



Hippocampal novelty activations in schizophrenia: Disease and medication effects

Carol A. Tamminga^{a,*}, Binu P. Thomas^a, Ronald Chin^a, Perry Mihalakos^a, Kenneth Youens^a, Anthony D. Wagner^b, Alison R. Preston^{c,**}

^a Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX, United States

^b Department of Psychology and Neuroscience Program, Stanford University, Stanford, CA, United States

^c Center for Learning and Memory and Department of Psychology, University of Texas at Austin, Austin, TX, United States

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ABSTRACT

We examined hippocampal activation in schizophrenia (SZ) with fMRI BOLD in response to the presentation of novel and familiar scenes. Voxel-wise analysis showed no group differences. However, anatomical region-of-interest analyses contrasting normal (NL), SZ-on-medication (SZ-ON), SZ-off-medication (SZ-OFF) showed substantial differences in MTL-based novelty responding, accounted for by the reduction in novelty responses in the SZ-OFF predominantly in the anterior hippocampus and parahippocampal cortex. These differences in novelty-based activation in the SZ-OFF group represent *disease* characteristics of schizophrenia without confounding effects of antipsychotic *medication* and illustrate the tendency of antipsychotic drug treatment to improve memory functions in schizophrenia.

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1. Introduction

Abnormalities in declarative memory performance and hippocampal function have been widely reported in SZ (Saykin et al., 1991; Stone et al., 1998; Aleman et al., 1999; Heckers, 2001; Nuechterlein et al., 2004; Titone et al., 2004; Brewer et al., 2005; Preston et al., 2005; Whyte et al., 2005; Weiss et al., 2006; Ranganath et al., 2008; Ragland et al., 2009; Shohamy et al., 2010; Tamminga et al., 2010). However, these findings do not clearly distinguish between disease and treatment effects on memory. In SZ, hippocampus shows *increased* basal blood flow (Medoff et al., 2001; Lahti et al., 2006; Malaspina et al., 2009) and *reduced* task-related activation, the latter during novel memory encoding (Andreasen et al., 1997; Eyler-Zorrilla et al., 2002; Jessen et al., 2003; Leube et al., 2003; Heckers et al., 2004; Holt et al., 2005; Keri et al., 2005; Ongur et al., 2006; Achim et al., 2007; Thermenos et al., 2007). The magnitude of psychotic symptoms correlates with hippocampal perfusion in SZ (Medoff et al., 2001; Lahti et al., 2006; Malaspina et al., 2009), with perfusion characteristics showing sensitivity to APD treatment (Medoff et al., 2001). Despite these observations, few studies have directly addressed the

impact of APD treatment on declarative memory activations with fMRI BOLD.

Novelty-related activation of MTL structures is reliably observed in healthy individuals (Stern et al., 1996; Tulving et al., 1996; Gabrieli et al., 1997; O'Kane et al., 2005), with the magnitude of novelty-related activation predicting subsequent memory performance (Kirchhoff et al., 2000; Preston et al., 2010). We postulated a priori that APDs would tend to ameliorate SZ-associated hippocampal dysfunction (see Fig. 2), especially in anterior regions, based on previous reports (Medoff et al., 2001; Shohamy et al., 2010).

2. Materials and methods

2.1. Participant characteristics

Research participants consisted of 20 normal (NL) and 27 schizophrenia volunteers (SZ), matched for age and educational level as the two most critical characteristics for memory function. Informed consent was obtained and protocol procedures approved by the UTSW institutional review board. SZ were categorized into on- or off-medication; these included 20 SZ-ON and 7 SZ-OFF (4/7: off 6.6 months; 1/7: off >2 months; 2/7: medication naive). All patient volunteers were recruited from clinics within Dallas County; SZ-OFF were medication-free voluntarily due to the burden of antipsychotic drug (APD) side effects. Group demographic and symptom data are included in Table 1. After excluding subjects if they had excessive motion in 2 or more scans, and any single scans (within subjects) with

* Correspondence to: C.A. Tamminga, UT Southwestern Medical School, NE5.110, 2201 Inwood Rd, Dallas TX 75390, United States. Tel.: +1 214 645 2789.

** Correspondence to: A.R. Preston, Center for Learning and Memory, University of Texas at Austin, 1 University Station C7000, Austin, TX 78712, United States. Tel.: +1 512 475 7255.

E-mail addresses: Carol.tamminga@utsouthwestern.edu (C.A. Tamminga), apreston@mail.clm.utexas.edu (A.R. Preston).

