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Subsequent memory effects in schizophrenia

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ABSTRACT

Differential neural activation at encoding can predict which stimuli will be subsequently remembered or forgotten, and memory deficits are pronounced in schizophrenia. We used event-related functional magnetic resonance imaging (fMRI) to investigate subsequent memory (SM) effects for visual fractals in patients with schizophrenia ($n=26$) and healthy controls ($n=28$). Participants incidentally encoded the fractals during an oddball task and 10 min later they made old/new recognition memory judgments on 30 target fractals and 30 foil fractals. We found evidence for subsequent memory (SM, subsequently remembered > subsequently forgotten) effects on regional brain activation in both groups but with distinct patterns. Region of interest (ROI) analyses in controls demonstrated SM activation in both medial temporal lobe (MTL) and fusiform cortex (FF), whereas patients showed SM effects only in the FF. There were no significant between group differences in MTL activation; however, patients demonstrated greater FF activation than controls. Notably, greater FF activation during successful encoding was associated with more severe negative symptoms. Exploratory whole brain analyses in patients demonstrated SM activation in the occipital pole, lateral occipital cortex, left inferior temporal gyrus, and fusiform cortex; whereas in controls there was no significant activation that survived correction for multiple comparisons. Our findings suggest that patients, particularly those with prominent negative symptoms, may activate FF as a compensatory strategy to promote successful encoding, with relatively less reliance on MTL recruitment.

1. Introduction

Memory dysfunction is central in schizophrenia, remaining stable over time and not accounted for by education, gender or medication status (Censits et al., 1997; Seidman et al., 1998; Aleman et al., 1999). Patients often suffer from specifically impaired episodic memory whereby memory for past events is compromised (Gold et al., 1992; Heinrichs and Zakzanis, 1998; Aleman et al., 1999; Cirillo and Seidman, 2003). During encoding of past events, differential neural activation occurs for stimuli that will be subsequently remembered compared to forgotten. This subsequent memory (SM) effect characterizes the neural activity that supports successful encoding (Brewer et al., 1998; Wagner et al., 1998; Paller and Wagner, 2002; Reber et al., 2002). SM has consistently been associated with activation in five brain regions: the medial temporal lobe (MTL), fusiform cortex (FF), left inferior frontal cortex, premotor cortex, and the posterior parietal cortex (Kim, 2011). Activation in these regions differs according to the way the stimuli are encoded, either incidentally or intentionally, and the stimuli type, visual or verbal.

Encoding of visual compared to verbal stimuli elicits the greatest SM activation in the medial temporal lobe and fusiform cortex, among these five main regions (Kim, 2011). Thus, the network required for SM can be divided into functional components including content processing and storage regions (Otten et al., 2001; Rugg et al., 2002; Kim, 2011). Content processing regions, such as the fusiform cortex, transform sensory input into internal representations that are interpreted downstream (Kirchhoff et al., 2000; Paller and Wagner, 2002). Storage regions, namely the medial temporal lobe, bind content representations into stable memory traces for retrieval during a subsequent encounter (Squire et al., 2004). Little work has assessed whether patients with schizophrenia demonstrate the same neural patterns related to subsequent memory as healthy subjects (Bonner-Jackson et al., 2008; Ragland et al., 2012).

We used event-related functional magnetic resonance imaging (fMRI) to investigate SM for incidentally encoded patterned visual stimuli – fractals – in patients with schizophrenia. Schizophrenia has been associated with functional impairment of the medial temporal lobe, evidenced by deficient patterns of activation during memory encoding and retrieval (Heckers, 2001; Preston et al., 2005; Ragland

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et al., 2009). It is less clear whether schizophrenia relates to functional impairment of the fusiform cortex, particularly when patients attempt to encode complex patterned visual stimuli such as fractals. Prior evidence suggesting impairment of the fusiform cortex relates primarily to deficits in facial processing (Gur et al., 2002; Quintana et al., 2003; Johnston et al., 2005). However, some results suggest that activation in the fusiform is preserved in patients (Yoon et al., 2006).

