

Implicit Memory for Spatial Context in Depression and Schizophrenia

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Deficits in explicit spatial memory, as well as abnormalities of the hippocampus and neighboring medial temporal structures, have been documented in schizophrenia and depression. Recent evidence relying on the contextual cueing paradigm has shown that integrity of these structures is crucial not only for explicit memory but also for implicit spatial memory. Using this paradigm, the authors show that implicit memory for spatial context is severely impaired in clinically depressed patients but reaches a normal level in schizophrenia patients, although in these patients, acquisition is slower than in controls. By contrast, implicit memory for isolated locations and colors is normal in both schizophrenia and depressed patients. These findings suggest an implicit memory impairment specific to spatial context in depression. The implications for research on the differences between schizophrenia and depression in abnormalities of the hippocampal system and for research on the neural correlates of contextual cueing are discussed.

Keywords: implicit spatial memory, unipolar depression, schizophrenia, visual search, contextual cueing

Our visual environment is overloaded with complex information but is also highly structured. Scenes typically contain invariants, with certain objects consistently appearing at the same location within a given context. Our visual system's sensitivity to such regularities may help us cope with information overload and improve our sense of control by increasing predictability (e.g., Biederman, Mezzanotte, & Rabinowitz, 1982).

Chun and Jiang (1998) developed the contextual cueing task and showed that the abstract spatial layout of a scene devoid of semantic cues can guide attentional deployment. In this task, subjects search for a known target (e.g., a rotated T) among distractors (e.g., rotated Ls). On each trial, the target and surrounding distractors form a specific spatial configuration that defines the visual context on this trial. Half of the configurations in each block of trials are repeated once in every block (old configurations), whereas the remaining configurations are generated anew in each block (new configurations). The target in each old configuration appears in a consistent location relative to its context on each repetition. Thus, global spatial layout on these trials is predictive of target location. A robust finding in such tasks is that search is faster for targets appearing in old configurations than for targets appearing in new configurations. This *contextual cueing* effect indicates that newly formed associations between spatial context and target location facilitate visual search.

Hippocampal Structures and Implicit Memory for Spatial Context

The hippocampus and adjacent medial temporal lobe (MTL; including entorhinal, perirhinal, and parahippocampal cortex) appear to play a central role in contextual cueing. Contextual learning in amnesic patients with MTL damage including the hippocampal formation was shown to be impaired relative to healthy controls (Chun & Phelps, 1999; Manns & Squire, 2001). In addition, one neuroimaging study revealed hippocampal involvement in normal participants performing the contextual cueing task (Preston, Sali-dis, & Gabrieli, 2001).

The hippocampus is traditionally associated with explicit memory or the ability to consciously recognize and recall events, as damage to the hippocampus produces severe amnesia but does not affect memory that is not accessible to conscious report (Squire, 1992). Implicit memory is thought to rely on nonhippocampal brain structures. However, Chun and Jiang (2003) showed that contextual cueing is driven by implicit memory representations acquired incidentally, rather than through conscious learning strategies. Thus, the reported associations between hippocampus and contextual cueing (Chun & Phelps, 1999; Preston et al., 2001) suggest that the hippocampus is essential not only for explicit memory but also for memory of spatial context, even when such memory is acquired implicitly.

This view converges with the relational account of hippocampal function (e.g., Eichenbaum, 1999), which postulates that a unique function of the hippocampus is to rapidly develop memory for the spatial context within which an important event occurs. Support for this account has come from animal research showing that hippocampus integrity is important for tasks requiring the formation of new long-term representations of the spatial relationship between distinct elements, but not for tasks tapping separate representations of distinct individual elements (e.g., Phillips & LeDoux, 1994).

