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Spatial serial order processing in schizophrenia

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Abstract

The aim of this study was to examine serial order processing deficits in 21 schizophrenia patients and 16 age- and education-matched healthy controls. In a spatial serial order working memory task, one to four spatial targets were presented in a randomized sequence. Subjects were required to remember the locations and the order in which the targets were presented. Patients showed a marked deficit in ability to remember the sequences compared with controls. Increasing the number of targets within a sequence resulted in poorer memory performance for both control and schizophrenia subjects, but the effect was much more pronounced in the patients. Targets presented at the end of a long sequence were more vulnerable to memory error in schizophrenia patients. Performance deficits were not attributable to motor errors, but to errors in target choice. The results support the idea that the memory errors seen in schizophrenia patients may be due to saturating the working memory network at relatively low levels of memory load.

Keywords: Schizophrenia; Serial order; Working memory; Sequence; Saturation

1. Introduction

In his landmark paper on *serial order*, Lashley (1951) pointed out that the ability to remember the order in which events occur is vital for effective interaction with the environment. The brain must be able to register when a particular stimulus appears with respect to all other incoming information. Without this serial order information, words and sentences would be scrambled, and it would be impossible to analyze causality and form plans of action.

A large body of literature has been devoted to the study of serial order recall (see Henson, 1998). Generally speaking, a subject is given a list of stimuli that they must remember for some time period before they use this information to inform a response. Normal subjects seem to perform well when memory load is below approximately seven items in a list (Miller, 1956). This limit in performance appears to define a point of saturation for working memory capacity. When working near this point of saturation, the normal pattern of error for serial recall is dominated by two well-described phenomena; primacy and re-

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cency. The primacy effect is the phenomena by which recall for the earlier items of a list is more accurate than for the later items. In contrast, the recency effect describes the observation that the accuracy for recall of a recently presented item is better than for items presented earlier. The combination of primacy and recency effects results in the pattern of positional errors seen in normal human subjects (Glanzer and Cunitz, 1966; Henson, 1998; Elvevag et al., 2003). First, there is a progressive increase in recall error for items in later positions in a list. This progressive increase then attenuates for the last items in a list.

Schizophrenia patients suffer from a breakdown in their ability to process serial order information under a variety of conditions (Bauman, 1971; Frame and Oltmanns, 1982; Weiss et al., 1988; Manschreck et al., 1991; Schwartz et al., 1991; Landro et al., 1993; Dominey and Georgieff, 1997; Goldberg et al., 1998; Dreher et al., 2001; Elvevag et al., 2001, 2003). Typically, a deficit in serial order processing presents as a deviancy from the normal error pattern described above. Manschreck et al. (1991) report that schizophrenia subjects show intact recency but compromised primacy effects. In a recent study, Elvevag et al. (2003) present results from a serial order task that probed for only one element of a letter list held in memory. That study supports the observations by Manschreck et al. concerning intact recency and compromised primacy effects. Elvevag et al. (2003) then argue that patterns of memory error can be used to test hypotheses about the underlying component processes of serial order working memory. This detailed approach to error pattern analysis, first proposed by Henson (1998), represents an important link between behavioral studies and models of cognitive processing.

The studies just reviewed use a variety of stimuli (letters, targets, digits, etc.) that relate to verbal and symbolic domains of memory. Spatial recall tasks, in which a series of targets for pointing movements are presented, offer an additional experimental design that is attractive for several reasons. First, spatial serial order tasks avoid the difficulty that language related stimuli can introduce into the interpretation of experimental results. Language abnormalities and thought disorder in schizophrenia have been well documented (Holzman et al., 1986; DeLisi, 2001). When linguistic sequencing is abnormal it is not clear whether the problem stems from abnormalities of processing language or of sequencing. Spatial tasks circumvent this problem, and thus should allow one to study memory phenomena at a more fundamental level. Spatial processing has been less well studied, but deficits in such processing by schizophrenia patients seem to stem from abnormalities in working memory rather than spatial processing per se (Park and Holzman, 1992; Chey et al., 2002). Basic spatial processing seems relatively spared in schizophrenia and, in some perceptual tasks, is even improved (Chey and Holzman, 1997). Second, spatial tasks allow for comparative studies of underlying neural substrates of memory in non-human primates and rodents. Considering that most psychoactive drug development relies heavily on testing in animal models, this type of research is especially important with respect to drug development for schizophrenia. In this respect, we followed the strategy of Park and Holzman (1992) and Park et al. (1999) who based their paradigm on a spatial recall task used by animal neurophysiologists (Fuster, 1973; Goldman-Rakic, 1987) when studying working memory in monkeys. The present study extends these observations by analyzing spatial working memory when increasing serial order processing demands are placed upon the subject. The task used here was modeled after a spatial serial recall task introduced by Barone and Joseph (1989) to study serial order working memory in monkeys.

