

SOCIOAFFECTIVE FACTORS MODULATE WORKING MEMORY IN SCHIZOPHRENIA PATIENTS

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Abstract—Working memory deficit in schizophrenia is a core cognitive feature of the disorder and is reliably associated with abnormalities of the prefrontal circuitry. Working memory deficits are also associated with impaired social functioning and present a major obstacle toward successful rehabilitation in schizophrenia. Although the role of prefrontal cortex in working memory has been extensively investigated, the intricate relations among the prefrontal circuitry, working memory and social behaviors are not clearly understood. In this study, we manipulated social context and observed its effects on spatial working memory. In experiment 1, the effects of social and asocial reinforcements on spatial working memory were examined in schizophrenic patients and healthy controls. The results show that social but not asocial reinforcements facilitated spatial working memory in schizophrenic patients. In experiment 2, the effects of human voice reinforcements (with or without affect) on working memory was investigated. Voice reinforcements did not facilitate working memory relative to the no-reinforcement condition. There was no difference between high-affect vs flat-affect voice conditions. In experiment 3, the effects of direct and indirect social interactions on spatial working memory were studied. Direct but not indirect social interaction facilitated working memory in schizophrenic patients. These results suggest that social context might facilitate working memory in schizophrenic patients perhaps by activating frontal lobe systems. In addition, the possibility of improving cognitive functions such as working memory using seemingly non-cognitive methods might lead to potential remediation strategies. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: schizophrenia, working memory, frontal lobe, social interaction, reinforcement, affect.

Working memory (WM) is an active short-term memory system that keeps track of changing features of stimulus events that are crucial in determining context-relevant responses. It is “a system for the temporary holding and manipulation of information during the performance of a range of cognitive tasks such as comprehension, learning and reasoning” (Baddeley, 1986). In Baddeley’s model of WM, temporary maintenance of information is supported by an active control system termed the central executive and modality-specific subsystems (e.g. verbal articulatory loop, visuospatial sketchpad). Deployment of attentional

resources, selection of control processes/strategies and coordination of information flow from the sub-systems are mediated by the central executive. Without the central executive, behaviors become distractible, stereotypic, perseverative and insensitive to context. This pattern of behaviors is seen in many patients with prefrontal lesions (Freedman and Oscar-Berman, 1986) and a majority of individuals with schizophrenia (see Park and Lee, 2002 for a review; Lee and Park, in press). Obviously, WM is crucial to successful functioning not only for complex cognitive functions under laboratory situations, but also in real-world situations (Cacioppo and Berntson, 2002). Intact WM enables us to initiate appropriate behaviors based on the information being held on-line in real time. Individuals with impairments in WM may have difficulties with a wide range of cognitive functions including language comprehension, problem-solving and planning, which then could lead to reduced social functioning.

Much is also known about the role of the prefrontal cortex (PFC) in WM and its regulation of behavior in non-human primates (see Fuster, 1997; Goldman-Rakic, 1987; 1991) and in humans (D’Esposito et al., 1997; McCarthy et al., 1994; Perlstein et al., 2002; Petrides et al., 1993; Postle et al., 2000; Smith et al., 1996; Wager and Smith, 2003). In nonhuman primates, WM has been studied extensively since the 1930s with the delayed-response task (DRT), first developed by Jacobsen (1935). A prototypical DRT involves the presentation of a stimulus, followed by a short delay period and the subsequent presentation of a set of alternative choices. The animal can select the correct stimulus among the alternatives *if* it can remember both the rules of the task and enough information about the location of the correct stimulus. The entire process calls for the existence of internal representations and the monkey’s ability to use that representation to act appropriately in the absence of external cues. This ability requires the animal to filter out or inhibit irrelevant information and instead focus on the main task. Lesions in the dorsolateral PFC abolish the ability to perform DRT (e.g. Jacobsen, 1935; Blum, 1952; Mishkin, 1957; Funahashi et al., 1989, 1990, 1993).

Lesions in the frontal cortex cause WM deficits but also profound changes in social behavior and emotion (e.g. Fulton and Jacobsen, 1935). The ways in which the frontal cortex regulates social and emotional behaviors are multifaceted. To understand the connection between WM and social/emotional behavior, it is helpful to note the role of PFC in the representation of both internal and external world and the representational guidance of behavior. The PFC is crucial for representing our knowledge of the social

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Abbreviations: DRT, delayed-response task; PFC, prefrontal cortex; RT, reaction time; WM, working memory.

world and social information processing (see Wood, 2003 for a comprehensive review). Consequently, WM deficits—present in individuals with prefrontal abnormalities—may set an upper limit on how much social information can be processed at any given point in time, thereby reducing the ability to guide social, interactional behavior appropriately. Conversely, it may also be useful to ask whether social information processing may modulate WM process by changing activation of the neural network that supports WM. Socially-relevant stimuli may facilitate encoding in WM by increasing stimulus-driven attention to the target (Awh et al., 2000; Awh and Jonides, 2001); spatial attention deploys efficiently to whatever is salient, arousing or novel in the environment.

One very important observation made by Fulton and Jacobsen (1935) in their study of prefrontal lesions is the emergence of social and emotional changes of an anergic quality in the monkey after frontal lobectomy in addition to a loss of WM and increased disinhibition. A variety of sources, ranging from neurophysiological studies of non-human primates to human neuropsychological data, point to evidence linking social functioning and the integrity of the frontal lobe systems (e.g. Jacobsen, 1935; Girgis, 1971; Eslinger and Damasio, 1985).