We aimed to investigate patterns of SM activation in patients with schizophrenia compared to healthy controls. We hypothesized that patients would demonstrate deficient medial temporal lobe activation, reflecting a compromised ability to bind visual representations into stable memory traces, but intact SM activation in the fusiform cortex, reflecting the ability to encode visual fractals. Greater effort for encoding by patients would result in greater fusiform activation. In that case, patients would demonstrate compensatory strategies for successful encoding by over-activating the fusiform relative to healthy controls. Given prior evidence that memory impairment in schizophrenia is associated with negative symptoms (Aleman et al., 1999), we assessed the relationship between SM activation abnormalities and negative symptom severity, in comparison to positive symptom severity.

2. Methods

2.1. Participants

The sample included 26 patients with schizophrenia (15 males) and 28 healthy controls (15 males), drawn from a larger sample that also included 36 family members of patients, resulting in 90 total participants. All participants were right-handed volunteers at the University of Pennsylvania Schizophrenia Research Center. Participants underwent standard assessment, including medical, neurological, psychiatric, neurocognitive, and laboratory tests. Psychiatric evaluation included clinical interviews, a structured interview (SCID-P, First et al., 1996), and collateral history from family, caregivers and records. Trained investigators administered symptom scales. Patients had a DSM-IV diagnosis of schizophrenia ($N=22$) or schizoaffective disorder ($N=4$), determined by consensus conference based on all available information and all were on an average of 287.2 mg of antipsychotic medication (in chlorpromazine equivalent units), predominantly on second generation antipsychotics ($N=19$) and some on first generation antipsychotics ($N=7$). Patients were clinically stable outpatients at the time of study and had been on medication for an average of 40 months. Symptoms were assessed with the Scale for Assessment of Negative Symptoms (SANS, Andreasen, 1984, average total SANS score $M=1.1$, S.D.$=0.6$). Symptoms were also assessed with the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984, average total SAPS score $M=0.6$, S.D.$=0.5$). Patients had no history of other disorders or events affecting brain function (i.e., current or history of substance abuse). After a complete description of the study, written informed consent was obtained from the participants. Healthy controls were similarly screened and had no Axis I disorder and no first-degree relative with such a disorder.

2.2. Procedure

During scanning, participants completed three tasks including an oddball task, a recognition memory task; and in between those tasks, participants completed an unrelated perceptual integration task. The perceptual integration task assessed the ability to perceive biologic motion using moving dot stimuli; results of this task will be presented elsewhere. In the 9-min oddball task, participants were instructed to respond to targets (green circle, 15% of trials) and refrain from responding to standard stimuli (red circle, 70% of trials). Without prior mention in the instructions, novel fractals would appear infrequently (15% of trials). Each novel fractal was a unique image and thereby distracting relative to the standard and target stimuli. Participants were not asked to remember the novel fractals; therefore the fractals were incidentally encoded. Incidental-encoding engages activation in the middle temporal lobe (Stark and Okado, 2003; Henson, 2005). Approximately 10 min after the oddball task, participants completed a 6-min recognition memory task that included 30 target fractals (used as novel stimuli in the oddball task) and 30 foil fractals. Stimuli in both the oddball and recognition memory tasks were presented in a random order on the screen for 1 s with a variable inter-stimulus interval ranging from 2 to 18 s. Participants were asked to discriminate between target and foils and responded with a button press to make old/new recognition memory judgments. Responses and reaction times were recorded.

After the scan, participants completed a web-based adaptation of a computerized neurocognitive battery (CNB) that included a shape memory task, consisting of 10 targets and 10 foils selected evenly from each type of shape (Glahn et al., 1997; Gur et al., 2001, 2012; Irani et al., 2012). Each stimulus was a blue two-dimensional shape (a triangle, square, pentagon, hexagon or octagon with varying degrees of shading) within a three-dimensional figure. Stimuli were presented for 1 s each on a computer screen and participants were asked to memorize the stimuli. Immediately after the study phase, participants made old/new recognition memory judgments, responses and reaction times were recorded. Participants received no feedback on whether or not their responses were correct.