In a recent review of the discrepant neuroimaging literature on working memory in schizophrenia, Manoach (2003) presents a model in which activation of brain regions during working memory tasks depends in a nonlinear manner on working memory load. The activity curve increases until the subject reaches the point of saturation, after which the activity drops off as the subject disengages from the task or engages an alternate strategy. Discrepant findings in the imaging literature on schizophrenia patients, she contends, may be the result of a reduced memory capacity in patients, which leads to saturation of the working memory network at loads that are significantly lower than in healthy subjects. Comparing schizophrenia patients versus normal control subjects could result in a differential effect in either direction depending upon the extent to which their activation curve is shifted downward along the memory load axis. The extent of this shift might differ with stimulus modality, medications, motivation, or other extrinsic factors.

Based on the capacity model (Manoach, 2003), we can make a simple prediction about performance in spatial serial order tasks. If serial order working memory in schizophrenia patients saturates earlier than in normal subjects, we can expect performance deficits at relatively low memory loads (three or four items). Based on the seminal work on memory capacity by Miller (1956), we predict that normal subjects will perform quite well at this level.

The prediction of a performance deficit in schizophrenia also raises questions about the nature of the deficit. The Manoach model, although helpful in forming the initial prediction about saturation, is less helpful in forming hypotheses about what type of signal processing deficits schizophrenics might show in a spatial serial recall task. The critical question of error patterns under conditions of saturation has been tested in an anatomically and physiologically constrained network model developed by Beiser and Houk (1998).

The Beiser–Houk model is based on single unit neurophysiology and the known anatomical connections from prefrontal cortex (PFC), through the basal ganglia (BG) and thalamus, and back to the PFC. This series of synaptic connections is thought to form a "loop" that detects, encodes and maintains the type of memory related activity that has been observed in primate recordings from PFC during performance of delayed working memory tasks (Fuster and Alexander, 1971; Fuster, 1973; Goldman-Rakic, 1987; Goldman-Rakic et al., 1990). The model uses the process of competitive pattern classification by caudate neurons to detect salient stimulus events represented in the population of cortical neurons. The classified information then induces activity within bistable cortical–thalamic loops that model the sustained working memory discharge seen in neurophysiological recordings in monkeys (Fuster and Alexander, 1971; Fuster, 1973; Funahashi et al., 1989; Goldman-Rakic et al., 1990) and imaging studies in humans (Petrides et al., 1995; Fiez et al., 1996; Owen et al., 1996; Braver et al., 1997; Cohen et al., 1997; Smith and Jonides, 1997). When given different sequences of targets in a simulated delayed working memory paradigm, the model produces distinct patterns of PFC activity for each of the different sequences.

In returning to the issue of capacity, it is critical to know how the model behaves when it becomes saturated. When the Beiser–Houk model was presented with the task of encoding longer and longer sequences, it had to enlist greater numbers of neurons and circuit modules to be successful. As the model was tested to the point of saturation (saturation was modeled by parametric increase of maximum synaptic weight), it produced two major error patterns. First, accuracy was reduced as the length of the sequence increased. Second, the model failed to accurately encode stimuli that were presented later in a given sequence. Essentially, the neural code became so dense that it lost the ability to incorporate additional information. Using this model as a basis for working memory saturation, we expect schizophrenia patients to show (1) deficits in longer sequences and (2) deficits that reflect errors in recall for items that are presented later in the sequence.

Another aspect of significant importance when studying performance deficits in schizophrenia subjects is that antipsychotic medications can have deleterious effects on motor components of the task. This could cause response inaccuracies due to eye–hand coordination rather than a cognitive deficit in working memory. In the present study, we use a simple method to calculate motor related error in targeting by estimating the motor error using data from both correct and incorrect choices of target. This procedure also allows for subsequent isolation and analysis of the mnemonic choice errors in individual trials.

2. Methods

2.1. Subjects

Clinically medicated chronic schizophrenia patients (11 women, 10 men) were recruited from a psychiatric residential care facility and a Northwestern Memorial Hospital outpatient unit. All subjects met DSM IV diagnostic criteria for schizophrenia and provided written informed consent to a protocol approved by the NMH IRB. An interview and patients' records were used to screen out patients with brain damage, serious head injury, mental retardation, illegal drug use, or tardive dyskinesia. Normal controls (11 women, 5 men) were recruited and screened for head injury, drug use and history of mental illness in self or family. Controls were interviewed to rule out DSM IV Axis 1 and 2 psychiatric disorders.