In this context, studying the functional parcellation of the dorsolateral versus orbitofrontal or ventromedial systems may provide very useful insight into the disintegration and fragmentation of cognitive, affective and social aspects of behavior in schizophrenia patients. Dissociation between spatial WM mediated by the dorsolateral PFC and non-spatial visual short-term memory mediated by the ventromedial/orbitofrontal system has been observed in the monkey (Bachevalier and Mishkin, 1986; Goldman-Rakic, 1987) and in humans (Freedman and Oscar-Berman, 1986). The orbitofrontal system is also important for affect regulation (e.g. Damasio, 1994; Girgis, 1971). In addition to the infamous case of Phineas Gage (Damasio et al., 1994), recent case studies of patients with lesions in the orbital and mesial frontal areas found blunting of emotion and increase in lethargy, without any deficits in standard cognitive functions, such as performances on the Wisconsin Card Sort task or intelligence tests (Eslinger and Damasio, 1985). An important outcome of orbitofrontal lesions, with respect to psychiatric disorders, is a total abolition of autonomic skin conductance response to emotionally arousing visual stimuli (Damasio et al., 1990). This decoupling of “feelings” from cognitive domains may have detrimental consequences. Patients with orbitofrontal lesions maintain intact intellectual functioning but are unable to make appropriate social decisions (Damasio et al., 1990; Bechara et al., 1997). Indeed, advantageous, cognitive decision-making seems to be guided by non-conscious autonomic biases in intact humans but patients with frontal lobe damage are not guided by anticipatory, autonomic biases and as a consequence, these patients do not make advantageous choices (Bechara et al., 1997).

In this context, it is helpful to consider Nauta's (1971) hypothesis on the role of the frontal cortex in autonomic control. He postulated that the orbitofrontal cortex is necessary for the visceral, interoceptive “gut feelings” that we

experience in response to events, real or imagined. Orbitofrontal lesions would result in “interoceptive agnosia,” an inability to use our normal visceral and somatic responses as critical cues to estimate the meaning or value of situations. In addition, examining the descending motor outputs of the dorsolateral prefrontal and the orbitofrontal systems suggests we may better understand their functions. The dorsolateral PFC projects directly to the superior colliculus, the supplementary motor area, the striatum and the tectum (Goldman-Rakic, 1987); such connections indicate that this system guides voluntary motor behavior. The orbitofrontal cortex, in contrast, projects to the brainstem, endocrine systems and spinal visceral motor structures related to the autonomic nervous system. These connections indicate that the orbitofrontal cortex regulates visceral and hormonal responses in the interoceptive domain (Nauta, 1971; Neafsey, 1990; Goldman-Rakic, 1987).

However, it must be noted that while the dorsolateral PFC and the orbitofrontal cortex have functional specializations, they are also connected to each other. It is this interconnection between the two systems that results in a smoothly functioning, self-regulating organism. Therefore, the frontal cortex including the orbitofrontal cortex and dorsolateral PFC controls and mediates cognitive and emotional behavior (e.g. Girgis, 1971; Neafsey, 1990), a finding that has important implications for understanding schizophrenia.

Affective or motivational abnormalities (e.g. flat affect, apathy, lack of spontaneity, withdrawal, alogia, anhedonia) characterize the negative symptoms of schizophrenia and are associated with impaired PFC functioning (Andreassen et al., 1992; Carter et al., 1996). Lack of spontaneity and anergia, seen also in the monkey after frontal lobectomy, may stem from deficits of representational guidance of voluntary action via WM (i.e. deficits of the dorsolateral PFC). Anhedonia may be related to a disconnection between the neural circuitry associated with “reward” function from the internal representation of action. Thus, affective deficits of schizophrenic patients may reflect an inability to generate evaluative representation and/or a difficulty in cross-indexing affect with internal representation of stimulus events. Affective information, which is often present during social interaction, sets context or value to the target and directs attention to it. Indeed, in healthy people, watching social interactions result in increased prefrontal activation (Iacobini et al., unpublished observations), which suggests that socially-relevant information recruits PFC.

Recently, interest in the role of affect on WM has steadily increased. Likewise, there has been a growing interest in the cognitive components of social functioning. However, despite the close relationship of emotion and social behavior, the shared influence of these functions on cognition has been neglected. A century ago, Bleuler wrote, “where affect is lacking, there will also be lacking the drive to pursue the external and internal processes to direct the paths of the senses and the thoughts, i.e. active attention will be lacking” (Bleuler, 1911). Bleuler's concept of active attention is akin to the modern concept of WM. His hypothesis predicts that diminished affective drive will

result in reduced active attention (i.e. WM), but the reverse may also be true; deficits in WM may result in reduced socio-affective functioning. In the case of schizophrenia, Bleuler's hypothesis needs to be tested. Does reduced socio-affective functioning result in WM deficits and conversely, does increasing socioaffective input improve WM function in schizophrenic patients?

The literature concerning the function of the PFC in emotion, social behavior, and WM yield a consistent theme: the PFC is essential when representationally-guided behavior is required whether cognitive, affective or social. The fragmentation of cognition, affect, and actions that is at the core of schizophrenia may reflect such deficits. Indeed, WM deficits in schizophrenia may be a core feature of the illness (Park and Holzman, 1992; Carter et al., 1996; Keefe et al., 1995; also see Lee and Park, in press, for a meta-analytic review). Up to about 80% of schizophrenic patients and about half of their unaffected, first-degree relatives show WM deficits (see Park and Lee, 2002). WM deficits in schizophrenia appear to be stable and unmitigated by current pharmacological treatment (Park et al., 1999). They are also associated with negative symptoms (Carter et al., 1996) and social functioning (Park and McTigue, 1997) and thus, may be a central rate-limiting factor for social rehabilitation (Gold et al., 2002). Therefore, understanding the link between WM and social function may be crucial for devising future rehabilitation strategies as well as expanding our understanding of how PFC mediates WM processes.