2.3. Image acquisition

Functional blood-oxygen-level-dependent (BOLD) data was acquired on a 3-T Siemens Tim Trio scanner using a quadrature head coil. Structural images were acquired axially using a magnetization prepared rapid acquisition gradient-echo (MPRAGE), T1-weighted sequence (repetition time/echo time (TR/TE)$=1630/3.87$ ms, field of view (FOV)$=240\times180$ mm^2, matrix$=256\times192$, slice thickness/gap$=1/0$ mm) with a voxel resolution of $0.9375\times0.9375\times1.00$ mm^3. This sequence was used for spatial normalization and for anatomic overlays of functional data. Functional images (178 images for the oddball task and 126 images for the recognition memory task) were acquired axially using a 40-slice gradient-echo (GE) echo-planar imaging (EPI) sequence (TR/TE$=3000/30$ ms, FOV$=240\times240$ mm^2, matrix$=64\times64$, slice thickness/gap$=3/0$ mm) with a nominal voxel resolution of $3.00\times3.00\times3.00$ mm^3.

2.4. Image processing

The fMRI data from the incidental-encoding (oddball) task was preprocessed and analyzed using FEAT (FMRI Expert Analysis Tool v 5.0.2.1), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The functional images were slice-time corrected, motion-corrected to the median image with tri-linear interpolation, high-pass filtered (100 s), spatially smoothed (5 mm full width half-maximum (FWHM) Gaussian isotropic kernel), and grand mean scaled. A brain extraction tool was used to remove non-brain areas from the high-resolution structural image (Smith, 2002). The functional images were coregistered to the structural image and transformed by trilinear interpolation into standard anatomical space (Jenkinson and Smith, 2001; Jenkinson et al., 2002) using the T1 Montreal Neurological Institute (MNI) template.

2.5. Statistical analysis

Subject-level time-series statistical analysis was carried out by using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001). Condition events were modeled with a canonical (double-gamma) hemodynamic response function and its temporal derivative. Event types modeled included: subsequently remembered fractals and subsequently forgotten fractals. The design matrix also included six motion parameters derived from motion correction, to reduce residual motion effects. Groups did not differ significantly in head motion ($t=0.70$, d.f.$=21$, $p=0.49$). The primary subsequent memory contrast of interest compared activation at encoding of correctly remembered novel visual fractals versus those that were forgotten (SM, subsequently remembered > subsequently forgotten).

After preprocessing, whole brain statistical analysis was completed for each individual in subject space, and resulting contrast maps were spatially normalized as mentioned above. Group level random effects analyses were performed in FSL, using FMRIB's Local Analysis of Mixed Effects (FLAME 1) (Beckmann et al., 2003; Woolrich et al., 2004) during estimation of statistical significance. Within-group analyses were accomplished by entering whole brain contrasts into one-sample t-tests. Between-group analyses used two-sample t-tests.

We selected the medial temporal lobe, consisting primarily of the hippocampus and amygdala, and the fusiform cortex as a priori regions of interest (ROI). Bilateral masks for these ROIs were drawn based on coordinates of peak activation from an SM activation meta-analysis of 74 fMRI studies (Kim, 2011). We drew 12 mm spheres around the coordinates, after converting from Talairach to MNI space and averaging the slightly asymmetric coordinates from the left and right peaks, thus producing symmetric bilateral masks (MNI coordinates: right peak, 20 −9 −20; left peak −20 9 −20). In addition, separate group level covariate analyses were performed in the MTL and FF ROIs for the SM contrast and performance on a shape memory test administered during the CNB. We tested the correlation between negative symptom severity and performance on CNB shape memory.

For all ROI analyses, significance thresholds were based on spatial extent, applying a minimum height threshold $z>=1.65$ and a cluster $p<0.05$. The cluster-size cutoff (102 voxels in the MTL ROI; 104 voxels in the FF ROI) was determined using Monte Carlo simulation (AlphaSim, D.B. Ward, http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html) within the relevant mask (Forman et al., 1995; Xiong et al., 1995).

We also completed exploratory whole brain analyses to investigate regions, beyond our a prior ROIs, that may be involved in the SM effect. In addition, separate group level covariate analyses were performed in the whole brain to assess the