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Hippocampus-Related Abnormalities in Schizophrenia and Depression

Abnormalities in the hippocampus and neighboring MTL in schizophrenia (Preston, Shohamy, Tamminga, & Wagner, 2005) and depression (Campbell & MacQueen, 2004) are the focus of considerable research. Specific patterns of memory deficits broadly consistent with hippocampal dysfunction have been documented in these conditions, namely, impaired explicit memory and preserved implicit memory (e.g., Bazin & Perruchet, 1996; Van Gorp, Altshuler, Theberge, & Mintz, 1999) and poor spatial memory (e.g., Elliott et al., 1996; Fleming et al., 1997). However, the tests used to probe spatial memory functions in these patients always required conscious recollection of the learned spatial information and did not specifically tap its relational aspect. Thus, it remains unknown whether schizophrenia and depressed patients show impairments in those aspects of spatial memory that have recently been specifically associated with hippocampal and MTL function, namely, implicit relational memory of spatial context.

Objective of the Present Study

We tested schizophrenia patients, unipolar depression patients (henceforth, "depressed" patients), and healthy control participants on the contextual cueing paradigm. We distinguished between (a) implicit memory for spatial context that relies on relational information (between context and target location) and is thought to depend on hippocampal structures (e.g., Chun & Phelps, 1999), (b) implicit spatial memory that relies on memory for isolated locations (target location) and is thought to be unrelated to the hippocampus (Eichenbaum, 1999), and (c) nonspatial implicit memory. To do that, we embedded a target-location repetition manipulation and a target-color repetition manipulation within the search task, in addition to the manipulation of configuration repetition across blocks (contextual cueing). That is, within a block, targets sometimes appeared at the same location or were of the same color on successive trials. Previous research has shown that observers are faster when the target appears at the same versus at a different location (Maljkovic & Nakayama, 1996) or has the same versus a different color (Maljkovic & Nakayama, 1994) on successive trials.

Finally, we assessed patients' attentional deployment abilities relative to healthy controls by using two display sizes and comparing search rates, or the additional time required to find the target for each distractor added to the search array. This comparison was important to ensure that any failure to find contextual cueing in the patient groups could not be attributed to a basic impairment in attentional deployment.

Specific impairment of implicit memory for spatial context in one or both patient groups should be reflected in a smaller advantage, if any, of the old-configuration condition over the new-configuration condition, relative to control participants, together with normative search rates and normative target-location and target-color repetition effects.

Method

Participants

Eighteen patients diagnosed with schizophrenia and 18 patients having a current depressive episode and diagnosed with unipolar

depression were recruited from the Shalvata Outpatient Program. Patients had no *Diagnostic and Statistical Manual of Mental Disorders* (DSM) Axis I mental-disorder comorbidity or borderline personality disorder. Inclusion criteria for patients were age (18 to 60 years), clinical status allowing participation in an outpatient program, and stable medication intake during the preceding month. Exclusion criteria were any significant or untreated medical illness. *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) diagnoses were confirmed by the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1997) conducted by a senior psychiatrist. Schizophrenia patients underwent structured interviews using the Positive and Negative Syndrome Scale for Schizophrenia (Kay, Fiszbein, & Opler, 1987).

Thirty-six healthy volunteers were divided into two control groups, one matched for age and gender with the schizophrenia group and the other matched with the depression group. Using the Structured Clinical Interview for Structured Clinical Interview for DSM-IV, two senior psychiatrists confirmed that each participant had no known psychiatric or current drug/alcohol condition.

All participants filled the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Table 1 provides demographic information for all participants and clinical information for patients.

Apparatus and Stimuli

Displays were presented on a computer monitor at a viewing distance of 50 cm. Figure 1 shows an example of the stimulus displays. The fixation display was a gray plus sign in the center of a black background. Stimulus displays consisted of either 8 or 12 letters ($0.74^\circ \times 0.5^\circ$ of visual angle each): one T (the target), rotated 90 degrees to either the right or left, and 7 or 11 Ls (the distractors), presented randomly in one of four orientations.

Each display appeared within a 10×10 matrix. Within each cell ($1.25^\circ \times 1.25^\circ$), each letter center was randomly jittered to prevent collinearities. Each display contained an equal number of pink, green, orange, and blue letters. These colors were randomly assigned to each item within a configuration.