Table 1

Demographic data for all groups. A consensus diagnosis of schizophrenia was established using DSM-IV criteria by two experienced clinicians. Other Axis I disorders, were excluded. Exclusion criteria included a DSM-IV diagnosis of organic brain disease, alcohol or substance abuse within the last month or dependence in the last 6 months, serious medical illness or any history of serious head injury. Additional exclusion criteria for all study volunteers included current use of non-prescription drugs, excluding nicotine or caffeine, presence of serious medical illness, or a history of serious head injury. Patient assessments included the Positive and Negative Symptoms Scale (PANSS) to assess symptom severity (Kay et al., 1988), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for neuropsychological status (Hobart et al., 1999), and the Birchwood Social Functioning Scale (SFS) for social functioning status (Birchwood et al., 1990). In the subsequent memory test, the NL correctly identified 45% of previously studied scenes; the SZ-ON, 38%; and the SZ-OFF, 27%, with a trend for a difference between groups ($F(2,35) = 3.13, p = 0.06$). The false alarm rate was 18% in NL, 20% in SZ-ON and 16% in SZ-OFF, and did not differ between the three groups ($F(2,35) = 0.08, p = 0.88$).

	NV (n = 18)	SV-on (n = 17)	SV-off (n = 7)
%female	72.2	23.5	28.6*
Age, years (SD)	40.3 (11.2)	42.1 (9.1)	36.7 (10.1)
Handedness, right/left	17/3	16/4	7/0
Education, years (SD)	13.9 (1.5)	14.2 (3.0)	12.7 (2.4)
Chlorpromazine equivalent, mg (SD)	–	556.5 (411.2)**	–
D-Prime (SD)	.92 (.38)	.74 (.65)	.47 (.32)
P(H)	.45 (.15)	.38 (.19)	.27 (.13) +
P(F)	.18 (.17)	.20 (.21)	.16 (.15)
PANSS: total (SD)	–	81.2 (9.8)	89.9 (16.4)
Positive	–	21.1 (3.6)	27.4 (3.7)*
Negative	–	19.5 (3.7)	18.3 (5.2)
General	–	40.7 (5.8)	43.7 (10.6)
RBANS: total (SD)	–	86.8 (19.1)	74.4 (13.9)
IM	–	93.4 (22.5)	80.7 (18.1)
VC	–	88.7 (22.5)	73.7 (13.5)
LANG	–	92.3 (12.3)	90.6 (10.8)
ATT	–	88.9 (20.2)	78.7 (21.8)
DM	–	84.9 (20.7)	72.7 (20.3)
SFS: total (SD)	156.1 (16)	124.7 (30.5)	109.7 (24.8)
WD	12.9 (2.1)	9.5 (2.8)	9.9 (2.4)
IP	9.0 (0.0)	6.5 (1.9)	6.4 (1.3)
ID	35.5 (3.2)	30.5 (6.9)	30.4 (16.6)
IDCP	38.5 (1.2)	34.9 (5.9)	35.6 (15.5)
REC	24.0 (6.3)	17.2 (8.3)	15.7 (5.2)
PS	26.3 (10.7)	20.1 (9.2)	16.4 (6.1)
EO	9.92 (0.3)	6.0 (3.9)	4.6 (3.3)

*NV has sample size of 14 for social functioning scale.

* $p < 0.05$; + $p = 0.06$; **16/17 SZ-ON were on 2nd generation APDs, including aripiprazole, olanzapine, risperidone, ziprasidone and seroquel.

excessive motion, a total of 18 NL and 24 SZ (17 SZ-ON and 7 SZ-OFF) were included in the analyses.

2.2. Task procedures

Participants were scanned using an event-related design with two trial types in the novelty task: novel scenes and familiar scenes, with subsequent memory testing (Paller and Wagner, 2002; Spaniol et al., 2009; Kim, 2011) (Fig. 1). Novel stimuli consisted of equal numbers of complex, colored indoor and outdoor scenes; familiar stimuli consisted of one indoor and one outdoor scene each presented 20 times prior to scanning.

