Impaired memory consolidation in schizophrenia and its relationship to Dentate Gyrus and Cornu Ammonis activity: fMRI evidence

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Introduction: It has been hypothesized, that one of the pathophysiological hallmarks of schizophrenia is impaired hippocampal function caused by hypofunctionality of the glutamatergic N-methyl-D-aspartate (NMDA) receptor[1]. The hippocampus is the primary site for early associative memory consolidation and the formation of new memories[2]. The region is uniquely positioned in a "hierarchy of associativity"[3] to integrate multi-modal inputs before redistribution of potentiated associations into the neo-cortex[4]. Two regions of the hippocampus, the dentate gyrus (DG) and the cornu ammonis (CA) are particularly relevant for these tasks because of their location in this hierarchy and of their underlying pharmacology. DG receives inputs from the entorhinal cortex which are relayed to the CA through reciprocal connections. Activity in the DG is therefore likely to drive downstream activity in the CA. Further, the CA in particular is densely populated with NMDA receptors which are central to memory consolidation and neural plasticity[5]. Studying memory consolidation in schizophrenia may therefore provide unique insight into the specific contributions of hippocampal pathology in the illness. However, to our knowledge no *in vivo* studies have employed tasks that assess rates of memory consolidation over time, or changes in activity in specific sub-systems within the medial temporal lobe related to memory consolidation. Recent advances in cytoarchitectonic mapping allow for the estimation of hippocampal responses in anatomically defined sub-regions such as the DG and CA[6]. The present study was hence designed to assess time-related changes in activity from early to later in learning in the DG and the CA during an object-location memory consolidation task[7] in young schizophrenia and control subjects.

Methods. Eleven patients (3 females, mean age=26 yrs) and eleven controls (HC) subjects (5 females, mean age=22 yrs) participated. Over the course of the study, subjects were required to learn the associations between nine unique equi-familiar common objects[8] and locations in a 9 x 9 grid. The object-location memory consolidation task was administered over eight iterations. Each iteration consisted of a sequence of four blocks (conditions): encoding (objects presented individually in their grid locations, 3s/object with subjects required to name the object), rest/rehearsal, retrieval (location cue, with subjects required to name the object associated with the location) and rest/rehearsal. fMRI was conducted on a Bruker MedSpec 4T system. 288 T2*-weighted gradient-echo echo-planar (EPI) images were acquired (TE=30ms; TR = 3s; TA=2s; flip angle = 90°; acquisition matrix = 64 x 64 voxels; FOV = 240 mm; 24 slices; 3.75 x 3.75 x 4mm) during the experiment. Data were analyzed using SPM2. Individual effects of interest maps constructed for each subject (p_{FWE}<.05) identifying maximally task driven voxels were overlaid on maximum probability maps of the CA and the DG[6]. Percent signal change for encoding (relative to the adjacent Rest/Rehearsal)[9] for the significant voxels within each area were computed separately for early (Block ≤ 4) and late learning for each ROI and hemisphere.

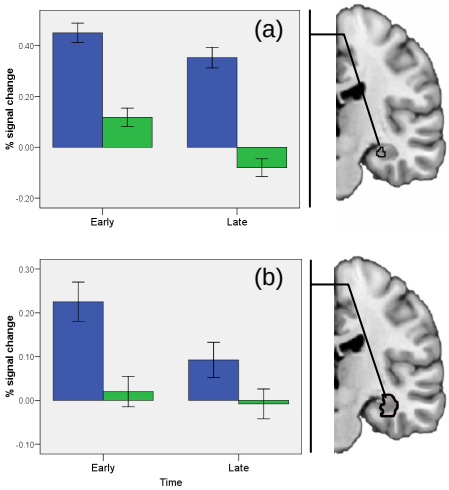

Figure 1. Right panels show outlines of maximum probability maps for the dentate gyrus (a) and cornu ammonis (b) on a coronal image (y=-22). Graphs depict percent signal change (relative to baseline) for controls (blue) and patients (green) plotted as a function of time. As seen, an impaired response is observed in schizophrenia patients in both the DG (a) and the CA (b) (see Results for details). Error bars in the graphs are ± sem across images.

Results. Block wise behavioral performance for all subjects were fit to negatively accelerated power functions, $y=1-e^{-kx}$, to capture learning dynamics[10]. Significantly, patients exhibited slower learning on average than controls (revealed by lower values of K, p<.05), indicating slower rates of consolidation. To assess the neural substrates of this difference, images were initially submitted to analyses of variance with group (control vs. patient), time of learning (early vs. late) and hemisphere (left vs. right) as factors. Strong right hemispheric lateralization was detected in both regions (p<10^{-6}) with no hemisphere x group interaction (p>.20) and subsequent analyses focuses on the right hemisphere. In the DG (Fig 1a), significant main effects of group and time were observed, ($F_{(1,2446)}$≥15.27, p<10^{-4}) indicating significant time-related changes in each group and significant hypo activity in schizophrenia patients. By comparison, in the CA (Fig 1b), a significant interaction, $F_{(1,2565)}$=4.2, p<.04, suggested lower activity during both stages of learning in patients, with time-dependent changes in response amplitude in controls. Pair wise contrasts, revealed significantly greater activity early in learning in controls (t_{1291}=2.19, p<.03) but not in patients (p>.20) suggesting group-related specificity in dynamic changes in activity in this region.

Discussion. These results indicate specific patterns of impairment during memory consolidation in two distinct hippocampal sub-regions in schizophrenia. In particular "upstream" hypoactivity during early stages of learning in the DG may affect response of the "downstream" CA sub-region leading to poorer memory consolidation and impaired learning. The results are notable for being the first to document regionally specific pathologies within the hippocampus using maximum probability maps in stereotactic space. Further they also document the relevance of this distinction in dissecting the functional pathology of this structure in schizophrenia. These results, considered with other studies in behavioral pharmacology[11] and post-mortem pathology highlight both the intricate functional organization of the hippocampus in the normal brain, and specific patterns of impairment in this organization in schizophrenia patients.

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