Procedure

Participants determined the orientation of the unique T by pressing the Z button with their left hand for left-oriented targets and the 3 button with their right hand for right-oriented targets. They had to respond as fast as possible, while maintaining high accuracy. Each trial consisted of the fixation display (500 ms) followed by the stimulus display (visible until response). Intertrial interval was 500 ms. Error trials were followed by auditory feedback. A 24-trial practice block preceded 14 blocks of 24 experimental trials, with short breaks allowed between blocks.

Twelve different configurations (six with eight letters and six with 12 letters) were generated anew for each block (*new configurations*). Twelve configurations (six with eight letters and six with 12 letters) were generated randomly and repeated once per block throughout the experiment (*old configurations*). The target always appeared in the same location within any particular old configuration. Target locations for old and new configurations were randomly chosen, with target eccentricity equated between

Table 1
Demographic and Clinical Characteristics of the Participants

Characteristic	Schizophrenia	Schizophrenia controls	Depression	Depression controls
Mean age (years)	25.4 (<i>SD</i> = 4.5)	25.1 (<i>SD</i> = 4.9)	38.8 (<i>SD</i> = 12.9)	37.6 (<i>SD</i> = 11.8)
Sex				
Male	13	13	11	11
Female	5	5	7	7
Illness duration (years)	4.3 (<i>SD</i> = 3.1)		10.6 (<i>SD</i> = 8.6)	
Hospitalizations (weeks)	16.2 (<i>SD</i> = 18.2)		8.3 (<i>SD</i> = 3.6)	
BDI mean score	14.2 (<i>SD</i> = 11.1)	1.8 (<i>SD</i> = 1.2)	24.8 (<i>SD</i> = 10.4)	1.7 (<i>SD</i> = 1.1)
PANSS mean score				
Negative symptoms	19.4 (<i>SD</i> = 3.6)			
Positive symptoms	22.9 (<i>SD</i> = 6.1)			
General symptoms	44.9 (<i>SD</i> = 10.7)			
Medication (no. patients)				
Atypical neuroleptic medication	10			
Typical neuroleptic medication	4			
Typical and atypical neuroleptic medication	4			
Mood stabilizers			3	
SSRI			3	
SNRI			3	
TCA			2	
TCA and SNRI			2	
Mood stabilizers and SSRI			2	
Mood stabilizers, SSRI, and atypical neuroleptic medication			3	

Note. BDI = Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); PANSS = Positive and Negative Syndrome Scale for Schizophrenia (Kay, Fiszbein, & Opler, 1987); SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

the old- and new-configuration conditions. Thus, the target could occupy the same location more than once within a block, which made it possible for the target to appear at the same location on successive trials and thereby allowed measurement of target-

location repetition effects. We randomized target orientation across trials and repetitions of old displays to eliminate context–response contingencies. Target- and distractor-color assignments in old configurations were preserved across repe-