The present study examined the effects of social reinforcement and social interaction on WM in both healthy people and individuals who are known to have WM deficits, schizophrenia patients. The major aim of the study was to investigate whether social stimuli and context might improve WM functioning in schizophrenia patients by indirectly recruiting the PFC systems.

Experiment 1. Effects of positive reinforcement on spatial WM performance of healthy and schizophrenic subjects

The PFC is involved in the brain reward mechanism (e.g. Goeders et al., 1986; Schultz, 2001; Tremblay and Schultz, 1999, 2000; Thut et al., 1997) and therefore, is likely to be implicated in anhedonic features of psychiatric disorders (e.g. negative or deficit symptoms of schizophrenia). At the cellular level, WM and reward-related activities may be mediated by the same neurons: PFC neurons involved in mediating DRT show enhanced activity during the delay when a preferred reward is anticipated than when it is not (Schall, 2001; Watanabe, 1996; Tremblay and Schultz, 1999, 2000). These findings suggest that reward or reinforcement should influence WM. Reward processing is mediated in part by the dopamine system (Schultz, 2001; Nakahara et al., 2004), which is, of course, central to the major pharmacological theories of schizophrenia. We asked whether it might be possible to improve WM function of chronic schizophrenic patients by introducing reinforcement.

EXPERIMENTAL PROCEDURES

Seventeen chronic outpatients (five women) with schizophrenia were recruited from a residential care facility. Twenty-seven healthy control subjects (nine women) who had no history of Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV, Spitzer and Williams, 1987) Axis 1 disorder in themselves or family was also recruited from the same urban area. Diagnoses were made according to DSM-IV criteria (Spitzer and Williams, 1987) from structured clinical interviews. Subjects were screened for the following criteria: substance use, neurological disorders or history of head injury. All subjects gave written, informed consent approved by the Northwestern University Institutional Review Board and were paid.

The mean age for schizophrenia group was 38.1 (S.D.=8.6) and that for the controls was 35.3 (S.D.=5.8). The mean years of education for schizophrenia group was 12.2 (S.D.=1.5) and that for the controls was 13.0 (S.D.=1.8). There was no difference between the two groups in age ($F(1,42)=1.618, P>0.21$) or education level ($F(1,42)=2.763, P>0.10$). There was one left-hander in the schizophrenia group and there were three left-handers in the control group.

Design and procedure

Subjects were required to come to the laboratory on three different days within a 2-week period. On each day, they participated in different conditions: human reinforcement, computer reinforcement and no reinforcement.

Subjects sat with their heads steady on a chin rest in front of a stimulus display monitor, which was fitted with a touchscreen (AccuTouch™ Ellinor Technology, Berks, UK). The touchscreen consisted of a glass plate covered with a tight fitting plastic cover sheet. Conductive coatings were applied to the glass plate and the plastic sheet so that light finger pressure caused internal electrical contact at the point of touch. This voltage was then digitized. Position accuracy was better than ± 4.6 mm, as measured on a multi-point sampling basis. Calibration was conducted by touching four reference points on the touchscreen. Subjects were calibrated at the beginning of each session.

Subjects fixated at the center and when they were ready to begin, the experimenter clicked a mouse to initiate a trial. A target appeared on the screen for 200 ms. Immediately after the target presentation, there was a 10-s delay period, during which subjects observed a series of black squares at the fixation spot. The black squares changed size occasionally. Subjects were asked to pay attention to how many times the square changed size. After 10 s, subjects were required to remember where the target had been and touch the remembered location accurately. This intervening task was introduced to insure that subjects were fixating at the center and to prevent idiosyncratic mnemonic rehearsal (see Park and Lee, 2002 for review).

After the subjects responded, they were presented with different types of reinforcing stimuli regardless of their actual performance. On the human reinforcement day, an experimenter sat next to the subject and said one of six set phrases ("excellent," "good job," "well done," "very good," "wonderful" and "great") after each trial in a random order. The experimenters were trained prior to the beginning of the study to deliver these phrases consistently and pleasantly by videotaping themselves and rehearsing until the delivery was reliable in both affective quality and speed. Each reinforcement period was about 5 s. After the reinforcement presentation, the experimenter clicked the mouse to get to the next trial.

On the computer reinforcement day, the same set of phrases was presented in a random order after each trial on the computer screen for 5 s. Then the experimenter clicked the mouse to get to the next trial. On the computer reinforcement day, the experimenter did not speak during the task.

