



The role of stimulus salience in CPT-AX performance of schizophrenia patients

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Abstract

CPT-AX performance deficit in schizophrenia is well documented but it is unclear what causes this impairment. Past studies have focused on the roles of sustained attention and context processing in CPT-AX but the role of working memory (WM) has not been fully examined even though encoding and maintenance of the cue in WM may be critical to CPT-AX. The major goal of this study was to investigate the effects of stimulus encoding in WM on CPT-AX. Encoding was manipulated by presenting different colored (i.e., salient) cue stimuli on 20% of the trials. WM maintenance was manipulated by varying the cue–target interstimulus interval (ISI). A control task (CPT-Single) that does not require WM but assesses sustained attention was also administered. Schizophrenia patients (SZ) were impaired compared with normal controls (CO) on the CPT-AX overall but not in CPT-Single. For both groups, CPT-AX accuracy improved on salient cue trials in the long ISI condition. In the short ISI condition, where accuracy was already high, the cue saliency effect was observed in the faster RT and SZ benefited significantly more than CO. The effect of target salience was not observed in the CPT-Single, which assesses sustained attention. These results suggest that the facilitation of WM encoding by enhancing cue salience may be a key to improving CPT-AX performance. © 2005 Elsevier B.V. All rights reserved.

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1. Introduction

Schizophrenia patients have shown deficits in various forms of the Continuous Performance Task (CPT) and depending on the exact task structure, impairments of sustained attention, context proces-

sing, working memory and/or other functions have been implicated. The basic form of CPT (CPT-Single) is thought to measure sustained attention in schizophrenia (Nestor et al., 1990; Nuechterlein, 1991; Rutschmann et al., 1977). Sustained attention involves the ability to remain vigilant over long periods of time and the ability to prepare and maintain readiness for response. In CPT-Single, individuals monitor a random series of single numbers or letters, presented continuously often at a rate of approximately one

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per second. Individuals must detect the target while withholding responses to non-targets. The task difficulty can be manipulated by degrading the stimuli (e.g., Nuechterlein et al., 1983). Schizophrenia patients show deficits in CPT-Single, but they show deficits more consistently in the other versions of the CPT (CPT-AX or CPT-IP) (Chen and Faraone, 2000), which require individuals to maintain stimulus items in temporary memory store. For example, in CPT-AX, individuals are asked to respond to letter 'X' only when it follows the letter 'A'. Thus, in CPT-AX, individuals must maintain the task instruction ('context') in working memory while attending continuously to the letters that are presented. Similarly, in CPT-IP, individuals are asked to respond if there are two consecutive identical stimuli.

It has been suggested that CPT-AX deficits in schizophrenia stem from an inability to maintain context (i.e., task instruction) (e.g., Cohen et al., 1999; Cohen and Servan-Schreiber, 1992). In CPT-AX, one must maintain the task instruction of responding only when a specific stimulus ('A') is followed by another specific stimulus ('X'), as well as holding in mind, each stimulus representation until a decision to respond or not can be made. Several functions are critical to successful performance in CPT-AX; encoding the stimulus (task-relevant information), maintaining task instruction and the stimuli in working memory (Oades, 2000), and generating appropriate response while inhibiting inappropriate response. Any difficulty at each step could result in an error. Thus, it is important to understand the specific role of each component in CPT-AX.

A few studies have attempted to investigate the underlying causes of CPT-AX deficit in schizophrenia by analyzing each component. Servan-Schreiber et al. (1996) modified the traditional CPT-AX by manipulating the frequency of cue–target sequence (A–X) and the delay between the cue and the target. The modified CPT-AX increased the frequency of the cue–target sequence to force individuals to use the cue information to inhibit habitual but inappropriate responses (responding to 'X' following a non-cue 'B'). To manipulate the difficulty of context maintenance, two delay conditions were used. In this study, schizophrenia patients showed a selective deficit when they were required to make a response based on task-relevant information (cue 'A') and when the

cue–target interval was increased. Similar findings have been reported in other studies (e.g., Barch et al., 2001, 2003; MacDonald and Carter, 2003). Therefore, schizophrenia patients seem to have difficulties maintaining task instructions in working memory ('maintenance difficulty') and using this information to produce appropriate response. However, maintenance difficulty may not be the only important contributor of CPT-AX deficit in schizophrenia. Elevevag et al., (2000) reported that the delay in CPT-AX was not necessary to impair the performance of schizophrenia patients. Thus, it is very possible that an additional component such as encoding of the cue may also contribute significantly to the CPT deficits in schizophrenia.