For the 21 schizophrenia patients, we assessed their general level of functioning (Schneider and Struening, 1983). On a five-point scale, schizophrenia patients had an average global general functioning rating of 4.2 (S.D., 0.3) with mean subscale ratings as follows: work skills, 3.8 (S.D., 0.7); physical functioning, 4.9 (S.D., 0.2); personal care, 4.7 (S.D., 0.4); interpersonal, 3.5 (S.D., 0.5); social acceptance, 4.6 (S.D., 0.4); activities, 4.4 (S.D., 0.3). All patients were medicated, with an average chlorpromazine-equivalent neuroleptic daily dose of 1054 mg (S.D., 786). The mean age of the schizophrenia patients was 34.9 (S.D., 10.3) and the mean education level was 13.8 (S.D., 2.2) years. The mean duration of illness was 13.9 years. The mean age of the control subjects was 33.1 (S.D., 11.0) years and the mean education level was 14.3 (S.D., 2.5) years. There were no significant statistical differences between the groups in age ($p = 0.53$) and education ($p = 0.08$). Two patients were left-handed while all other participants were right-handed. Informed consent was obtained from all subjects. All participants were paid equally for their participation.

2.2. Apparatus

A Macintosh computer fitted with a "touchscreen" (TrollTouch™, Valencia, CA) presented stimuli. A touchscreen records the point of contact that a person makes on a computer screen. Subjects were seated with their head 45 cm from the computer with their hands resting on the computer desk in front of them. A calibration procedure was administered to ensure that the touch screen was working properly. Calibration involved touching four fixed reference points on the touchscreen. A head and chin rest was used to minimize head movement. For both calibration and testing, subjects used the index finger on their dominant hand to touch the screen.

2.3. Procedure

The basic format of the task proceeded as follows. A trial began with a subject fixating on a point located in the center of the touchscreen. When they were ready, they clicked the computer mouse button in front of them. There was a 1500-ms lag following a mouse click during which only the fixation point was present on the screen. After the lag, the fixation point disappeared and a black target was presented for 800 ms. When the target disappeared, the center fixation point returned for 700 ms. For longer sequences, the presentation of another target for 800 ms followed by the fixation point for 700 ms was repeated until the sequence was completed. Subjects were instructed to remember the sequence and location of the targets. The presentation of the target sequence was followed by a response screen in which all possible target locations were displayed for 2000 ms. After 2000 ms, the targets turned from black to gray as a cue to touch the first target in the remembered sequence. After a touch was recorded, the targets turned black again. They remained black for another 2000 ms and then turned gray again as a cue to touch the second target in the sequence. This pattern continued until the subject had been given the opportunity to respond once for each target in the sequence.

Tasks were adapted from a single unit recording study in monkeys by Barone and Joseph (1989) in order to promote comparison with animal neurophysiology. All subjects were allowed to practice the test until they understood the directions. There were four different target conditions (sequence lengths 1–4). Sequences of lengths 1–2 were presented in blocks of 12 trials while sequences of lengths 3–4 were presented in blocks of 24 trials. Each subject was tested on 1 block of each trial type. The spatial layout of the possible target positions was identical for the one-, two- and three-target conditions. Two of the three target positions were 3 cm below and 11 cm to the right (R) or left (L) of the center fixation point. The third target position (U) was located 6.5 cm directly above the fixation point (forming the points of a triangle R–L–U). For the four-target condition, the target positions were arranged in a square format. The two upper positions (UL and UR) were 6 cm above the fixation point and the two lower positions (LL and LR) were 6 cm below the fixation point. The horizontal distance between the two top or bottom positions was 11.4 cm. The procedure is illustrated in Fig. 1. The fixation point was a centrally located circle 20 pixels in diameter (approximately, 0.8 cm). The order of presentation of the target sequence conditions was counterbalanced across subjects. Sequences were randomly selected. No target was ever repeated within a sequence.