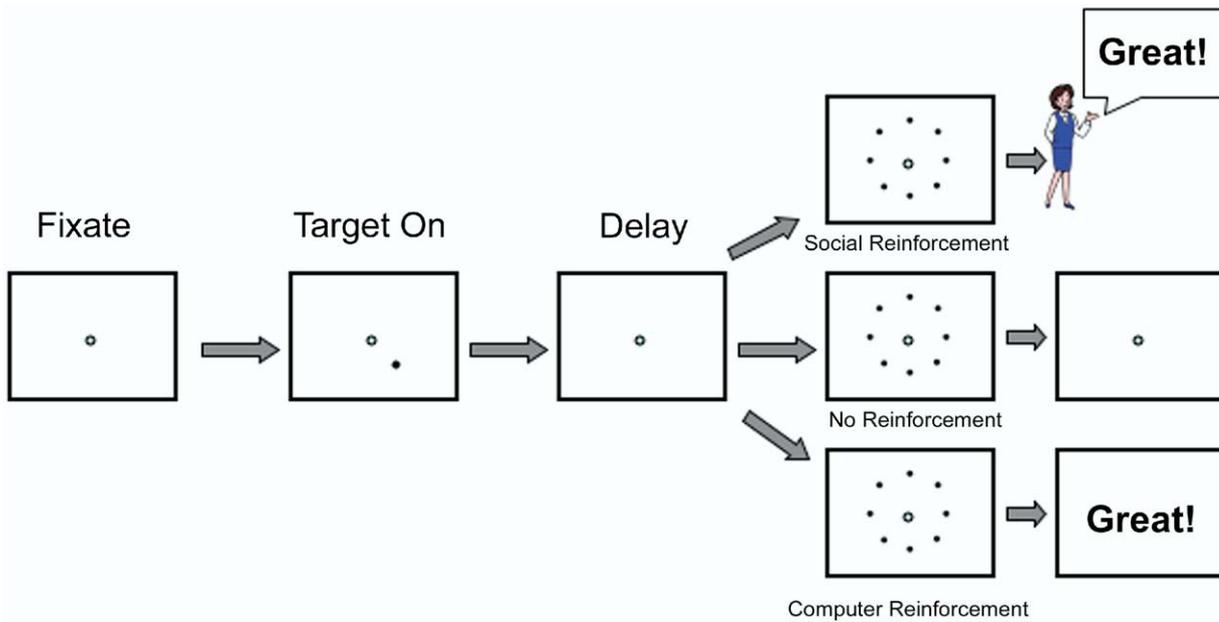


Fig. 1. Procedure for Experiment 1.

On the no reinforcement day, subjects completed each trial of the spatial WM task followed by 5 s of blank screen and then the experimenter clicked the mouse to get to the next trial. The experimenter did not speak during the experiment.

The three reinforcement days were counterbalanced across subjects to prevent potential effect of order of presentation of different reinforcement types. There were two different experimenters. The experimenters were also counterbalanced across subjects. There were 32 trials per day. See Fig. 1 for procedure.

RESULTS

Error distance, as measured by the distance between the target center and the subject’s touch point in pixels was used to assess accuracy. Response times were measured in milliseconds.

Error distance

A repeated-measures ANOVA was conducted on the error distance with the diagnostic group as the between-

subjects factor and the reinforcement type as the within-subjects factor. There was a main effect of diagnostic group ($F(1,42)=19.87, P<0.0001$) such that the mean WM error distance was greater for schizophrenia patients ($m=47.2, S.D.=25.7$) than the healthy controls ($m=23.0, S.D.=12.7$) overall. There was also a main effect of the reinforcement type ($F(2,84)=8.60, P<0.0004$). WM error distance was largest for the computer-reinforcement condition ($m=35.4, S.D.=26.9$), followed by the no-reinforcement condition ($m=31.7, S.D.=21.5$) and the social reinforcement condition ($m=29.9, S.D.=17.1$). This main effect is attributed to the error patterns of the schizophrenic group as can be seen in the interaction between the diagnostic group and the reinforcement type ($F(2,84)=9.56, P<0.0002$). The WM error distance did not vary across the different reinforcement types in the control subjects but it did in the patient group. See Fig. 2.

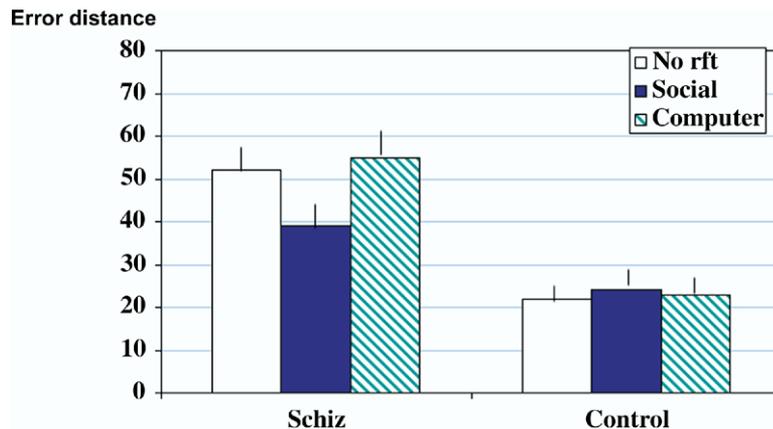


Fig. 2. Working memory error distance for the three reinforcement conditions.

Potential experimenter effect. Although we trained prior to the beginning of the study in order to minimize potential differences in the delivery of the reinforcement phrases between different experimenters, we tested the effect of having different experimenters on the error distance. A multi-factorial repeated-measures ANOVA showed that there was no main effect of the experimenter ($F(1,42)=0.016$, $P>0.90$), no interaction between the experimenter and the diagnostic group ($F(1,42)=0.047$, $P>0.82$) and no interaction between the experimenter, diagnostic group and the reinforcement type ($F(2,84)=0.80$, $P>0.45$).

Reaction times (RT)

A repeated-measures ANOVA was performed on the RT. There was a main effect of diagnostic group ($F(1,42)=68.87$, $P<0.0001$) such that the mean RT was greater for schizophrenia patients ($m=3700.0$ ms, $S.D.=1224.2$) than the healthy controls ($m=1672.5$ ms, $S.D.=333.2$) overall. There was no main effect of the reinforcement type ($F(2,84)=1.49$, $P>0.23$) or an interaction between diagnostic group and reinforcement type ($F(2,84)=0.60$, $P>0.55$). See Fig. 3.