2.3. fMRI data acquisition

MR imaging was performed on a 1.5 Tesla Signa LX General Electric whole body-scanner with a phased array whole head coil. Head movement was minimized using foam padding and a head restraint strap. In plane anatomical images were acquired using a two dimensional T1-weighted SPOiled GRass (SPGR) sequence (TR = 18 ms, TE = 26 ms, FOV = 230 mm, matrix size = 256×256 , flip angle = 30°); 19 5-mm oblique coronal slices were acquired perpendicular to the main axis of the hippocampus, with the first slice starting at the anterior edge of the corpus callosum. An additional three dimensional T1-weighted SPGR volume (TR = 18 ms, TE = 26 ms, FOV = 230 mm, matrix size = 256×256 , flip angle = 90° ; 124 1.5-mm slices) was acquired for registration and normalization. Functional data were acquired using a T2*-weighted gradient echo pulse sequence (TR = 1.5 s, TE = 20 ms, FOV = 230 mm, matrix size = 64×64 , flip angle = 90°) with the same slice prescription as the 2D SPGR images.

2.4. fMRI data analysis

Data were preprocessed and analyzed using AFNI, SPM5 (Wellcome Imaging Neuroscience, London, UK), and custom Matlab routines. At the individual participant level, voxel-wise analysis was performed under the assumptions of the General Linear Model (GLM) (Friston et al., 1995; Holmes et al., 1997; Friston, 2003; Friston et al., 2003). A statistical threshold of $p < 0.05$, FDR corrected for multiple comparisons, and an extent threshold of five or more contiguous voxels were implemented for these voxel-based analyses. Two-sample t-tests assessed differences in novelty responses (novel–familiar) between NV and SV.

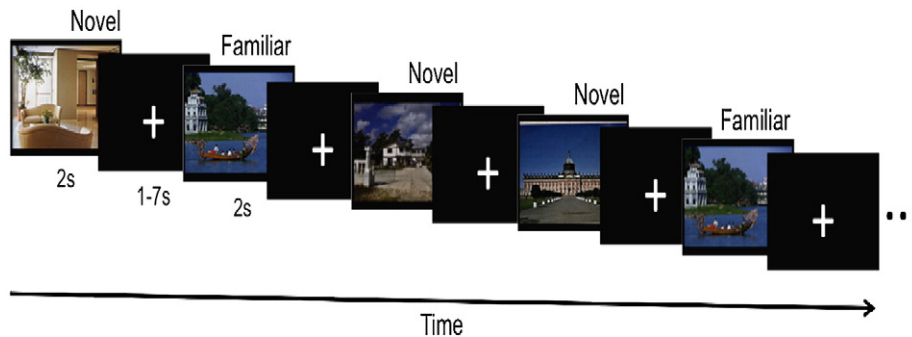


Fig. 1. Novelty detection task. Participants were presented images of indoor and outdoor scenes in one of two conditions: novel and familiar. Novel trials consisted of equal numbers of new indoor and outdoor scenes presented in random order during functional scanning; one indoor and one outdoor scene served as familiar stimuli and were presented 20 times each prior to scanning. During functional scanning, each stimulus was presented for 2 s jittered with 1–7 s null events. Participants performed an incidental encoding task, identifying the stimulus as ‘indoor’ or ‘outdoor’. Five functional runs were performed, each consisting of 120 trials (40 novel, 40 familiar, and 40 cross-hair fixation stimuli); fixation trials served as null events to introduce jitter. Trial/condition order was pseudorandom, and was optimized for event-related analysis. All trials consisted of a 2-s stimulus followed by a 1-s ITI. During scanning, participants performed an incidental encoding task, identifying stimuli as either indoor or outdoor scenes (responses were indicated by a button press, using a keypad under the participant’s right hand). After scanning, subjects were given a surprise memory test where they were presented with 400 stimuli, the 200 scenes from the incidental encoding scans and 200 new scenes not previously viewed in the experiment. Participants made self-paced recognition memory judgments, using a 3-point scale (1 = new; 2 = unsure; 3 = old).

