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Commentary

Deficient Hippocampal Habituation in Psychosis: A Manifestation of Hippocampal Overactivity?

Daphne J. Holt

Schizophrenia is associated with the disruption of many forms of learning and memory, including episodic, working, and associative memory, as well as other cognitive deficits, such as impairments in attention and language processing. The lack of specificity of the cognitive deficits linked to schizophrenia has presented a conundrum for researchers. One proposed explanation for the varied findings is that one fundamental component process that represents a necessary "building block" of more complex forms of cognition is altered, and this alteration leads to secondary changes in an array of seemingly independent cognitive domains.

One such candidate "building block" mechanism is habituation, which can be defined as the decrement over time in the magnitude of behavioral or neural responses to repeated presentations of a stimulus (1). Habituation is the physiological manifestation of one of the simplest forms of learning, essentially a quantitative expression of familiarity. Habituation of responses to a previously perceived stimulus increases the efficiency of many brain functions, by permitting an organism to filter out irrelevant stimuli (i.e., shift neural resources away from unimportant, familiar information) to focus on the most salient experiences in the environment. This ubiquitous and fundamental filtering function of habituation is thought to serve as an essential necessary first step in the sequence of operations involved in a diverse range of more complex forms of cognition.

Historically, deficits in habituation were first identified in schizophrenia using well-validated physiological measurements, such as the habituation of eye blink or skin conductance responses to repeated auditory stimuli (2). Taken together with findings from studies of sensorimotor gating (such as those demonstrating reductions in prepulse inhibition of eye blink or electrophysiological responses), such habituation deficits have been cited as evidence for an overall "failure of inhibition" in the brain in schizophrenia. This inhibitory failure is hypothesized to interfere with the ability to distinguish important from unimportant sensory information, in turn leading to altered cognition.

Other evidence for deficits in inhibitory processing in schizophrenia has come from neuroimaging research. Studies using a wide range of imaging approaches, including positron emission tomography, task-based and resting-state functional magnetic resonance imaging (fMRI), and measurements of cerebral blood volume have detected abnormal increases in activity in the medial temporal lobe in schizophrenia, particularly in the hippocampus (3,4). These increases in medial temporal lobe activity have been linked to the severity of positive symptoms in some studies and to cognitive deficits in others.

A potentially related set of findings is the evidence from fMRI studies for abnormally reduced habituation of the hippocampus in chronic schizophrenia (5–7). Response habituation in the brain is thought to reflect a process of active inhibition (1); thus, such deficits in habituation add to the evidence for alterations in inhibitory function in psychotic illness. Critically, correlations between hippocampal habituation magnitudes and memory performance (6), as well as social functioning (7), suggest that reduced hippocampal habituation in schizophrenia contributes to key symptoms of psychotic illness.

One persistent, remaining question about these and other abnormalities of the hippocampus in schizophrenia is related to the timing of these changes during the course of the illness, i.e., do these deficits in hippocampal habituation represent a cause or a consequence of the illness? Testing for early-in-the-illness manifestations of such findings has been a common approach used to address this question, based on the idea that if the findings are present early they are more likely to represent a manifestation of the disease process itself.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Avery *et al.* (8) examine this question with respect to hippocampal habituation deficits in schizophrenia. They conducted an fMRI study in 70 healthy subjects and 62 individuals at an early stage of a psychotic disorder (43 who were diagnosed with schizophreniform disorder, and 17 and 2 with diagnoses of schizophrenia and schizoaffective disorder, respectively). The average duration of psychosis in these patients was only 7 months. Avery *et al.* (8) carefully measured habituation of the responses of the anterior and posterior hippocampus separately to repeated presentations of emotionally neutral face and object stimuli, over two different time scales: 1) rapid (during a 10-second window after the peak novelty response) and 2) slow (over the full 2 minutes of stimulus exposure). During data collection, a low-level behavioral task was performed by subjects to permit the assessment of the level of attentional engagement during the scans. Importantly, in the fMRI analyses, variation in magnitudes of initial novelty responses to the stimuli was controlled for, and the two groups did not differ with regard to mean novelty response levels. Behavioral performance during scanning and slow habituation of the hippocampus did not differ between the two groups. However, rapid habituation of the anterior hippocampus to repeated presentations of objects was significantly lower in the early psychosis patients compared with the control subjects. Moreover, performance on a relational memory task (administered outside of the scanner) was significantly worse in the psychotic group than in the control subjects and correlated with hippocampal habituation in the control group, extending previous evidence for an

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association between hippocampal habituation and memory function (6).