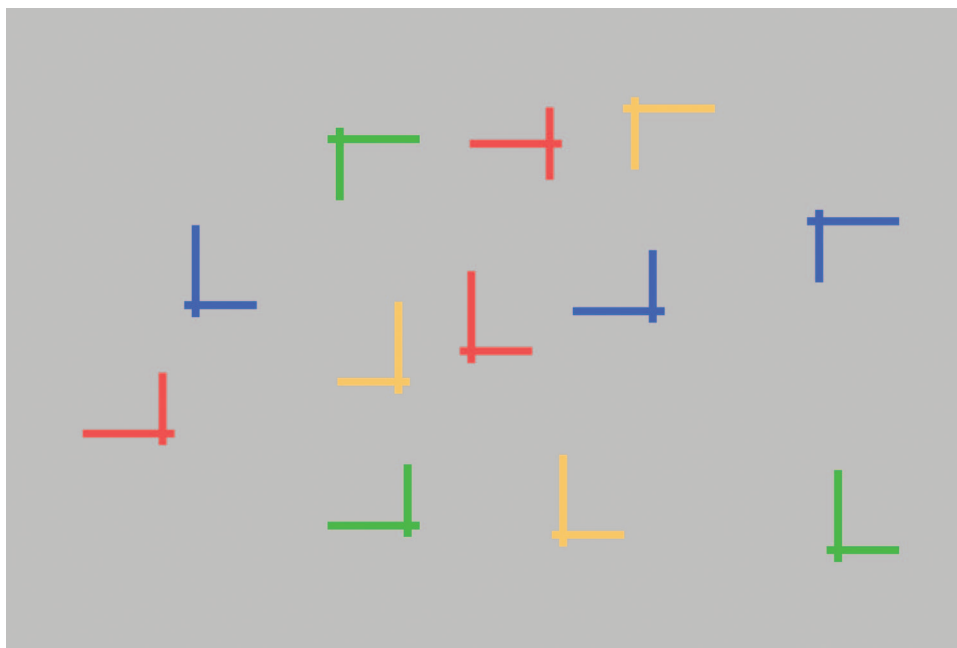


Figure 1. Sample search display. Participants searched for a T among rotated Ls and indicated whether it was rotated to the right or to the left.

titions. Old and new configurations were randomly mixed within each block.

Results

Mean reaction times (RTs) on correct trials are presented in Figure 2. Error trials (2.4% and 1.8% for schizophrenia patients and their controls, respectively; 2.1% and 1.9% for depressed patients and their controls, respectively) and outliers (less than 1% of all correct trials in each group) were removed from all RT analyses. Accuracy data yielded no significant effects and are therefore not discussed further.

Contextual Cueing

An analysis of variance with configuration (new vs. old), experiment half (first vs. second),¹ and display size (8 vs. 12) as within-subject factors and group (schizophrenia, schizophrenia control, depression, depression control) as a between-subjects factor was conducted on mean RTs. Groups differed in overall RTs, $F(3, 68) = 3.45, p < .02$, with schizophrenia and depression patients being slower than their controls, $t(34) = 2.61, p < .02$, Cohen's $d = .80$, and $t(34) = 1.97, p < .06$, Cohen's $d = .67$, respectively, and not differing from each other ($t < 1$, Cohen's $d = .07$).

Mean RTs were faster on old- than on new-configuration trials, $F(1, 68) = 41.36, p < .0001$. This effect was modulated by an interaction with group, $F(3, 68) = 4.20, p < .009$, indicating a between-group difference in learning to use repetition of context to speed visual search, and with experiment half, with a larger advantage for old than for new configurations in the second relative to the first experiment half, $F(1, 68) = 15.36, p < .0002$.

Separate analyses with experiment half and configuration as factors were conducted for each group. Depressed patients showed no interaction between configuration and experiment half ($F < 1$) and no configuration effect in either experiment half ($F_s < 1$; Cohen's $d_s = .01$ and $.03$ for the first and second halves, respectively). This interaction was significant for their controls, $F(1, 17) = 9.18, p < .008$, with a smaller effect in the first, $F(1, 17) = 17.12, p < .0007$, Cohen's $d = .30$, than in the second experiment half, $F(1, 17) = 38.05, p < .0001$, Cohen's $d = .42$. Significant Group \times Configuration interactions confirmed that depressed patients differed from their controls on contextual cueing in both the first and second experiment halves, $F(1, 34) = 4.37, p < .05$, and $F(1, 34) = 9.30, p < .005$, respectively.