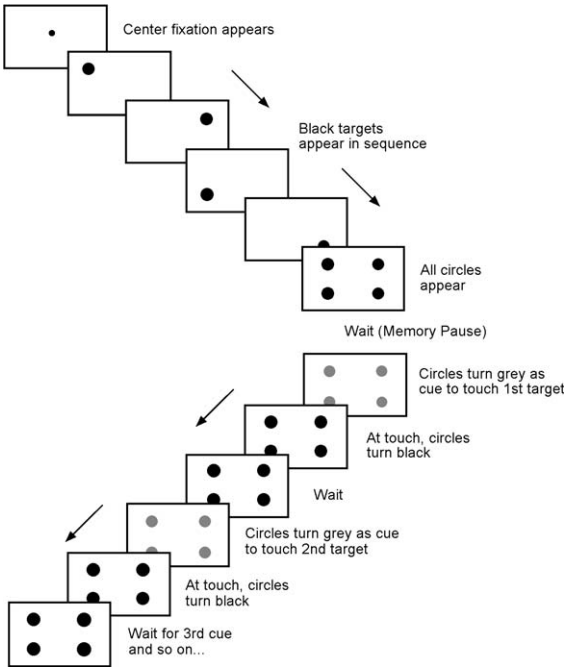

Fig. 1. Diagram of the task for the four-target condition. Time progresses from top to bottom. The rectangles represent the stimulus screen at progressive time points. The task begins with a fixation point and the subject presses the computer mouse button to initiate a trial. Subjects are then shown a sequence of four targets followed by a memory delay period. After this memory period, they must point out the targets in the correct serial order by pressing the target location on the touch sensitive screen. Responses are cued by the dimming of the target positions. All target positions remain visible throughout the response period.

2.4. Scoring

Subjects were instructed to touch the center of the chosen target to indicate their response. We measured the Euclidean distance in pixels between the center of the correct target (a circle 40 pixels in diameter, approximately 1.6 cm) and the point of the subject response. This measure was defined as 'error distance'. Error distance was subsequently divided into two categories: sensorimotor and mnemonic choice errors. Sensorimotor error was defined as error due to motor inaccuracy in placing the finger accurately on the desired location. Mnemonic choice error was defined as error due to an incorrect choice of target. For an incorrect response, this number would be quite large (>100 pixels, approximately 4.0 cm) while the values for a correct response are quite small (0–30 pixels).

The difference between the "mnemonic choice" and "sensorimotor accuracy" components of a response can be illustrated clearly in histograms of error distance. Fig. 2 summarizes the responses of a schizophrenia patient for the four-target sequence condition. The cluster of responses around the error distance = 0 represent correct responses with a small "sensorimotor accuracy" component. The responses clustered around $x = 300$ pixels show the choice of a target that was directly horizontal or vertical to the correct target, while the responses clustered around $x = 425$ show a choice of the target that was directly diagonal. These

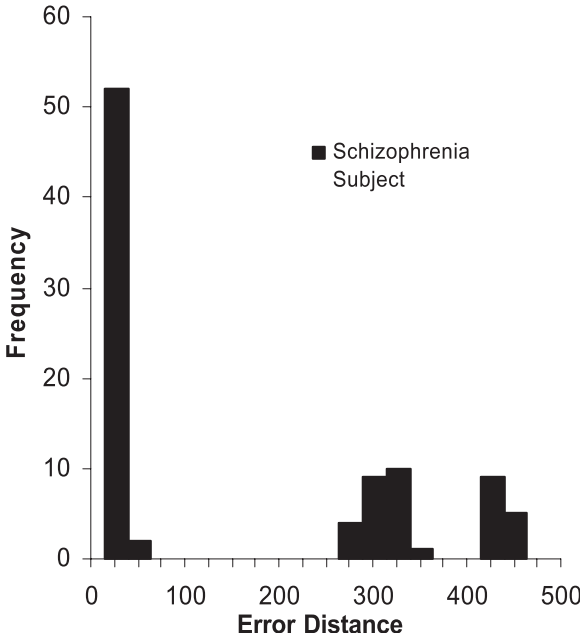

Fig. 2. Widely separate distributions of correct and error response distances. The histogram shows the frequency of errors as a function of their distance in pixels from the correct target choice. The cluster of responses around the error distance = 0 represent correct responses with a small "sensorimotor accuracy" component. The responses clustered around $x = 300$ pixels show the choice of a target that was directly horizontal or vertical from the correct target. The cluster around $x = 425$ pixels shows a choice of the target that was directly diagonal. These values are as expected; a mnemonic choice error in this sequence condition (sequence length of 4) indicates that the subject has responded incorrectly and placed their response in close proximity to one of the other targets. Two of the incorrect targets are 300 pixels away from the correct target while one is 425 pixels away. The range of values for the correct responses appears to be smaller than the range for incorrect responses only because all error distances were calculated as positive values from the center of the correct target. Error bars indicate standard error.

values are as expected; a mnemonic choice error in this sequence condition (sequence length of 4) indicates that the subject responded incorrectly and placed a response close to one of the other targets. Two of the incorrect targets are 300 pixels away from the correct target while one is 425 pixels away. The range of values for the correct responses appears to be smaller than the range for incorrect responses in Fig. 2 because all error distances were calculated as positive values from the center of the correct target.