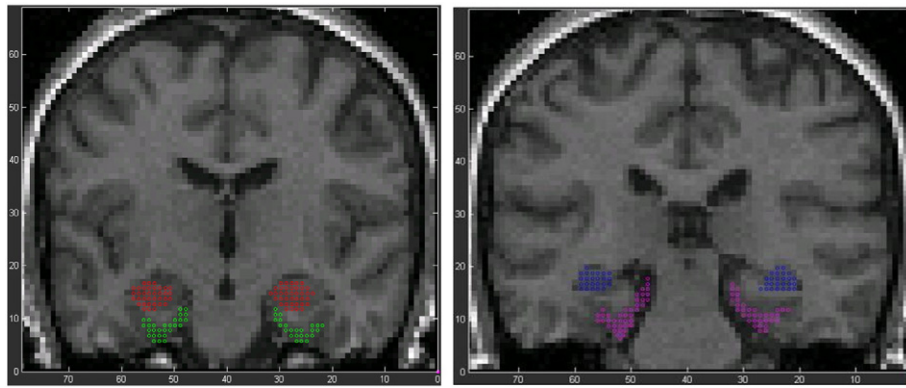


Fig. 2. Hippocampal ROIs. ROIs were drawn onto each volunteer's 3D T1-weighted SPGR image, as illustrated. Anterior hippocampus (A-Hipp; red) and perirhinal cortex (PRc, green) were drawn on the 3 coronal sections starting 4.5 mm posterior to the anterior edge of the corpus callosum; 9 mm posterior to the last anterior slice was used to demarcate the boundary of the posterior hippocampus (P-Hipp, purple) and parahippocampal cortex (PHc, pink). For each ROI, the deconvolved signal was extracted for individual participants using a finite impulse response function implemented in MarsBar (<http://marsbar.sourceforge.net/>). Integrated percent signal change was determined by calculating the area under the curve for the period of time 3–9 s post-stimulus onset for each condition. To assess how processing of novel stimuli differed across groups, ROI data were submitted to a mixed effects ANOVA in an exploratory framework, with trial type (novel, familiar) and region (A-Hipp, P-Hipp, P/ERC, PHc) as within-subject factors and group (NLV SZ-ON, SZ-OFF) as a between-subjects factor. A separate exploratory ANOVA assessed whether the pattern of novelty response in each region differed as a function of group. Planned comparisons further assessed pairwise differences between the response of each region to novel and familiar scenes for each participant group.

As a complement to voxel-based GLM analyses, an anatomically based region-of-interest (ROI) analysis was performed to further assess how medication status affected novelty-based responding. Four

anatomical ROIs were defined for each participant using the 3D T1-weighted image and standard anatomical landmarks (Duvernoy, 1998) (Fig. 2).

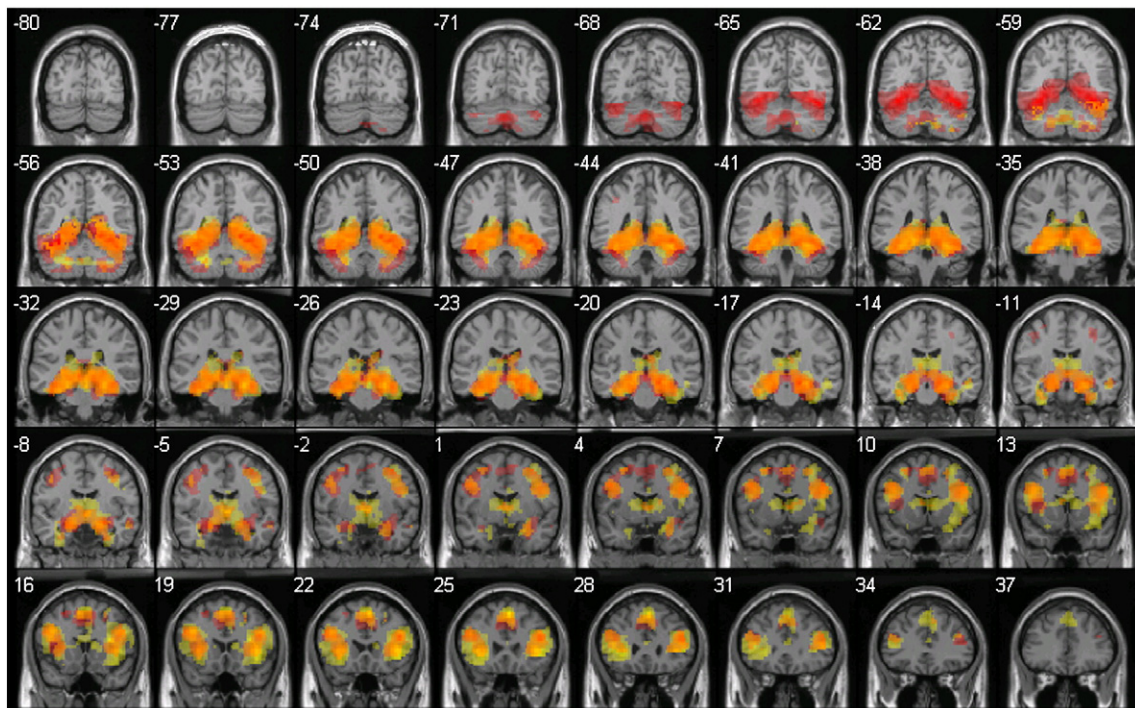
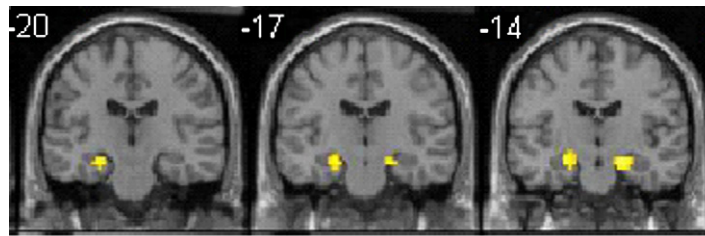