Schizophrenia patients showed a significant interaction between configuration and experiment half, $F(1, 17) = 13.49, p < .002$, with no effect of configuration in the first experiment half ($F < 1$, Cohen's $d = .01$) and a significant effect in the second one, $F(1, 17) = 15.23, p < .002$, Cohen's $d = .34$. This interaction was also significant for their controls, $F(1, 17) = 9.54, p < .007$, with a smaller effect in the first, $F(1, 17) = 11.76, p < .004$, Cohen's $d = .30$, than in the second experiment half, $F(1, 17) = 29.68, p < .0001$, Cohen's $d = .40$. Follow-up Group \times Configuration analyses showed that schizophrenia patients tended to differ from their controls on contextual cueing in only the first experiment half, $F(1, 34) = 3.98, p < .06$, not in the second one ($F < 1$).

Mean RTs were faster in the second relative to the first experiment half, $F(1, 68) = 110.81, p < .0001$, reflecting overall

improvement from practice with the task, which did not differ between groups ($F < 1$). Response times were longer with the large relative to the small display size, $F(1, 68) = 179.31, p < .0001$. This effect did not interact with group ($F < 1$), indicating that search efficiency was comparable across groups (Cohen's $d = .66, .71, .50$, and $.69$ for the schizophrenia, schizophrenia control, depression, and depression control groups, respectively).

Target-Location and Target-Color Repetition Effects

An analysis of variance with target-location repetition (repetition vs. no repetition)² and group (schizophrenia, schizophrenia control, depression, and depression control) as factors, revealed faster RTs when the target location repeated relative to when it changed on successive trials, $F(1, 68) = 152.89, p < .0001$. Both the schizophrenia and depression groups showed numerically larger location effects than their controls (Cohen's $d_s = 1.09$ vs. $.83$ and $.72$ vs. $.51$, respectively), but this difference was significant for only depression patients, $F(1, 34) = 5.23, p < .03$, not for schizophrenia patients ($F < 1$; see Figure 3, Panel A).

An analysis of variance with target-color repetition, display size, and group as factors revealed faster RTs when the target color repeated relative to when it changed on successive trials, $F(1, 68) = 58.77, p < .0001$. This effect did not interact with either group or display size, ($F_s < 1$, Cohen's $d_s = .30, .32, .28$, and $.40$ for the schizophrenia, schizophrenia control, depression, and depression control groups, respectively; see Figure 3, Panel B).

Discussion

Our results show a dissociation in implicit memory for spatial context between unipolar depression and schizophrenia. Depressed patients showed no search facilitation for repeated configurations (contextual cueing). By contrast, although contextual cueing acquisition was slower in schizophrenia patients than in healthy controls, the two groups reached the same facilitation level on repeated-configuration trials in the second experiment half. Implicit memory impairment in depressed patients appeared to be specific to memory for spatial context, as these patients showed normal overall improvement following practice with the task, normal color priming, and an even larger location priming effect than healthy controls. It should be noted, however, that the mechanisms at play in contextual cueing versus in location and color priming are likely to differ on aspects other than the contextual nature of the memory traces. Namely, configuration repetitions occurred across blocks, thus at longer lags than color or location repetitions, which occurred on successive trials. In addition, discrimination between configurations was more difficult than discrimination between locations or colors. Further research should clarify the roles of repetition lags and discrimination difficulty in the contextual cueing impairment observed in depressed patients.

¹ The same results were obtained when the first and last experiment thirds, instead of experiment halves, were compared.

² Display size was not included as a factor because there were too few repeated target-location trials for each display size to conduct a meaningful analysis.