In estimating the sensorimotor error, we assumed that the target location closest to the subject's response point was the chosen target. We then calculated the average distance between the subject's response point and the center location of the closest target. This gave us an indication of how accurate a subject was in touching a target once a target had been chosen. In calculating mnemonic choice error, we determined which target constituted a correct response based on the sequence presented and calculated the average distance between the subject's response and the center location of the correct target. If this distance was greater than 100 pixels, the response was classified as a mnemonic error.

2.5. Statistical analysis

Repeated-measures ANOVA was used to compare schizophrenia and control groups with respect to sensorimotor error, mnemonic choice error, and the number of errors at each position in the sequences of length 4. For the sequence of length 4, we performed a linear trend analysis to test for correlation between error rates and sequence position. In cases of significant interactions, independent sample *t*-tests were used for clarification.

3. Results

3.1. Group differences in motor and mnemonic errors

Schizophrenia patients did not show evidence of sensorimotor problems in performing the experimen-

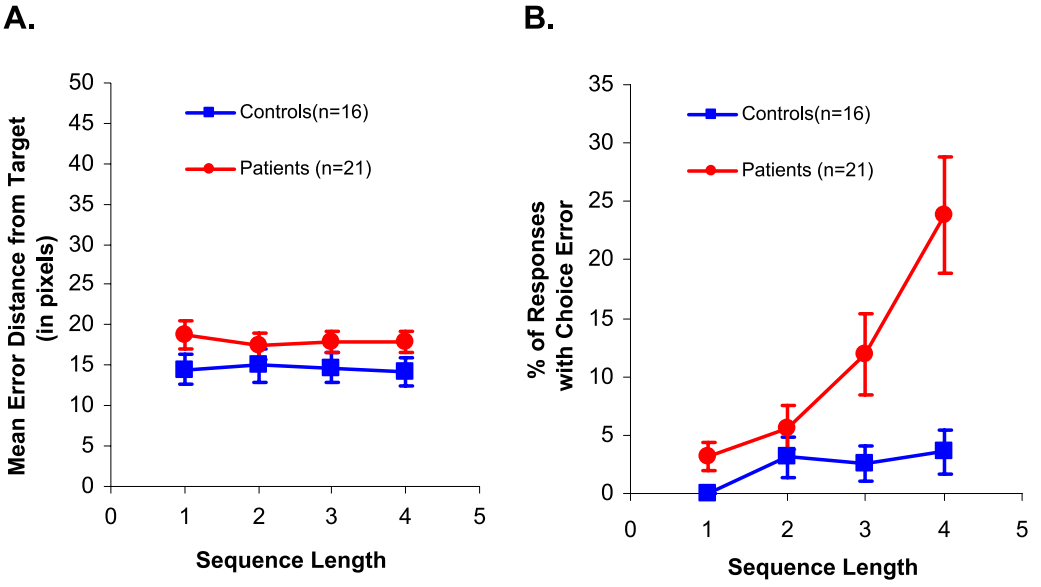

Fig. 3. Percentage error rates for sensorimotor (A) and mnemonic choice (B) components of response. (A) shows the lack of difference in sensorimotor error between the two groups ($F[1,35]=2.19$, $p=0.15$). One pixel was approximately 0.4 mm. (B) shows the % of mnemonic error for the two groups as a function of sequence length. There was a main effect of diagnosis ($F[1,35]=11.26$, $p=0.002$). Schizophrenia patients made more mnemonic choice errors than did the controls. There was a main effect for the target sequence conditions ($F[3,105]=15.73$, $p=0.0001$). Longer sequences elicited more mnemonic choice errors than shorter sequences. There was also an interaction between the diagnosis and sequence condition ($F[3,105]=5.57$, $p=0.001$), indicating that as the number of targets increased, schizophrenia patients made significantly more mnemonic choice errors than controls. Error bars indicate standard error.

tal task (Fig. 3A). A repeated-measures ANOVA on the mean error distance of the sensorimotor accuracy component for all responses showed no main effect of diagnosis on the sensorimotor accuracy component ($F[1,35]=2.19, p=0.15$). Schizophrenia patients were as accurate as controls in moving their fingers to the chosen targets. There was no main effect of the sequence conditions ($F[3,105]=0.69$, $p=0.56$) indicating that motor sloppiness did not increase as the number of targets increased. There was no interaction between diagnosis and sequence condition ($F[3,105]=0.64, p=0.59$). These results indicate that schizophrenia patients are able to move their fingers accurately to visual targets.