This study shows that diminished habituation of the anterior hippocampus is present early in the course of psychotic illness. Given the simplicity and ease with which hippocampal habituation can be measured using fMRI, one possible next step for this line of research is for abnormal hippocampal habituation to join the ranks of other candidate biomarkers of hippocampal hyperactivity in schizophrenia to be tested further as potential intermediate targets in trials of novel therapeutics for the illness (3). Before moving to this stage, however, some additional information would strengthen the case for this candidate biomarker.

First, a quantitative determination of the optimal stimulus for measuring hippocampal habituation in humans (and in those with schizophrenia in particular) is necessary. Published results have been somewhat variable in terms of the stimulus [e.g., faces vs. objects (6,8)] linked to impaired hippocampal habituation in schizophrenia. Because the magnitude and speed of behavioral habituation correlates with the intensity of the initial stimulation and the stimulus presentation frequency (1), identifying stimuli with reliable effects in terms of salience or novelty, while optimizing presentation frequencies, will likely increase the consistency of these measurements and findings.

Second, in addition to the anterior hippocampus, diminished habituation in schizophrenia has been observed in visual cortex (6,8). In light of the large body of work that has identified early sensory abnormalities and habituation deficits to sensory inputs in schizophrenia, studies could be conducted that examine responses of the whole brain, using a range of stimulus types of different sensory modalities, and potentially using imaging modalities with higher temporal resolution than fMRI (e.g., magnetoencephalography). These experiments could determine whether reductions in habituation in schizophrenia are most prominent in the hippocampus or at earlier stages of information processing.

Finally, most patients enrolled by Avery *et al.* (8) were diagnosed with schizophreniform disorder, which could in theory evolve into a nonaffective or an affective psychosis over time. Thus, further consideration of the specificity of these findings to nonaffective psychosis is warranted. Similarly, if hippocampal habituation deficits are selectively linked to memory deficits, a transdiagnostic model of these deficits could be tested; hippocampal habituation abnormalities may be present only in individuals with certain types of cognitive impairment, independent of diagnosis. This type of model is supported by the highly replicated finding of abnormal amygdala habituation in patients with autism spectrum disorder (ASD) (9). Correlations between amygdala habituation deficits and social dysfunction, sensory overresponsivity, and variation in serotonin transporter genotypes within samples of patients with ASD (9) suggest that poor amygdala habituation in ASD is limited to a specific ASD subgroup that is characterized by particular symptoms or genetic traits. Because a similar clinical and genetic heterogeneity exists within the syndrome of schizophrenia, links between hippocampal habituation deficits and symptoms or traits expressed variably across individuals could provide important clues about the cognitive and cellular processes that rely on or mediate the habituation of hippocampal activity.

Surprisingly, although the highly conserved behavioral characteristics of habituation have been studied extensively in a range of organisms (e.g., *Drosophila*, *Aplysia*, rats, and humans) for almost a century, still little is known about the cellular and molecular mechanisms of habituation (1). Hippocampal overactivity in schizophrenia has been proposed to arise from a deficiency in gamma-aminobutyric acidergic interneuron function (4) and/or to elevated levels of extracellular glutamate (10) within the hippocampus. Future cross-species studies may advance our knowledge of these mechanisms by using identical or similar experimental paradigms to measure neural habituation in humans and other mammalian species. But even now, the high degree of replication and convergence of findings across studies conducted to date can inspire some tentative optimism that greater clarity about the mechanistic basis of hippocampal abnormalities in schizophrenia is forthcoming.

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Article Information

From the Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, and the Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts.

Address correspondence to Daphne J. Holt, M.D., Ph.D., Department of Psychiatry, Massachusetts General Hospital, 149 13th St, Charlestown, MA 02129; E-mail: dholt@mgh.harvard.edu.

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