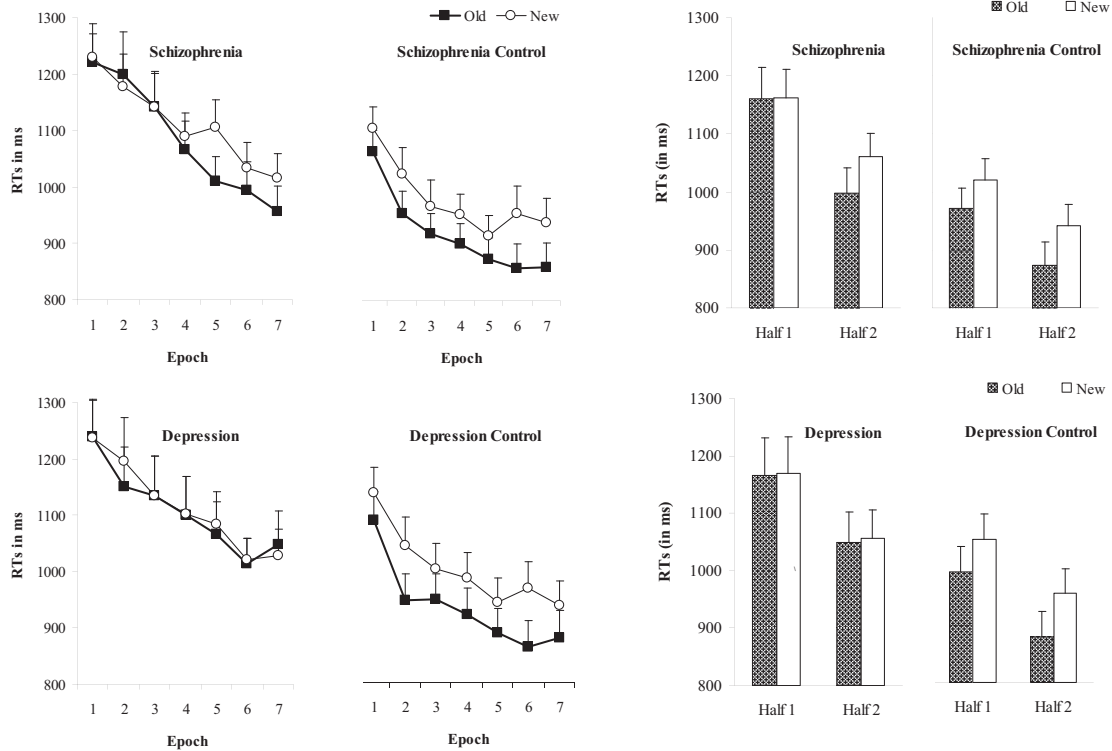


Figure 2. Mean reaction times (RTs) for old versus new configurations as a function of experiment half (right panels) and epoch (two consecutive blocks; left panels) for each group.

Impaired Contextual Cueing in Depression

Our novel finding of an association between depression and impairment in implicit spatial learning is consistent with recent findings in animals. Rats that underwent the learned helplessness procedure or were subjected to chronic mild stress, two behavioral manipulations thought to produce a depressive state in rats, showed impairments in spatial learning and changes in hippocampal neuroplasticity, which were reduced by antidepressant treatment (Song, Che, Min-Wei, Murakami, & Matsumoto, 2006). Our findings may suggest that in humans, also, effects of depression on implicit spatial learning may be mediated by abnormalities in

hippocampal activity. One may speculate that a causal link between depression and impaired implicit spatial memory, as was demonstrated in rats, may also exist in the opposite direction. That is, lack of sensitivity to regularities in the environment may undermine depressed individuals' sense of control and induce stress, which may, in turn, exacerbate depression.

Slow Buildup of Contextual Cueing in Schizophrenia

The pattern of results observed in schizophrenia patients has three main implications. First, consistent with previous findings (e.g., Chun & Jiang, 1998), only very few exposures to a given