To examine the 'mnemonic choice' component, a repeated-measures ANOVA was conducted on the number of incorrect responses (those that had error distance values greater than 100 pixels) for sequence conditions 1–4. There was a main effect of diagnosis ($F[1,35]=11.3$, $p=0.002$). Schizophrenia patients made more mnemonic choice errors than did the controls. There was a main effect for the target sequence conditions ($F[3,105]=15.7$, $p=0.0001$). Longer sequences elicited more mnemonic choice errors than shorter sequences. There was also an interaction between the diagnosis and sequence condition ($F[3,105]=5.57$, $p=0.001$), suggesting that as the number of targets increased, schizophrenia patients made significantly more mnemonic choice errors than controls. This conclusion was confirmed using post hoc two-tailed *t*-tests to compare the two control groups at each sequence length. There were no significant group differences at sequence length of 2 ($t[35df]=0.88$, $p=0.30$) but both sequence length 3 ($t[35df]=2.22$, $p=0.004$) and length 4 ($t[35df]=3.38$, $p=0.003$) showed significant

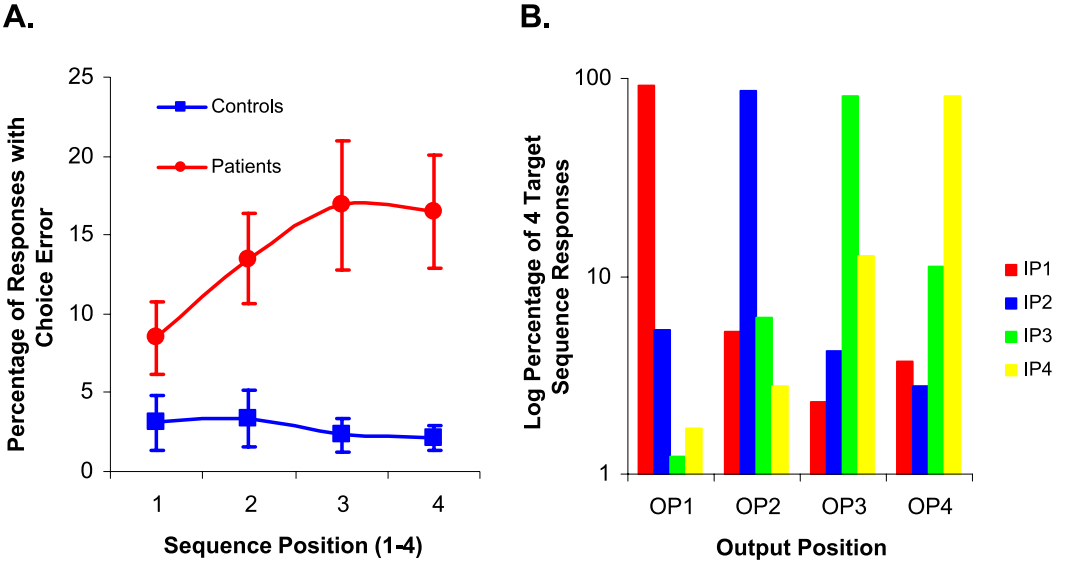

Fig. 4. Patterns of error distribution seen in the schizophrenia population increased for later positions in the sequence. Panel A shows the percentage of responses with mnemonic error for both groups as a function of the sequence position of the target in the sequence 4 condition. There was a significant main effect for diagnosis ($F[1,35]=9.38$, $p=0.005$) indicating that schizophrenics made more choice errors than controls. For within-subject contrasts, a test for a linear effect showed a trend level significance for position ($F[1,35]=3.65, p=0.07$) indicating that later positions had more choice errors. The interaction between diagnosis and position for the linear trend analysis was significant ($F[1,35]=6.76, p=0.02$) indicating that schizophrenics performed worse than controls in the later positions. Error bars indicate standard error. The errors show an interesting pattern of clustering illustrated in Panel B. This logarithmic plot shows the distribution of responses for schizophrenia patients plotted by sequence position for the sequence 4 condition. Input position (IP) refers to the serial position of an element in the initial sequence presentation (in the sequence presentation ABCD, element "B" occupies IP2). Output position (OP) refers to the serial position in the response sequence that a subject provides from memory. A correct response matches OP with IP. Choice errors have discrepancies in OP and IP that cluster around the OP. As anticipated from Panel A, the correct responses of schizophrenia subjects decrease steadily with sequence position and then level off at about 83% for positions 3 and 4. Choice errors are more frequent adjacent to the correct choice.