There is no doubt that encoding difficulties play a central role in WM deficits of schizophrenia patients (Fuller et al., 2005; Lencz et al., 2003; Tek et al., 2002). However, no study has explicitly examined the role of stimulus encoding in CPT-AX. To investigate the role of encoding difficulty in CPT-AX in schizophrenia patients further, we examined the effects of presenting salient stimuli. We manipulated the attentional salience of the cue to test whether a salient cue could draw attention more efficiently to the stimulus at the encoding stage. Such stimulus-driven attention at encoding stage could improve the CPT-AX performance overall in individuals who are known to have attention and WM deficits.

2. Methods

2.1. Participants

Sixteen outpatients (5 women and 11 men), who met the Diagnostic and Statistical Manual of Mental Disorder—4th edition (DSM-IV) (American Psychiatric Association, 1991) criteria for schizophrenia were recruited from the Outpatient Clinic of the Vanderbilt Psychiatric Hospital, Nashville, TN. Fourteen healthy controls (7 women and 7 men) were recruited through advertisements from the local community. The exclusion criteria for all participants were: (1) substance use within the past 6 months, (2) head injury, (3) neurological disorder and (4) mental retardation. In addition, control participants were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder or

(2) a family history of psychotic illness. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) were used to evaluate symptom severity in the patients. Mean BPRS total score was 27.0 (± 16.7). Mean SANS score was 30.2 (± 20.7), and mean SAPS score was 29.8 (± 25.4). All patients were taking atypical antipsychotic drugs (clozapine, risperidone or olanzapine) at the time of testing. Mean illness duration of the patients was 12.8 (± 8.2) years.

SZ group and CO group were comparable in age (38.5 years, S.D.=9.9 and mean=34.5 years, S.D.=9.8, respectively, $t_{28}=1.1$, NS) and education (12.6 years, S.D.=1.9 and mean=14.6 years, S.D.=1.8, respectively, $t_{28}=-2.9$, NS). Three SZ patients were left-handed and one SZ patient was ambidextrous. All other participants were right-handed. There was no significant group difference in the proportion of women ($\chi^2=1.55$, NS) or right-handedness ($\chi^2=1.91$, NS). All participants were given a complete description of the procedure and they gave written informed consent. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All subjects were compensated for study participation.

2.2. Continuous Performance Task (CPT)

Three versions of CPT were administered in this study and the order of three tasks was counterbalanced across subjects. To test the effect of stimulus salience on CPT performance, 20% of trials in each task contained a salient stimulus. In CPT-AX, a red cue (red A) was used in 20% of the cue–target sequence trials. In CPT-Single, a red target (red X) appeared in 20% of the trials. The detailed description of each task is provided below.

2.2.1. Apparatus and procedure

All experiments were conducted on a Macintosh iMac computer with a 15-in. screen. MacStim™ (White Ant Publishing, Melbourne, Australia) was used to program the tasks. Participants were tested individually in a quiet room with normal interior lighting. The unrestricted viewing distance to the screen was 50 cm.

At the beginning of each task, participants fixated at the center of the screen. When they were ready to begin, they pressed the spacebar to initiate the trial. Then a letter (visual angle=1.1°) was presented at the center of the screen for 250 ms with an interstimulus interval (ISI) of either 1000 ms or 3000 ms before the next letter appeared. For CPT-AX, participants were asked to press the key if the target (letter X) was followed by the cue (letter A) regardless of the color of the cue (red or black). For CPT-Single, participants were asked to press the key whenever they saw the target (letter X) regardless of its color. It is important to note that participants were told that the color of the letters is unimportant in performing the task.

2.2.2. CPT-AX

Single letters were presented sequentially at the center of the screen for 250 ms each. Participants were asked to respond if they saw an X following A, regardless of the color of the cue (red or black). The standard procedure for CPT-AX was modified in 2 ways. First, the frequency of cue–target sequences (A–X) was increased so that these occurred 70% of the total trials. A randomly chosen non-cue letter preceded the target (e.g., B–X) in 10% of trials, the cue was followed by a distracter (e.g., A–Y) in another 10% of trials, and a randomly chosen non-cue letter preceded a distracter (e.g., B–Y) in the remaining 10% of trials. Increasing the frequency of cue–target sequences served to engage participants more actively in the task and to introduce a strong bias or tendency to respond to occurrence of the letter X. The second modification involved varying the ISI (i.e., delay) to test participants' ability to maintain cue information over time, to test the working memory component in CPT-AX. Two ISIs were used: 1000 ms and 3000 ms. Each participant was tested in 2 blocks of CPT-AX task, one with the short ISI (delay=1000 ms) and the other with the long ISI (delay=3000 ms). In each case, the proportion of the target and non-target events remained the same (A–X, 70%; B–X, 10%; A–Y, 10%; B–Y, 10%).

