Reduced fronto-hippocampal connectivity in schizophrenia during associative learning: Relevance for NMDA-mediated synaptic dysplasticity

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Introduction: Recent work has suggested that schizophrenia is characterized by N-methyl-D-aspartate (NMDA)-related synaptic dysplasticity[1]. NMDA is one of the main ionotropic glutamatergic receptors involved in excitatory neurotransmission which is crucial in memory consolidation. The detection, consolidation and long-term potentiation of correlated spatio-temporal patterns of neuronal activity is a centerpiece of learning and memory[2], and hippocampal NMDA receptors, particularly in regions such as the cornu ammonis (CA) are known to in part perform all of these functions associated with learning[3]. It is therefore logical to assess disordered connectivity in schizophrenia in the context of learning and memory. However, whereas studies have assessed hippocampal function in schizophrenia with fMRI[4], none have done so in the context of learning and consequently none have examined functional connectivity during learning. In this report we assessed differences in functional connectivity between hippocampal and cortical regions in early course schizophrenia patients during memory encoding in an associative learning task[5]. Functional connectivity was assessed with psycho-physiological interaction (PPI)[6] in SPM2 using a seed region drawn from the CA region, estimated in stereotactic space[7,8].

Methods. Eleven early course schizophrenia patients (3 females, mean age=26 yrs) and eleven control subjects (5 females, mean age=22 yrs) participated in the study. Briefly, nine unique equi-familiar common objects[9] were randomly associated with locations in a 9 x 9 grid. Each of eight blocks in the experiment involved sequentially presented conditions of 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. Contrast maps (Encoding > Rest/Rehearsal) were created for each subject and thresholded at p_{FWE}<.05 within a right CA mask[8] (separate analyses indicated preferential right CA involvement in the task). For each subject, the first eigenvariate drawn from a 2mm radius ROI centered on the maximum intensity peak within the CA was convolved with the Enc > Rest/Rehearsal contrast in a first level effects of interest analysis, capturing modulation of activity across the cortex by activity within the seed voxel[6]. Individual effects of interest maps were submitted to second level analyses to assess group-wise differences in connectivity in HR compared to HC. Contrast analyses were restricted to a priori masks of lateral Brodmann areas 9 & 46 and the hippocampus[10].

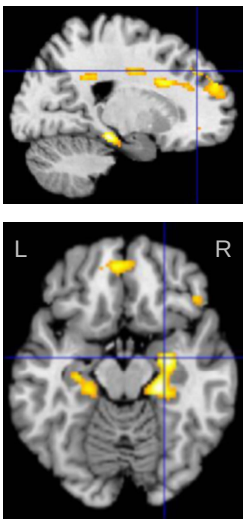

Fig 1. (a) Sagittal view depicting significance peak in Brodmann area 9 (cross-hairs) of reduced CA-frontal connectivity in schizophrenia. (b) Axial view of the medial temporal lobe showing bilaterally reduced intra-hippocampal connectivity in schizophrenia.

Results. Significantly reduced connectivity during encoding, (Contrast structure: $SCZ_{(Enc>Rest)} < HC_{(Enc > Rest)}$) was observed in dorso-lateral prefrontal cortex and across the ipsi- and contra-lateral medial temporal lobe. Clusters of significance are rendered in sagittal and axial views in Fig 1. Significance peaks are depicted (cross-hairs) for BA 9, t_{19}=3.79, p_{FDR}<.05, x=20, y=37, z=35 (Fig 1a) and in an axial view of the medial temporal lobe, t_{19}=4.65, p_{FDR}<.02, x=26, y=-12, z=-10 (Fig 1b) respectively.

Discussion. These results suggest that in schizophrenia, memory consolidation is characterized by reductions in fronto-hippocampal connectivity, specifically associated with activity in the cornu ammonis. To our knowledge, they are the first to demonstrate disordered fronto-hippocampal functional connectivity in schizophrenia in a task that specifically engages this encoding-retrieval network. We speculate that the deficits in connectivity are a direct signature of the hypothesized NMDA receptor hypofunction in the CA in schizophrenia[11]. Reduced plasticity of the cortical response in the CA may lead to impaired associative memory consolidation and relate to reduced coherence within the fronto-hippocampal memory circuit. Our ongoing studies are designed to probe the links between behavioral pharmacology[12], systems neuroscience[13] and clinical science[14] in an effort to dissect the pattern of specific deficits within the medial temporal lobe and its interactions with other cortical regions in schizophrenia.

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