Potential experimenter effect. There was no main effect of the experimenter ($F(1,42)=1.22$, $P>0.28$) no interaction between experimenter and the diagnostic group ($F(1,42)=1.20$, $P>0.28$) and no interaction between the experimenter, diagnostic group and the reinforcement type ($F(2,84)=0.74$, $P>0.48$).

DISCUSSION

In experiment 1, we examined the effects of different reinforcement types on spatial WM. Spatial WM was impaired in schizophrenia patients compared with control subjects but on the social (human) reinforcement day we observed a small yet significant reduction in WM error distance. Although the computer reinforcement was equivalent to the human, social reinforcement in terms of content, it failed to facilitate WM in schizophrenia patients.

On all three days, there was an experimenter in the room but only on the social reinforcement day was there social (human) feedback. Thus, giving feedback in a social context seems to be helpful for those who have deficits in WM. However, it is unclear whether facilitation of WM is an outcome of having a social context because there are some important differences between the two reinforcement types. The modality of presentation of the reinforcement was different. The computer reinforcement was presented visually on the computer screen whereas the social/human reinforcement was auditory and visual, at least. A related possibility is that reading the reinforcement phrases on the computer screen may have distracted their attention away from the next trial. Secondly, the human reinforcement had an overtly affective component in that the tone of voice was enthusiastic whereas the computer reinforcement did not. Therefore it could be argued that the non-verbal aspects of reinforcement presentation were not equivalent in terms of sensory modality, channels of information processing and affective quality. Another related possibility is that reading the “reward” phrases after making responses is not a rewarding experience whereas hearing someone say the same phrases is rewarding. Therefore, merely reading these phrases on the computer screen is not likely to activate the reward circuitry in the brain. A related point is that although the rewarding phrases were predetermined and repeated at random and we practiced the delivery of these phrases so that we would be consistent in affective tone and intensity, it is not possible for humans to generate identical speech sounds at different times. So there would have been small variations in the way the reward phrases were delivered. In contrast, in the computer condition, the reward phrases really were identical and most subjects may have habituated after a few trials. Therefore, the reward phrases presented on the computer screen are unlikely to have resulted in affective changes in the subjects.

In order to address these issues better, we designed a second experiment in which we presented reinforcement phrases with or without affect via voice recordings

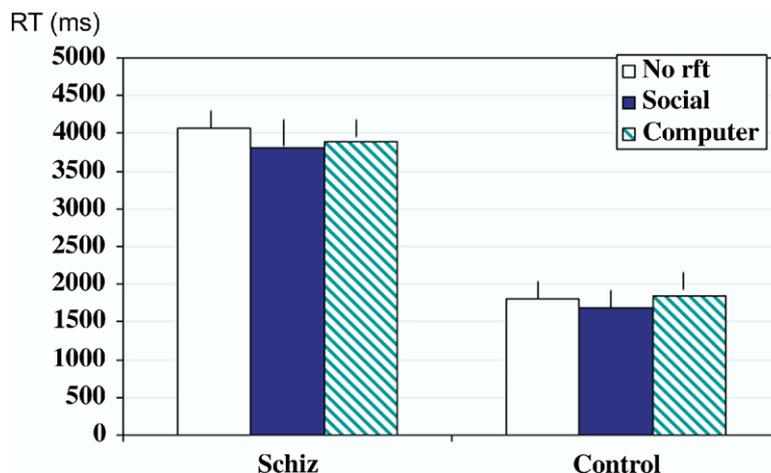


Fig. 3. Working memory RT (ms) for the three reinforcement conditions.

after each trial. Since the voices were taped, the reward phrases would be completely consistent over time.

Experiment 2. Effects of auditory (voice) reinforcement with or without affect on spatial WM of schizophrenia patients

In experiment 1, we observed facilitation of WM in schizophrenia patients upon receiving positive statements from a real person. When we presented the same phrases on a computer screen, there was no facilitation of WM in schizophrenia patients. However it was not possible to conclude that the social quality of the reinforcement delivered by a human was responsible for the facilitation of WM for several reasons. The computer presentation of the reinforcement phrases was visual whereas the human delivery was visual and auditory at the very least. Hence the amount of non-cognitive information available was much greater in the human condition. The human presentation of the reinforcement included affective component because the experimenters were trained to sound enthusiastic and positive when they delivered these phrases whereas the computer presentation had no affective quality.

In order to test whether the social context of the reinforcement delivery is important, we removed the human from the experiment and instead we used voice recordings to deliver reinforcement phrases. On half the trials, the voice reinforcements were enthusiastic and euphoric. On the other half of the trials, the voice had no affective quality. We expected the affective reinforcement to have a greater effect on spatial WM performance than the no-affect reinforcement.

Method

Subjects. The recruitment and exclusion criteria were the same as in experiment 1. Thirteen (five women) schizophrenia outpatients who met the DSM-IV diagnosis were recruited from an outpatient clinic and from a residential care center. Eighteen control subjects (eight women) were recruited from the same urban area. Mean age of the patients was 39.7 (S.D.=6.3) and the mean

years of education was 12.0 (S.D.=1.4). Mean age of the controls was 37.83 (S.D.=4.7) and the mean years of education was 12.8 (S.D.=1.6). There was no difference in the age ($F(1,29)=0.88, P>0.35$) or education level ($F(1,29)=1.97, P>0.17$) between the two groups. There were one left-hander in the schizophrenia group and two left-handers in the control group. All subjects gave written, informed consent approved by the Northwestern University Institutional Review Board and were paid.