Fig. 3. Voxel-wise analysis of novelty-based responses. Functional images were corrected to account for differences in slice acquisition times in AFNI. Using SPM, the functional images were then realigned to the first volume in the time series to correct for motion. The T1-weighted 2D structural image was co-registered to the mean T2*-weighted functional volume computed during realignment. The structural image was then spatially normalized into common stereotactic space using the MNI template brain. The spatial transformation calculated during normalization of the structural image was then applied to the functional volumes, which were re-sampled to 2-mm isotropic voxels. After normalization, the functional images were spatially smoothed using an 8-mm FWHM Gaussian kernel. For statistical estimation, an anatomically specified mask derived from the T1-weighted anatomical image was created for each participant to ensure that all voxels in the brain were included at the analyses phase. Regressor functions were constructed for all novel and familiar trials by modeling stimulus-related activation as a stick function convolved with a canonical hemodynamic response function (HRF). Parameter estimates for each regressor were estimated using a least squares approach to multi-linear regression (Josephs, 1999). The time series was filtered with a 128-s high pass filter to remove low frequency variations within the functional data. Contrast images comparing novel and familiar trials were generated in the individual participant analysis, and then analyzed across participants using a mixed effect GLM, treating participants as a random effect allowing for population inference (Holmes and Friston, 1998). The contrast of novel relative to familiar scene stimuli was similar across SZ (red) and NL (yellow) groups. Novelty-based responses in several brain regions, including the hippocampus, overlapped across groups (orange).

- a) The voxel-wise correlation of novelty responding with the successful memory of novel stimuli during task (d')



- b) The voxel-wise correlation of novelty responding with RBANS-DM, measured apart from the novelty scan.

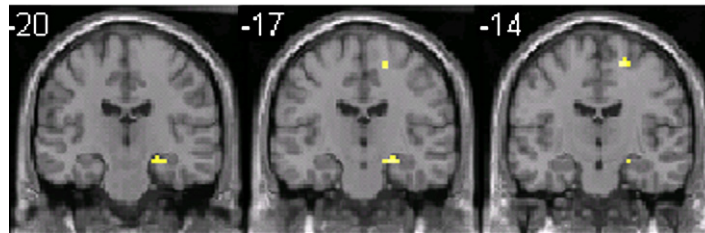


Fig. 4. Correlation between novelty responding and declarative memory status. To assess whether or not the BOLD activations correlated regionally with any behavioral manifestations in the SZ-ON, voxel-wise correlations were carried out between novelty activations and successful memory (measured with d') and with subscale scores on the RBANS. Novelty activation was linearly related to performance on successful memory (d') bilaterally and on the declarative memory scale of the RBANS (RBANS-DM) within the left hippocampus (cluster size = 72). For these performance-related analyses, we used a statistical threshold of $p < 0.001$, uncorrected for multiple comparisons, and an extent threshold of five or more contiguous voxels to identify significant effects, given the exploratory nature of the analysis.

3. Results

3.1. Group demographics and task performance

NL, SZ-ON, and SZ-OFF were matched on age and educational level (all $F < 1.1$), both critical to memory function. Neuropsychological (RBANS) or social function (Birchwood SFS) measures were not different between patient groups (Table 1; $0.12 < p < 0.99$). Relative to SZ-ON, SZ-OFF had modestly higher levels of positive symptoms on PANSS-POS ($F(6,16) = 3.9$; $p < 0.001$). Subsequent memory for novel scenes presented during scanning was evaluated immediately after scanning in an unexpected recognition memory test (Table 1), with the rates of performance accuracy (d') being 0.92 for NL, 0.74 for SZ-ON, and 0.47 for SZ-OFF ($F(2,35) = 2.01$; $p = 0.15$).