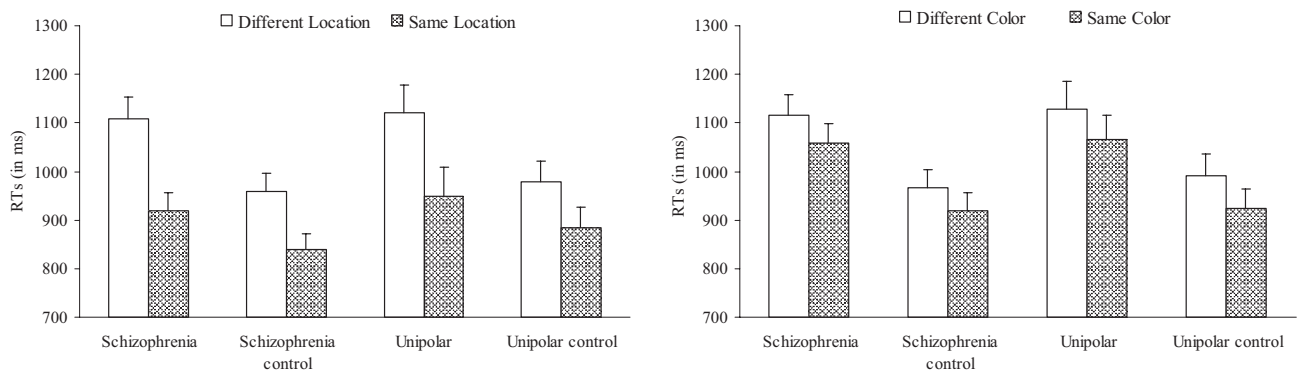


Figure 3. Mean reaction times (RTs) as a function of target-location repetition (left panel) and target-color repetition (right panel) for each group.

spatial context sufficed to produce an advantage for old configurations in control subjects (see Figure 2). By contrast, although schizophrenia patients eventually achieved a normative level of contextual cueing, such learning required more exposures. This finding may bridge between human and animal research on the function of the CA3 subfield of the hippocampus. Integrity of CA3 in rats was shown to be necessary for one-time rapid learning of novel spatial context but not for memory acquired incrementally over several days (e.g., Nakazawa et al., 2003). Thus, the finding that schizophrenia patients were impaired for rapid implicit learning of spatial context but not for learning following repeated exposures is consistent with documented abnormalities of CA3 in schizophrenia (Preston et al., 2005).

Second, the present findings provide new insights into schizophrenia patients' abilities in perceptual organization and memory for novel stimuli. Silverstein, Bakshi, Nuernberger, Carpinello, and Wilkniss (2005) reported that schizophrenia patients' ability to recognize highly structured visual patterns increased as a function of experience but did not improve for unstructured patterns. They concluded that schizophrenia patients are impaired in consolidating novel, unstructured visual information into memory traces, thus limiting the benefit of consistent experience of elements going together. Here, the visual context on any search display was unstructured because item locations were randomly assigned. However, although schizophrenia patients required more exposures than did their controls to form memory traces of such unstructured spatial configurations, they clearly improved with experience, as reflected by the normal contextual cueing benefit observed in the second experiment half. Taken together, these findings suggest that schizophrenia patients may be slower, rather than unable, to encode and retain complex and unstructured spatial patterns and may be specifically impaired in using these representations for explicit report.

Finally, the finding that contextual cueing occurs in schizophrenia patients supports the notion that different neural mechanisms might underlie transitive inference (TI) and contextual cueing. The TI task is used to assess capacities for systematic organization of knowledge and logical inference. Schizophrenia patients were found to be impaired on TI (Titone, Ditman, Holzman, Eichenbaum, & Levy, 2004), yet achieved relatively good performance on contextual cueing in the present study. This dissociation is consistent with recent findings on the effects of midazolam on memory. Midazolam is a drug thought to inactivate the hippocampus, although precise anatomic localization of its effects requires further investigation. Park, Quinlan, Thornton, and Reder (2004) showed that midazolam causes profound explicit memory deficits and impairs performance on the contextual cueing task, whereas Frank, O'Reilly, and Curran (2006) showed that midazolam indeed produces amnesia but actually improves performance on TI. Thus, the dissociations between TI and contextual cueing on schizophrenia patients' performance and on the effects of midazolam, may call for a refinement of the relational view of the hippocampus, according to which both tasks are functions of the hippocampus. On the basis of these findings, one may speculate that certain hippocampal structures might be specifically dedicated to implicit learning of spatial relational information and unrelated to relational judgments of the type required for successful performance on TI. Posterior hippocampus might be a good candidate. Indeed, lesions of the dorsal hippocampus of rats, corresponding to pos-

terior hippocampus in primates, were found to result in greater impairment of spatial memory than corresponding lesions in anterior hippocampus (Moser & Moser, 1998). In addition, reduced volume of posterior hippocampus was reported in unipolar depression (Neumeister et al., 2005), whereas schizophrenia was associated with smaller volumes of anterior hippocampus (Bilder et al., 1995, but see Weiss, DeWitt, Goff, Ditman, & Heckers, 2005, for conflicting evidence).