Procedure. The task was identical to the one described in experiment 1 except that the reinforcement was delivered via built-in speakers of the computer. After each trial, a reinforcement phrase (via a female voice) was automatically presented. The content of the phrase was identical to the set of six reinforcement phrases used in experiment 1. There were two types of voices: “high-affect” or “flat-affect.” The same person recorded both types of voice stimuli. In the high-affect condition, the voice was enthusiastic and euphoric. In the flat-affect condition, the voice was toneless. The intensity and the speed of the voice stimuli were matched across the conditions and phrases.

RESULTS

Repeated-measures ANOVA was used to examine the WM error distance and RT in relation to reinforcement types.

Error distance

There was a main effect of the diagnostic group ($F(1,29)=18.88, P<0.002$). Schizophrenia patients had greater error distance than the controls. There was no main effect of reinforcement type ($F(2,58)=0.232, P>0.79$). There was no interaction between the diagnosis and reinforcement type ($F(2,58)=0.87, P>0.42$). See Fig. 4.

RT

There was a main effect of diagnosis ($F(1,29)=56.21, P<0.0001$). Schizophrenia patients were slower than con-

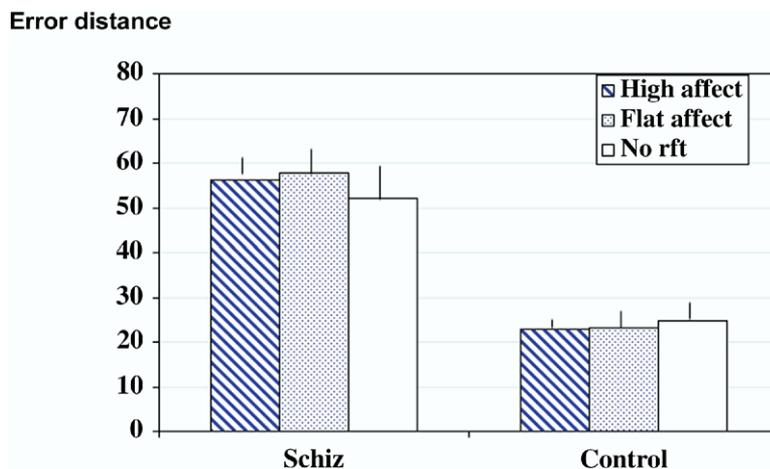


Fig. 4. Working memory error distance for high-affect voice, flat-affect voice and no reinforcement conditions.

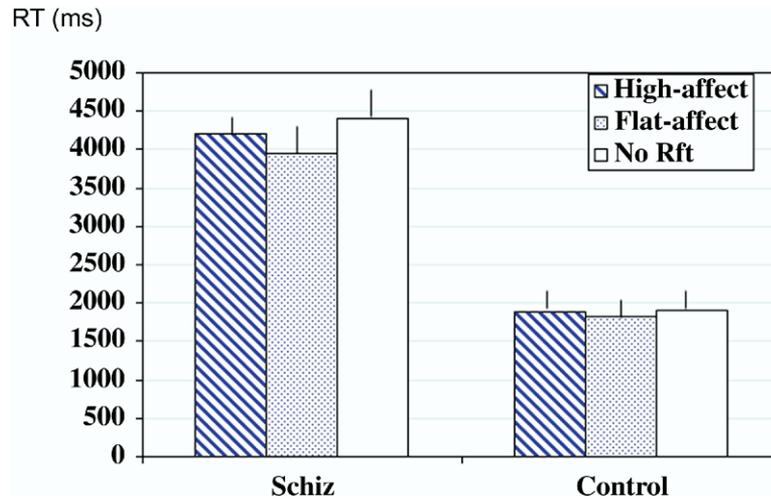


Fig. 5. Response times for high-affect voice, flat-affect voice and no reinforcement conditions.

trols. There was no main effect of reinforcement type on RT ($F(2,58)=1.36$, $P>0.26$). There was no interaction between diagnosis and reinforcement type ($F(2,58)=0.75$, $P>0.47$). See Fig. 5.

DISCUSSION

We compared two voice reinforcement conditions (high vs flat affect). There was no difference in WM error or RT between the two voice conditions and these conditions in turn did not differ from the no-reinforcement condition. These results indicate that voice reinforcements did not facilitate WM in schizophrenia patients and suggest that the social nature of human reinforcement in experiment 1 might be important.

One caveat is that we presented rewarding phrases regardless of performance and such non-contingent reinforcement strategy may have different behavioral consequences compared with contingent reinforcements. The reason we chose to reinforce all subjects regardless of performance was because of the known WM deficit in schizophrenic patients, which would result in a high number of error trials, which would in turn reduce the number of rewarded trials compared with that in normal controls. To avoid having unequal numbers of reinforced trials across individuals, we decided to present rewarding phrases after each trial but one disadvantage of this strategy was that we were unable to monitor the effects of performance-contingent reinforcement on behavior. On the other hand, it is important to note that schizophrenic patients are impaired in self-monitoring including error monitoring (e.g. Frith and Done, 1989; Frith et al., 2000). If they are unaware of their own errors, not receiving reinforcement on error trials may lead to negative affect (e.g. frustration). Therefore, to study the effects of non-contingent versus contingent reinforcement, one would have to be certain that schizophrenic patients are able to monitor errors and this would entail excluding a significant number of these patients.

For the general purpose of facilitating WM in schizophrenia patients, our data indicate that even non-contin-

gent reinforcement strategy may be effective. What might be the mechanism driving the facilitation of WM in the social/human reinforcement condition? Social interactions and situations present the most difficult, complex and challenging problems for the cortex, especially the frontal lobe and hence may be the most reliable source of frontal cortical activation. For example, watching videotaped social interactions activate the frontal cortex (Iacobini et al., unpublished observations). However, the on-line social information processing demanded by passively watching other people interact with one another, compared with having to engage directly in a social interaction would presumably require different levels of attention and effort. We hypothesized that direct engagement of the individual in a social interaction would require greater social information processing on-line and therefore be more effective in recruiting the frontal cortex.