differences. For sequences of length 1, a single sample *t*-test was used to compare schizophrenic responses against the null hypothesis because the control subjects had no errors (and thus no variance) ($t[20df] = 2.61$, $p = 0.020$). These results (plotted in Fig. 3B) show schizophrenic patients make substantial errors in their choices of spatial targets.

3.2. Positional error analysis

We also examined the distribution of mnemonic errors across the different positions in a sequence (i.e., in a sequence of ABCD, the letter A is in position 1, B is in position 2, etc.). A repeated-measures ANOVA was done for the number of choice errors at each position in the trials of sequence length 4. There was a significant main effect for diagnosis ($F[1,35] = 9.38$, $p = 0.005$) indicating that schizophrenia patients made more choice errors than controls. For within-subject contrasts, a test for a linear effect showed a minor effect of position ($F[1,35] = 3.65$, $p = 0.07$) indicating that later positions had more choice errors. The interaction between diagnosis and position for the linear trend analysis was significant ($F[1,35] = 6.76$, $p = 0.02$) indicating that schizophrenia patients performed much worse than controls in the later positions (Fig. 4A). This point was supported by post hoc two-tailed *t*-tests comparing the groups at each position. The tests show a minor effect at position 1 ($t[35df] = 1.82$, $p = 0.08$), a greater effect at position 2 ($t[35df] = 2.75$, $p = 0.01$) and even greater effect at position 3 ($t[35df] = 3.05$, $p = 0.005$) and position 4 ($t[35df] = 3.39$, $p = 0.003$).

It is also interesting to illustrate the distribution of responses for schizophrenia subjects plotted by sequence position for the sequence 4 condition (Fig. 4B). Input position (IP) refers to the serial position of an element in the sequence presentation (in the sequence presentation ABCD, element "B" occupies IP2). Output position (OP) refers to the serial position in the response sequence that a subject provides from memory. A correct response matches OP with IP. Choice errors have discrepancies in the OP versus IP relationship. As expected from the plot in Fig. 4A, the correct responses of schizophrenia subjects decreased with sequence position, leveling off at about 83% for positions 3 and 4 (Fig. 4B). The clustering of choice errors around the correct response document a tendency for subjects to confuse targets with closer input positions rather than those with input positions farther away in the sequence, a result that is consistent with Henson's (1998) Start–End model.

4. Discussion

The present results demonstrate that schizophrenia patients have considerable difficulty performing a serial order working memory task for spatial location. In line with our predictions based on the Manoach (2003) capacity model (see Introduction), mnemonic choice error increased dramatically and reached nearly 25% when a sequence of four targets was presented (Fig. 3B). Capacity for the processing of serial working memory appears to be a function of the point at which the system becomes saturated with activity. Saturation leads to increased error in the schizophrenia population for memory loads at which normal subjects have little difficulty. Our results agree with the capacity model's prediction that early saturation reveals itself as poor performance at lower serial order working memory loads.

We also found that the errors made by schizophrenia patients were more frequent for the later positions in the longest (four-target) sequence (Fig. 4A). This result confirms another prediction made in Introduction, one based on the Beiser and Houk (1998) network model of serial order encoding. As the number of spatial locations becomes larger, this model enlists a greater number of neurons and circuit modules to encode the sequence. Its capacity eventually saturates, and stimuli that are presented later in the sequence become poorly encoded. The agreement of error patterns in the model with the behavioral data from the current study (Fig. 4A) supports the concept that spatial serial working memory deficits in schizophrenia subjects are due to saturation of the relevant network at a lower capacity.