CPT-AX with ISI of 3000 ms had 100 trials. CPT-AX with ISI of 1000 ms had 200 trials. CPT-AX with 3000 ms ISI had fewer trials than CPT-AX with 1000 ms ISI so that the total task time could be equal per condition.

2.2.3. CPT-Single

Single letters were presented centrally on screen for 250 ms each with an ISI of 1000 ms and participants were asked to identify the target (letter X) regardless of its color. There were 273 trials in CPT-Single.

3. Results

3.1. Global performance of schizophrenia (SZ) and control (CO) groups in CPT

Overall hit rate, overall false alarm rate, and reaction time (RT) are presented in Table 1 and percentage errors for specific error types are presented in Table 2. Repeated-measures ANOVA was used to examine whether SZ showed different performance in the overall hit rate, overall false alarm, and RT of CPT-AX compared with CO. For overall hit rate, there was a main effect of the diagnostic group in CPT-AX; SZ patients were less accurate in detecting the AX sequence than controls ($F(1,28)=8.84, p<.01$). There was no other significant effect. There was also a main effect of the delay; both groups were less accurate with the longer delay ($F(1,28)=150.36, p<.0001$). The delay-by-group interaction was not significant. This suggests that the delay did not have a differential effect on the SZ group compared with the CO group.

For RT on the CPT-AX, SZ patients were slower than the CO participants overall ($F(1,28)=12.30, p<.01$). There was also a main effect of the delay; both groups were slower in the longer ISI condition ($F(1,28)=20.68, p<.001$). A significant delay-by-group interaction ($F(1,28)=5.08,$

Table 1
Performance of SZ and CO groups in CPT

	SZ	CO
<i>CPT-AX with ISI 3000 ms</i>		
Hit rate	.89 (.10)	.96 (.08)
False alarm rate	.07 (.11)	.02 (.04)
RT (ms)	661 (211)	461 (85)
<i>CPT-AX with ISI 1000 ms</i>		
Hit rate	.91 (.08)	.98 (.02)
False alarm rate	.09 (.11)	.03 (.04)
RT (ms)	479 (85)	400 (83)
<i>CPT-Single</i>		
Hit rate	.95 (.06)	.99 (.01)
False alarm rate	.12 (.08)	.05 (.06)
RT (ms)	419 (78)	407 (84)

Values are given as mean (S.D.).

Table 2

Percentage errors in non-target trials in CPT-AX and CPT-Single

		SZ	CO
CPT-AX with ISI 3000 ms	A–Y	1 (3)	2 (6)
	B–X	15 (26)	4 (7)
	B–Y	3 (5)	0 (0)
CPT-AX with ISI 1000 ms	A–Y	7 (8)	4 (6)
	B–X	17 (26)	3 (6)
	B–Y	4 (8)	0 (0)

Values are given as mean (S.D.).

$p<.05$) indicated that increasing the delay between the cue and the target had a larger effect on SZ patients than in CO.

No significant main effect was found in the overall false alarm rate. However, when we separated each type of errors, SZ group made more BY errors than did CO group in CPT-AX with ISI 3000 ms ($t_{28}=-2.4, p<.05$; see Table 2). In CPT-Single, group difference was significant only in the false alarm rate ($t_{28}=2.25, p<.05$), showing that SZ group made more false alarm responses than did the CO group (see Table 1).

3.2. Effect of stimulus saliency on CPT-AX

The effects of the stimulus saliency were examined by comparing the trials with the salient stimuli (i.e., infrequent red letters) with those trials with regular stimuli (i.e., black letters) using repeated measures ANOVA (see Fig. 1).

For CPT-AX with ISI 3000 ms, SZ patients were less accurate than the CO ($F(1,28)=5.01, p<.05$) in detecting the AX sequence, regardless of cue saliency (i.e., the color of the cue). The main effect of the cue saliency ($F(1,28)=12.28, p<.001$) showed that salient cues (i.e., red As) improved the performance of both groups (Fig. 1a). The group-by-cue saliency interaction was not significant. SZ patients showed slower RT than did the CO ($F(1,28)=10.89, p<.01$) but there was no main effect of cue saliency and no group-by-cue saliency interaction on the RT (see Fig. 1b).

