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Psychosis is Emerging as a Learning and Memory Disorder

The difficulty in developing mechanistic models for psychiatric diseases may be that we are using the incorrect disease targets. Recently, clinical scientists have been attempting to examine alterations in dimensions of cognition and affect, rather than diagnoses of neuropsychiatric disease for clues to neural mechanisms of psychopathology. The RDoCs (Research Domain Criteria) (http://www.nimh.nih.gov/research-funding/rdoc/nimh-research-domain-criteria-rdoc.shtml) system is a leading example of this reorientation. In RDoCs, dimensions of cognition and affect (alterations of which combine to compose the psychiatric diseases that we know) are the unifying, homogenous units generating psychopathology. 'Psychosis' is a ready example and can be conceptualized as a learning and memory disorder. We have been studying this dimension across psychotic diagnoses, with the goal of identifying the normal cognition system(s) whose pathology could generate psychosis (Ivleva *et al*, 2012).

The hippocampus is altered in schizophrenic psychosis, with structural, functional, and molecular pathology; specifically, psychosis is associated with increases in basal hippocampal activity and reductions in associational memory processing (Tamminga *et al*, 2010). The hippocampus is one of the most actively studied regions in brain; initial studies were focused on human memory, stimulated by HM, and more recent research has greatly extended early studies to explicate systems of signaling molecules involved in memory computations, as well as changes in synaptic plasticity underlying learning and memory. Hippocampal structures, including subfields, fiber pathways, and the one-way trisynaptic circuit, are critical in generating normal memory behaviors; subfields contribute uniquely to memory. Memory behaviors emerge from the smooth functioning and proper connectivity of dentate gyrus and the cornu ammonis fields of CA3 and CA1 (Liu *et al*, 2012). Neural activity in the mossy fiber pathway from DG to CA3 can cause categorical changes in CA3 activity, dependent on the level of afferent stimulation from DG (Pelkey and, McBain, 2008). And within CA3, the recurrent collateral system is dependent on a controlled positive feed-forward system for productive 'pattern completion' function (Kremin and Hasselmo, 2007). Molecular and anatomic synaptic markers of memory-associated plasticity are well described (Abraham and Bear, 1996). These protein markers of normal memory behavior can be examined in human tissue to test for psychosis risk factors that could underlie psychosis.

It is plausible that psychosis is dependent on a pathologically increased level of neuronal function in CA3, which exceeds the associational capacity of this subfield and results in mistaken and false associations, some with psychotic content, which then get consolidated, as normal memory, albeit with psychotic content. These memories utilize normal declarative memory neural pathways, including limbic and prefrontal cortical regions, even though they have psychotic content. To demonstrate these ideas will require convergent sources of evidence from humans with psychosis using multimodal brain imaging, behavioral testing, and human tissue chemistry to create confidence in this kind of a novel approach. Our recent findings, including increased molecular plasticity-related proteins in CA3 accompanied by increased perfusion in CA3 and CA1 measured by MR, show the power of convergent methodologies. Finding the common elements in hippocampal pathology across the psychotic disorders would support new dimensional disease concepts.

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DISCLOSURE

The author is a Science Council Member in NAMI Scientific Council, Brain & Behavior Research Foundation (formerly NARSAD) and NIMH Board of Scientific Counselors; on the Editorial Board of American Journal of Psychiatry; an organizer at the International Congress on Schizophrenia Research; *ad hoc* consultant for Intra-Cellular Therapies, Astellas Pharma US, PureTech Ventures, Eli Lilly and Sunovion; has received Kempf Award from American Psychiatric Association; and is the Scientific Advisor to Lieber Institute for Brain Development/John Hopkins, Baltimore.

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