedly change our perceptions.

The researchers reviewed high-quality structural magnetic resonance imaging in a large sample of patients in Australia with well-established diagnoses of epilepsy and psychosis. The study also included a prospectively obtained sample and included an equal number of control patients with epilepsy but without psychosis. The scans were comprehensive in that they included the entirety of the hippocampal region and could assess dimensions of the full hippocampus from head to tail.



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Therefore, the researchers could compare anterior and posterior regions more effectively than in previous studies. Comparisons were also made between temporal and extratemporal seizure foci and apparent postictal and interictal psychosis.

Although the sample was blended in terms of prospective and retrospective records and the scanner type varied, the sample was matched well with controls. The findings were intriguing. The main result was that the posterior hippocampus volume was markedly reduced bilaterally, if psychosis was present. The other regions of the hippocampus were not significantly reduced in psychosis, except for the body of the hippocampus on the left side.


Additionally, no apparent differences were present in terms of epilepsy subtype, even for temporal lobe foci. This seems counterintuitive given existing reports, including Flor-Henry et al, about psychosis and temporal lobe pathology. Even more intriguing, the volume reduction did not vary as a function of interictal or postictal timing of the psychotic symptoms. This is also counter to conventional wisdom for treatment. Typically, if the psychosis in epilepsy is deemed postictal or peri-ictal, then clinicians are more apt to regard the symptoms as seizure related and primarily treat with anticonvulsants. Antipsychotic medications tend to be less commonly used in those circumstances. However, if the psychosis is interictal and not as clearly related to timing of seizure events, then the psychosis is more likely to be considered an independent condition and treated with an antipsychotic.

The hippocampal volume reduction appeared more dependent upon psychosis than upon any other identified factor. The location of the volume loss in the posterior region is significant as well. The posterior hippocampus reportedly plays a different role than other regions of the hippocampus. It is more directly connected to subcortical regions of the brain and also to dopaminergic networks, consistent with most treatment approaches for psychosis that modulate dopamine function. The fact that psychosis in epilepsy was primarily related to volume loss in this region is notable.


Of course, it cannot be denied that any purely volumetric analysis is an oversimplification, and the same is true for this study. There are many different methods of volumetric analysis, plus the anterior hippocampus has been similarly implicated in psychotic illness.^{3,4} Consistent with this study, previous work suggested greater impairment of the left side.⁵ There also may be age-related changes in functional

connectivity that could play a critical role in vulnerability to the development of psychosis.⁶ While these details are important, particularly to explain psychotic networks, they may not be as important for this analysis. The aim here is to compare subtypes of epilepsy and their correlation with psychosis. In that way, the comparisons are still valid.

Despite our new understanding of the importance of the posterior region of the hippocampus, etiologic explanations may still be elusive. However, at least we know now that even if the timing of the actual symptoms varies, the underlying problem is structural. The timing of psychotic symptomatology, for example, postictal, interictal, and so on, may be irrelevant. This in itself is a major paradigmatic change. The fact that psychotic symptom presence is more associated with a structural finding than with the timing of the seizure activity forces reexamination of how we define the reality of this comorbidity.

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