Attentional Deployment During Visual Search in Depression and Schizophrenia Patients

A corollary finding of the present study is that, despite substantially slower overall RTs, both depressed and schizophrenia patients deployed their attention as efficiently as did control participants. To our knowledge, search efficiency in depressed patients has not been studied before. A study by Hammar, Lund, and Hugdahl (2003) showed that unipolar depression patients are impaired in effortful search but not in automatic search, but RTs, rather than search slopes, were used to assess performance. Thus, the observed impairment may result from general lack of motivation when performing a difficult task, for instance, rather than from search efficiency. Studies examining search efficiency in schizophrenia have yielded mixed results (e.g., Mori et al., 1996, vs. Fuller et al., 2006). Fuller et al. (2006) suggested that deficits in the deployment of attention in schizophrenia may become apparent only with difficult enough tasks and when speed-accuracy tradeoffs are prevented. However, schizophrenia patients showed normative search slopes in the present study, although the search task was difficult (98 ms/item in control participants), and no speed-accuracy tradeoff was observed in any of the groups, including the schizophrenia group. Thus, the conditions under which schizophrenia patients are impaired in visual search efficiency remain undetermined.

In addition to providing fine-grained characterization of memory deficits in depression and schizophrenia, the present dissociation on contextual cueing between the two patient groups may have implications for the study of hippocampal and MTL abnormalities in these psychiatric conditions and for the study of the neural correlates of implicit memory for spatial context. On the one hand, despite extensive research, how abnormalities of hippocampus and MTL differ between schizophrenia and depression remains unclear. These have been studied using a myriad of methods (see Campbell & MacQueen, 2004, and Harrison, 2004, for reviews on depression and schizophrenia, respectively). Abnormalities were reported in the hippocampus (e.g., Sheline, Wang, Gado, Csernansky, & Vannier, 1996, and Altshuler et al., 2000), parahippocampus (Altshuler, Casanova, Goldberg, & Kleinman, 1990, and Bowen, Najlerahim, Procter, Francis, & Murphy, 1989), and entorhinal cortex (Beckmann & Jakob, 1991) of depression and schizophrenia patients and in the perirhinal cortex of schizophrenia patients (e.g., Sim et al., 2006).

On the other hand, although there is general agreement that damage to the hippocampus and MTL impairs contextual cueing performance, which of these structures underlie implicit memory for spatial context is controversial. Indeed, Manns and Squire (2001) showed that patients with partial atrophy restricted to the hippocampus exhibited normal contextual cueing, whereas patients

with lesions to the hippocampus also extending to MTL and lateral temporal cortex did not benefit from contextual learning. Related findings were recently reported by Bohbot, Allen, and Nadel (2002) with the invisible sensor task, which relies, at least in part, on implicit memory for spatial context. Patients with lesions to parahippocampal cortex were severely impaired on this task, whereas patients with lesions to hippocampus sparing parahippocampal cortex showed no deficit. Thus, it remains unclear whether damage to a specific part of the hippocampus that might have been spared in Manns and Squire's patients, extensive damage to the hippocampus, or damage to structures adjacent to it is necessary to disrupt contextual cueing, and, more generally, implicit memory for spatial context.

An important contribution of the present findings, therefore, is that research on hippocampal and MTL abnormalities in depression and schizophrenia may benefit from advances in research on the neural mechanisms underlying contextual cueing, and vice versa.

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