Experiment 3. Effects of direct vs. indirect social interactions on spatial WM

In this experiment, we probed the role of social interaction in WM. The main question was whether it is possible to improve the spatial WM performance of schizophrenia patients by placing them in simulated direct and indirect social situations. If watching social interactions activates PFC (Iacobini et al., unpublished observations), there may be an indirect benefit to WM from being exposed any types of social scenes. However, schizophrenic patients have PFC abnormalities and therefore watching a social scene may not be effective. In this experiment, we examined the effects of watching two types of social scenes that differed mainly in one aspect, that of direct vs indirect engagement of the viewer.

Method

Subjects. Thirty-two healthy controls (16 women) and 13 schizophrenic outpatients (six women) were recruited. These subjects had not participated in the previous two experiments. Mean age of the patients was 41.9

(S.D.=8.3) and the mean years of education was 12.3 (S.D.=3.7). Mean age of the control subjects was 37.9 (S.D.=4.8) and the mean years of education was 13.8 (S.D.=4.2). There was no difference in the age ($F(1,43)=2.87, P<0.13$) or education level ($F(1,43)=2.26, P<0.28$) between the two groups. There were one left-hander in the schizophrenia group and one left-hander in the control group. All subjects gave written, informed consent approved by the Northwestern University Institutional Review Board and were paid.

Design and procedure

Subjects were tested on two consecutive days (direct vs indirect social interaction conditions). At the beginning of each session, which always began at the same time in the afternoon (2:00–2:30 pm), blood pressure and heart rate were measured (baseline). Then they performed the spatial WM task. There were 24 trials. Heart rate and blood pressure were measured again (post-WM 1). Immediately afterward, they watched a film clip for 15 min. At the end of the film clip, the heart rate and the blood pressure were measured (post-film). Then subjects participated in the spatial WM task. There were 24 trials. After the task, heart rate and the blood pressure were measured (post-WM 2/ baseline 2).

Film clips (15 min each) were used for simulating social interactions. The clips were approximately equivalent in the lengths of verbal utterances (13 min for the direct and 12.67 min for the indirect clips). A panel of three undergraduate students rated both clips to be about the same in difficulty level, interest and pleasantness.

In the direct social interaction condition, the film clip was from a shopping network broadcast in which the salesperson tries to sell a skincare product that is suitable for both men and women. Since the purpose of her “infomercial” is to convince the viewers to buy her products, she talks and asks questions directly to the viewers and she makes direct eye contact (looks directly into the camera) such that the overall effect of the clip is a simulation of one-to-one conversation. Therefore the viewer is very much engaged in this “conversation” and the clip simulates a direct social interaction situation.

In the indirect social interaction condition, the film clip was a scene from a well-known film (*Grumpy Old Men*) showing three people interacting with one other. The scene did not involve the viewer directly (i.e. no direct eye contact, no direct talking to the viewer). Although the film as a whole was a comedy, the clip we chose was not a funny scene and no laughter was elicited. So the viewer observed three people engaged in ordinary daily activities and conversing with one another (i.e. subjects observed social stimuli) but the viewer was not directly involved in the activities of these characters.

Because these two video clips may have differential arousing effects, we measured blood pressure and heart rate. We chose these physiological measures because they are not invasive and they do not interfere with the experimental setup (cf. the skin conductance measures which are incompatible with many tasks that may require

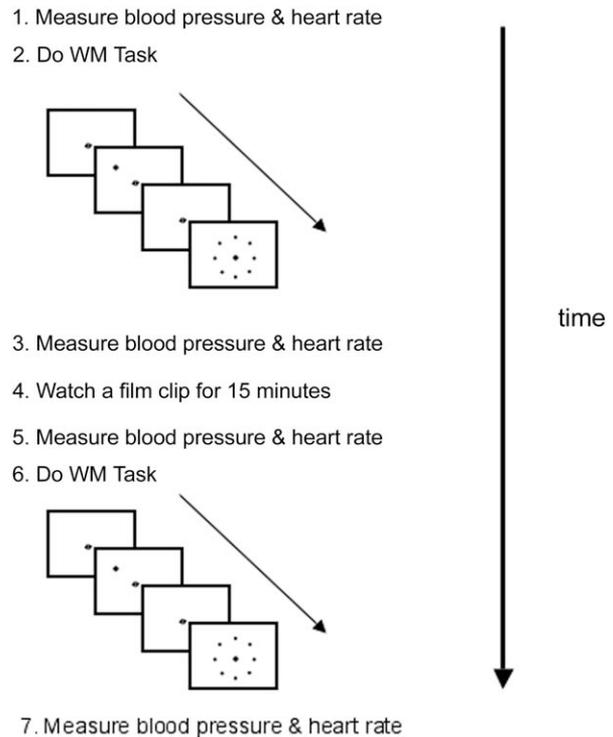


Fig. 6. Schematic diagram of the procedure in Experiment 3.

key presses). See Fig. 6 for a schematic diagram of the procedure.