For CPT-AX with ISI 1000 ms, SZ group was less accurate than CO group ($F(1,28)=10.98, p<.01$), but there was no main effect of cue saliency and no group-by-cue saliency interaction (Fig. 1c). However there was a main effect of the diagnostic group on the RT ($F(1,28)=5.95, p<.05$) and a main effect of cue saliency on RT ($F(1,28)=16.58, p<.001$). SZ group was slower than CO group in detecting targets and both groups were faster at detecting the target in salient cue trials. There was also a group-by-cue saliency interaction on RT ($F(1,28)=5.32, p<.05$) such that the saliency effect was larger for the SZ group (Fig. 1d).

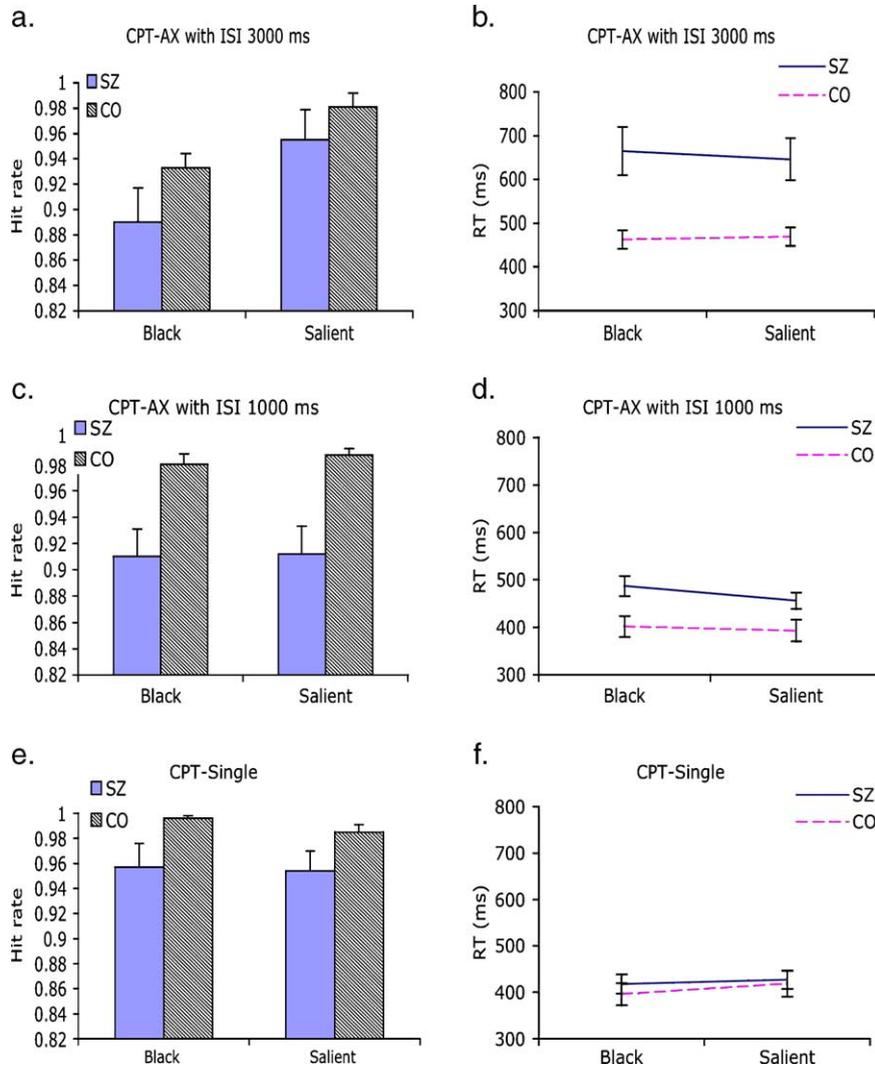


Fig. 1. Performance of CO group and SZ group in CPT. (a) Accuracy in CPT-AX with ISI 3000 ms. (b) RT in CPT-AX with ISI 3000 ms. (c) Accuracy in CPT-AX with ISI 1000 ms. (d) RT in CPT-AX with ISI 1000 ms. (e) Accuracy in CPT-Single. (f) RT in CPT-Single. Error bars represent the standard error of the mean.

In CPT-Single, there was neither group difference nor cue saliency effect on accuracy. Unexpectedly, both groups were slower when the salient stimulus (i.e., red X) was presented ($F(1,28)=7.57, p<.05$). See Fig. 1e and f.