3.2. Voxel-based analysis

We contrasted novel and repeated scene trials separately for NL and SZ (Fig. 3; Supplementary Tables 1 and 2). A two-sample t -test comparing novelty-based responding across the NL and SZ groups did not reveal significant differences between groups in any region. These between group comparisons, however, do not take into account the possibility that novelty responses may differ across individuals within the schizophrenia group as a function of memory performance. Therefore, we performed an exploratory regression analysis weighting the novel vs. familiar contrast by successful memory performance (d') and by a neuropsychological measure of declarative memory (RBANS-DM) using a $p = 0.001$ threshold. To control for the effects of active psychosis on cognitive performance, we limited both regressions to the SZ-ON group. We observed a positive correlation between novelty responses and successful memory (d') in hippocampus bilaterally (Fig. 4a); a positive correlation between novelty responses and the RBANS-declarative memory (DM) score was also observed in left hippocampus (Fig. 4b). SV-ON individuals with the highest levels of declarative memory function, (using d' or with RBANS-DM) showed the greatest novelty activation in hippocampus.

Similar correlations between novelty responses and other RBANS subscales did not reveal significant relationships in any brain region.

3.3. Disease vs. medication effects in MTL subregions

ROI analyses focused on the directly assessed hippocampus novelty activations in volunteers with and without APDs. We contrasted responses across the three groups in the four ROIs (Fig. 2). No

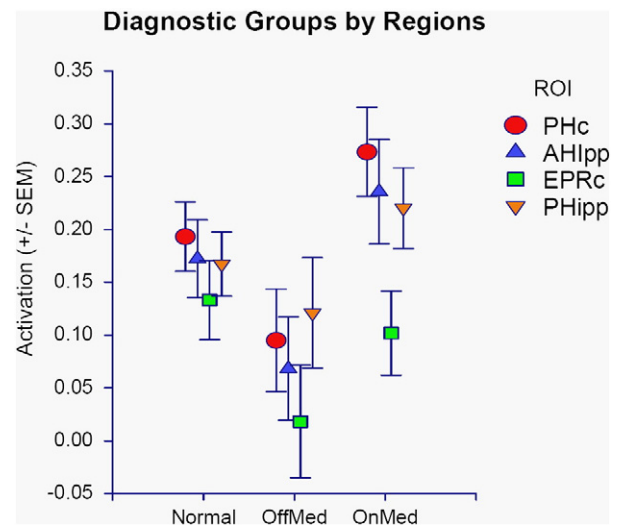


Fig. 5. Effect of group and medication status on responses to novel scenes within MTL ROIs. Activation (mean \pm SEM) during novel scene stimuli is illustrated in the hippocampus proper [AHipp (blue), PHipp (orange)], and in the entorhinal/perirhinal cortex [E/PRc (green) and parahippocampal gyrus, PHc (red)]. The SZ-OFF group showed significantly reduced novelty responses in AHipp and PHc compared with the NV and the SZ-ON groups, with no difference in activation between the SZ-ON and NV groups. Moreover the SZ-OFF activation was lower than NV in E/PRc, and lower than SZ-ON in PHipp.

group \times hemisphere effects were observed with ANOVA ($F(1,41) = 2.28$, $p = 0.14$); therefore, ROI data were pooled across hemisphere. We examined how activation in the four anatomically defined hippocampal regions differed as a function of group, using a three-way mixed-effect ANOVA, with group, trial type, and region as factors. A significant trial type \times group interaction was observed ($F(2,41) = 3.45$; $p < 0.04$); MTL activation during novel scenes significantly differed across groups ($F(2,41) = 3.45$; $p < 0.04$), with posthoc testing showing reduced activation in the SZ-OFF group relative to both NL and SZ-ON ($p < .05$). The group \times region interaction was also significant ($F(6,123) = 3.28$; $p < 0.005$), suggesting that schizophrenia and medication status were specific to particular MTL regions. Posthoc comparisons revealed that overall activation in A-Hipp and PHc was significantly reduced in the SZ-OFF group relative to the NL and SZ-ON (each at $p < .05$; Fig. 5). In addition, SZ-OFF showed reduced activation compared with NL in P-Hipp ($p < .05$), and to SZ-ON in the E/PRc ($p < .05$).