Investigations of working memory capacity and its relationship to schizophrenia may serve to link clinical, behavioral and physiological data. Based on the physiology of BOLD fMRI brain imaging, the capacity model makes important predictions about the behavior of both healthy and compromised individuals (Manoach, 2003). Tasks that challenge serial working memory capacity are accompanied by decreased ac-

tivity (local blood flow) in dorsolateral prefrontal cerebral cortex. This drop-off in activity may reflect a shift in strategy to confront the higher capacity demands of the task at hand. A strategy shift would most likely involve the recruitment of alternative neural networks for task completion, which could explain the drop-off in activity in one brain area accompanied by increases in others (Manoach, 2003). A PET study of early Parkinsonian patients doing the Tower of London task (Dagher et al., 2001) showed that patients diminish caudate nucleus activation while recruiting the hippocampus. The interpretation was that Parkinson's patients can employ a shift in strategy to compensate for faltering processing capabilities in their basal ganglia. Although schizophrenia and Parkinson patients differ on many measures of cognitive functioning, the critical point is that poor performance of one brain network can elicit a shift in cognitive strategy that utilizes an alternative network.

It is interesting to note that the capacity model does not speak specifically to where along the processing stream problems are occurring. A deficit in performance could arise from problems with the detection of a target sequence, its encoding into working memory, maintenance of that working memory over time, recall or decoding of the working memory, its execution, or any combination of these basic stages of processing. Conceivably, difficulties at different stages in processing would lead to different patterns of error. The error pattern seen in our results (Fig. 4A) are consistent with the basic error pattern seen in the Beiser–Houk network model when the model is saturated with input and incapable of detecting and encoding all relevant stimulus characteristics. This finding leads us to propose that one fundamental problem in schizophrenia may be faulty detection or encoding. It would be interesting to test whether the Beiser–Houk model reproduces the clustering of choice errors around the correct response shown in Fig. 4B. Although encoding is represented in the thalamo-cortical stage of the network model, the detection of the serial order of targets is specific to caudate nucleus, and maintenance is thought to engage several reciprocal excitatory circuits including a linkage through the cerebellum. These ideas might be tested with functional imaging.

One feature of serial order processing that is not explained by the Beiser–Houk model is the recency effect, or attenuation of error for the most recently presented items in a list. This is an important issue to consider since schizophrenia patients show intact recency effects (Manschreck et al., 1991; Elvevag et al., 2003). Our data also appear to be consistent with an intact recency effect. In the four-target condition, positional error showed a steady increase only up to position 3; in position 4, it leveled off and may even have declined (Fig. 4A). As discussed earlier, tasks that challenge working memory capacity are accompanied by imaging changes consistent with a shift in strategy that recruits alternative networks in different parts of the brain. The Beiser–Houk model would have to incorporate those additional networks in order to address the phenomena of strategy shift.

The concept of strategy shift may be especially relevant when considering permutations of the delayed recall task, such as the probed recall paradigm (Elvevag et al., 2003). This paradigm tests knowledge of sequence order by probing one position at a time rather than by having the subject recall the entire sequence. Schizophrenia subjects made more errors for elements that had to be remembered longest, suggesting that the deficit is one of working memory maintenance. However, it is unclear whether a subject who is recalling an entire sequence, as opposed to just one element within it, would use the same strategy. Although the maintenance hypothesis might also account for some of the current findings, the potential discrepancy in mnemonic strategy makes it difficult to compare across tasks. In addition, Elvevag et al. (2003) used verbal stimuli (letter strings) while our task used spatial stimuli (targets). While we cannot rule out the possibility that subjects used a verbal strategy to memorize locations, it seems unlikely given the nature of the stimuli used.

The above considerations highlight some of the advantages of using an interdisciplinary approach in attempts to understand serial order working memory problems. Behavioral studies document how performance relates to task design and difficulty. Functional brain imaging has great potential for highlighting differences in processing strategies by revealing activity in alternative brain networks in patients versus controls, or in response to changes in task difficulty. Network modeling has potential for pinpointing discrete stages of signal processing. By making parallels between behavioral work, imaging and network modeling, we encourage complementary studies in all

three fields that may lead to a more complete understanding of working memory operations and the deficits seen in schizophrenia.

To summarize the strengths and limitations of this study, one positive feature is the use of spatial targets to assess serial order processing in schizophrenia. This method may open the possibility of exploring whether or not generalizable deficits in serial order processing contribute to some of the language and thought disorders that are prominent in schizophrenia. A second advantage is that use of spatial targets allows ties to animal neurophysiology and thus opens the possibility of investigating deficits in neural signal processing mechanisms that might lead to an animal model of schizophrenia or its treatment. One limitation is that the spatial pattern used here may have been too simple to eliminate the possibility that the patients used a verbal strategy. An imaging study would help to clarify this and related issues. Another limitation is that the network model used to guide the interpretation of our data does not explain the recency effect that is seen both in language tasks and in our spatial serial order data.

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