4. Discussion

This study investigated the effects of stimulus saliency at encoding stage on CPT-AX performance. Schizophrenia patients showed improvement in CPT-

AX when the cue (critical task-relevant information) was made more salient (i.e., infrequently presented red A) to increase the stimulus-driven attention at encoding stage. Although the effect of cue saliency was found in both ISI conditions of CPT-AX, its effect was manifested differently. In the longer delay condition, the cue-saliency effect was observed in the increased accuracy in both groups. This effect was not a result of a speed-accuracy trade-off. In the CPT-AX with short delay, the cue-saliency effect was observed in faster RTs while the accuracy remained

unchanged and this effect was larger in SZ than CO. What is clear is that SZ benefit from cue saliency either in terms of increased accuracy or faster RT.

It is important to note that the benefit of the stimulus saliency was observed either in terms of increased accuracy or faster RT. Past studies of CPT performance in SZ report accuracy measures but not RTs (e.g., Chen and Faraone, 2000). However, it is also possible that group differences may not be detected when *each group trades speed for accuracy differently* (Chee et al., 1989). Therefore it is crucial to report RT data along with accuracy. Our data suggest that speed and accuracy may be affected differently in SZ depending on the delay between the salient cue and the target in CPT-AX and underscores the importance of measuring both speed and accuracy.

The stimulus saliency did not have the same effect in CPT-Single, which is thought to tap mostly sustained attention rather than WM or context maintenance. Salient targets in CPT-Single did not affect accuracy, but surprisingly they slowed down performance of both groups. Although this result is completely unexpected, similar finding has been reported. Goodin et al. (1996) showed that reaction time for rarely presented stimuli was slower than for frequent stimuli in the choice reaction time task. It is possible that the novelty of the salient target may momentarily inhibit the behavioral response while participants decide on the correct identity of the target. Further studies are necessary to understand why slow RTs are observed for salient stimuli.

One of the main findings of this experiment was that stimulus saliency aided performance in CPT-AX but not in CPT-Single. In CPT-Single, both groups had over 95% of accuracy when they were given non-salient stimuli so there is a ceiling effect on accuracy. It is also important to note that CPT-Single does not tap into the same cognitive function as CPT-AX. CPT-AX requires greater goal-directed attention and WM than CPT-Single. One must maintain the preceding cue during the delay in CPT-AX, and actively use this cue to direct attention to the target. In contrast, CPT-Single does not require WM and consequently, stimulus saliency that may aid WM during encoding may play a reduced or negligent role in CPT-Single.

The results of this study suggest that an extrinsic, stimulus saliency facilitates encoding of the task-

relevant information in CPT-AX but it is unclear whether WM maintenance is similarly affected by cue saliency. It is also important to note the fact that the salient feature of the stimulus was task-irrelevant in this context yet it facilitated the task performance. It is possible that schizophrenic patients have inefficient encoding of stimuli, which impairs their performance on a variety of tasks (e.g., Hartman et al., 2003; Tek et al., 2002). Such inefficient encoding may be due to reduced attentional-orienting to the target events, which may then be remediated by increasing stimulus-driven attention. In other words, schizophrenia patients may not be able to guide and control attention via internal goals (or intention) and, as a result, may have difficulties in processing task-relevant information at encoding stage but there is room for improvement if the stimuli themselves are more salient.

It has been shown that “bottom-up” factors may bias encoding of stimuli into WM in healthy individuals (Schmidt et al., 2002; Woodman et al., 2003). Our results suggest that the effects of bottom-up factors in WM may be important contributors to the observed CPT-AX deficits in schizophrenia. The facilitating effects of stimulus saliency in schizophrenic subjects were also observed in visual search tasks (Carr et al., 1998; Mori et al., 1996). These studies implicate that schizophrenia patients may benefit from extrinsically salient stimuli (i.e., bottom-up factors) even when they have difficulties in assigning saliency to stimuli endogenously based on internal goals (i.e., top-down control) (Kapur, 2003).

To summarize, we found that increasing the cue saliency improved the performance of schizophrenia patients in CPT-AX. This suggests the important role of encoding in CPT-AX in schizophrenia. Moreover, schizophrenia patients were as sensitive to implicit “context” (i.e., what color a stimulus is when color is irrelevant to the task goal) as normal controls. This finding also suggests that it is necessary to specify and elaborate the definitions of “context” to better understand context-processing deficits in schizophrenia.

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