The pattern of novelty response in each region was also compared across the three groups using mixed-effects ANOVA. In A-Hipp, a significant group \times novelty interaction obtained ($F(2,41) = 4.15$, $p < 0.05$), with significant novelty responses in NL and SZ-ON, but no novelty-related activation in SZ-OFF relative to NL ($t(41) = 3.35$, $p < 0.01$) and SZ-ON ($t(41) = 3.07$, $p < 0.01$) (Fig. 6a). In P-Hipp, activation to novelty was apparent in each group, as neither the main effect of group ($F(2,41) = 1.46$; $p = 0.24$) nor the group \times novelty interaction ($F(2,41) = 1.62$; $p = 0.21$) were significant. In PHc, a significant effect of group ($F(2,41) = 3.98$, $p < 0.05$) and a trend for a group \times novelty interaction ($F(2,41) = 2.92$, $p = 0.07$) obtained, with a reduced PHc activation in SZ-OFF compared to SZ-ON ($p < .05$) (Fig. 6b). In E/PRc, there was no main effect of group, but a trend for a group \times novelty interaction ($F(2,41) = 2.95$, $p = 0.06$), with no novelty response in SZ-OFF ($p < .05$ posthoc). Posthoc comparisons did not reveal any significant differences between SZ-ON and NL in any of the four ROIs examined ($p > 0.05$).

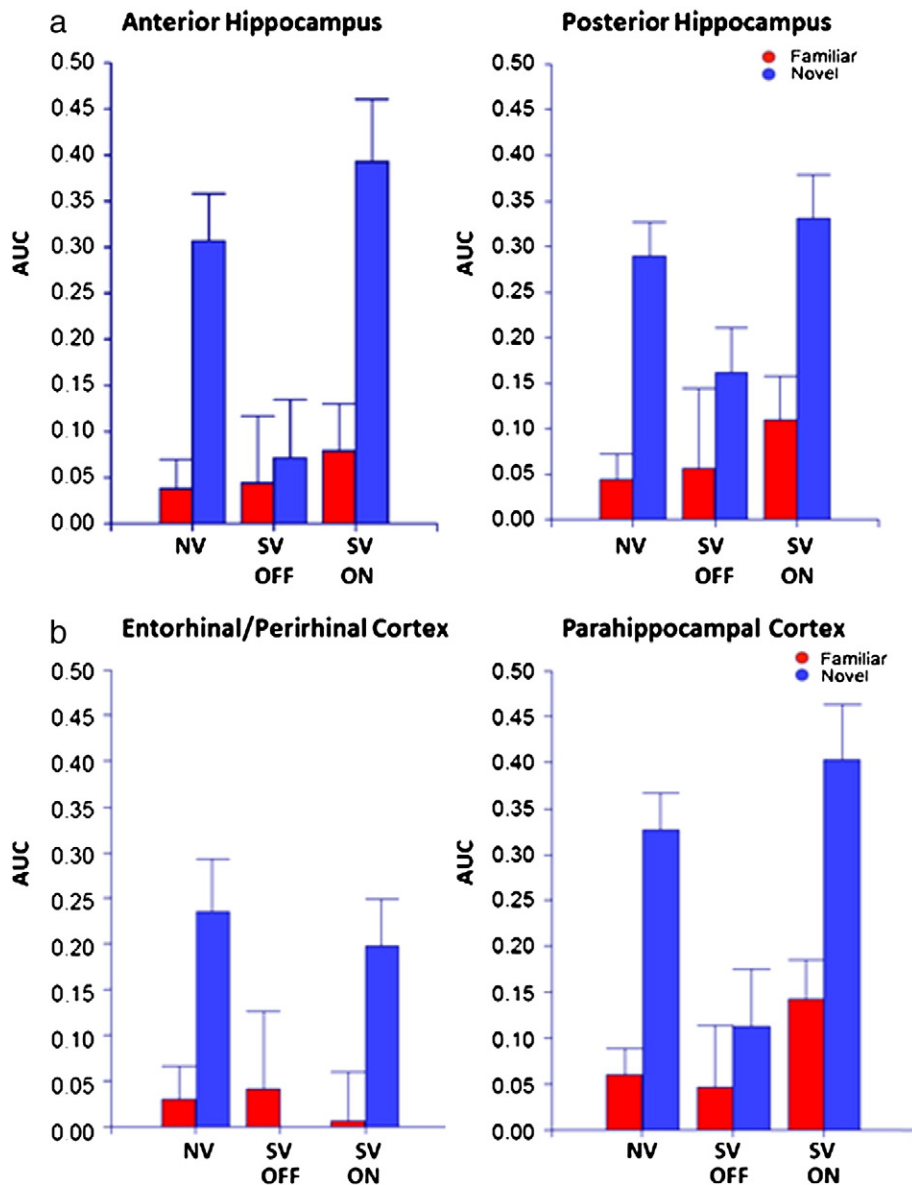


Fig. 6. Response to novel and repeated scene stimuli in a) hippocampus proper and b) parahippocampal gyrus. In the hippocampus proper, a significant group \times novelty interaction was observed within the anterior hippocampus but not in posterior hippocampus; activation in AHipp was significantly reduced in the SZ-OFF relative to NV and SZ-ON, but did not differ between the groups in PHipp. In the parahippocampal gyrus, E/PRc and PHc activation showed a trend for a group \times novelty interaction, with the magnitude of novelty related activation being reduced in the SZ-OFF patients relative to the NV or SZ-ON groups.

4. Discussion

The present observations show that the treatment of SZ with APDs tends to normalize otherwise absent or blunted hippocampal activation to novel stimuli, as seen in SZ-OFF. There were no activation differences to novelty responding in SZ-ON compared to NL, as assessed using both voxel-wise and anatomically defined ROI analyses. However, when SZ-OFF volunteers were contrasted with either the NL or SZ-ON individuals, ROI analyses revealed that the SZ-OFF demonstrated significantly reduced or absent novelty-driven hippocampal activation. Importantly, this effect differed by region, with novelty-related reductions in SZ-OFF being most predominate in A-Hipp and PHc. We propose that effects of APDs on hippocampus might represent an additional therapeutic mechanism of these medications in psychosis.

The effects of midbrain dopamine signaling on memory especially motivational or 'adaptive memory', is currently an area of active examination (Wittmann et al., 2005; Adcock et al., 2006; Shohamy and Wagner, 2008; Kuhl et al., 2010; Shohamy and Adcock, 2010). However, contrasts between APD conditions using hippocampal activation with memory tasks have not been assessed directly. Here, we report functional differences as a result of APD treatment that are consistent with studies identifying reduced hippocampal activation in first-break SZ (Reske et al., 2009) and in the SZ prodrome (Allen et al., 2011). Moreover, perfusion is increased in first-break (Schobel et al., 2009) and drug-free SZ (Medoff et al., 2001; Lahti et al., 2006), again consistent with the blunted activation observed here. Together with studies showing altered structure and spectroscopic metabolites in hippocampus in at-risk SZ populations (Wood et al., 2010; Capizzano et al., 2011), the present findings highlight pervasive alterations in hippocampus due to disease.

Supplementary materials related to this article can be found online at doi:10.1016/j.schres.2012.03.019.

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NIH MH062236 "Examination of Limbic Cortex in Schizophrenia" (CT): This application seeks to identify and characterize the nature and localization of anatomic and chemical abnormalities in the limbic cortex of schizophrenic (hippocampus, entorhinal cortex, and anterior cingulate) contributing to the pathophysiology of the disease.

NIH MH83957 "Antipsychotic Influence on Altered MTL Neuronal Activity in Schizophrenia (CT): This grant will test the elements of a new model with in vivo brain imaging using measures of basal activity and relational memory probes, correlating alterations in neural activity with characteristics of the illness.

NARSAD Distinguished Investigator Award (CT): NARSAD is an acronym for National Alliance for Research on Schizophrenia and Depression. The NARSAD Distinguished Investigator Grant provides support for experienced investigators (full professor or equivalent) conducting neurobiological and behavioral research.

NARSAD Young Investigator Award (ARP): The NARSAD Young Investigator Grant provides support for the most promising young scientists conducting neurobiological research.

Contributors

Carol A. Tamminga¹,
Binu P. Thomas¹,
Ronald Chin¹,
Perry Mihalakos¹,
Kenneth Youens¹,
Anthony D. Wagner²,
Alison R. Preston³
¹, Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX
², Department of Psychology and Neuroscience Program, Stanford University, Stanford, California
³, Center for Learning and Memory and Department of Psychology, University of Texas at Austin, Austin, TX.

Conflict of interest

Tamminga is on the Scientific Advisory Board of Intracellular Therapies, PureTech Ventures, and an ad hoc advisor for Eli Lilly, Sunovion, Astellas, and Merck; she is an expert witness for Bradley Arant Boulton and Cummings and an unpaid volunteer for the International Congress on Schizophrenia Research.

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