RESULTS

WM errors

The error distance of spatial WM task for the two social interaction conditions were recorded. There was a main effect of diagnosis ($F(1,43)=11.41, P<0.0017$). WM error distance was greater for schizophrenic patients than controls overall. There was a main effect of time (i.e. before and after watching the film clip) ($F(1,43)=5.21, P<0.028$). There was a main effect of the type of social interaction ($F(1,43)=2.98, P<0.04$, one-tailed,) and an interaction between type of social interaction, diagnosis, and time ($F(1,43)=3.20, P<0.04$, one-tailed). Schizophrenic patients showed an improvement in WM after they watched the direct social interaction film clip but not after the indirect social interaction film clip ($F(1,12)=3.98, P<0.03$, one-tailed). Normal control subjects performed better after both types of film clips ($F(1,31)=11.84, P<0.0017$) but a trend toward interaction showed that they may also benefit more after the direct social interaction condition ($F(1,31)=2.42, P<0.06$, one-tailed). See Fig. 7.

Arousal measures

Heart rate. There was a main effect of diagnosis ($F(1,43)=10.8, P<0.0023$). Higher heart rate was observed in schizophrenic subjects ($m=90.4, S.D.=16.0$) than normal controls ($m=77.1, S.D.=13.7$). There was a

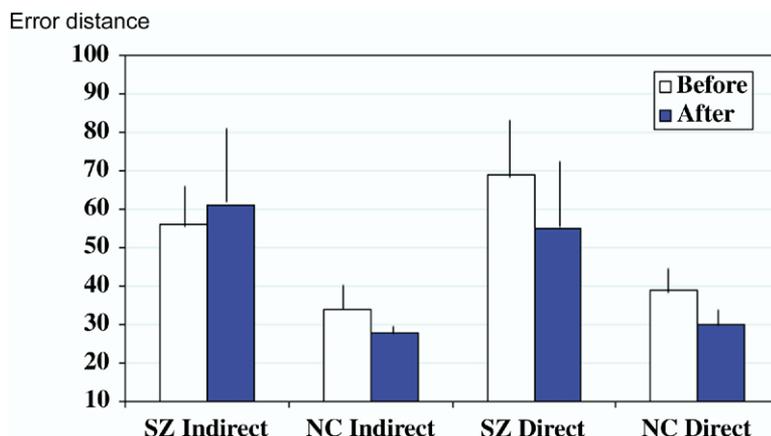


Fig. 7. Working memory error distance before and after watching the film clips.

main effect of time of measurement ($F(3,129)=2.57$, $P<0.058$) such that for both groups, heart rate declined throughout the testing session. There was an interaction between time of measurement and diagnosis ($F(3,129)=2.65$, $P<0.053$) such that for normal controls, there was a steady decrease in heart rate from the beginning of the session to the end of the session. But schizophrenic patients had the lowest heart rate after watching the film and their heart rate increased at the end of the session. See Fig. 8.

Blood pressure. Systolic and diastolic blood pressures were recorded. No significant effects were observed in the blood pressure data except for the main effect of the systolic blood pressure being higher than diastolic pressure for all subjects ($F(1,43)=510$, $P<0.0001$). There was no main effect of diagnosis on blood pressure ($F(1,43)=0.10$, $P>0.92$). There was no effect of social interaction type ($F(1,43)=0.75$, $P>0.39$), nor time of measurement ($F(3,129)=1.76$, $P>0.16$).

Correlations among arousal measures and WM score. We did not find any significant correlations between arousal measures and WM errors.

DISCUSSION

We found that after simulated direct social interaction, there was an improvement in WM in schizophrenic patients. Such facilitation was not observed after watching the indirect social interaction film. Normal control subjects showed a significant improvement after both types of films but especially after the direct social film clip. These results suggest that watching social scenes may facilitate PFC functioning and as a “side-effect,” we might observe an improvement in WM as well. In healthy controls, the benefit of watching social scenes was highly significant. In schizophrenic patients who, as a group, tend to show abnormal PFC functioning, the benefit of watching social scene was not as large but they also showed an improvement in WM, especially after watching the direct social film clip.

One might also interpret this result as a direct outcome of a practice effect. However, a general practice effect does not account for the fact that both groups performed better in the direct social interaction condition. The order of presentation of the direct and indirect conditions was counterbalanced across subjects so it seems unlikely that sub-

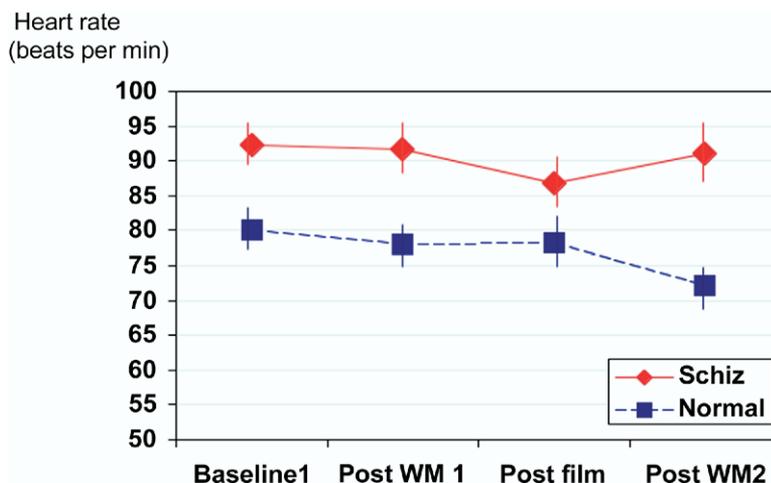


Fig. 8. Heart rate at the 4 time points.

jects were getting more of a practice effect in the direct social condition compared with the indirect social condition.

We did not observe significant differences in heart rate or blood pressure in direct vs indirect conditions. So very simple measures of arousal did not differentiate these two conditions. However, it is possible that a more precise measure of arousal (e.g. galvanic skin conductance) could detect differences in arousal between these two conditions and it remains to be tested.

Our results suggest that WM performance can be modulated by the kind of social situation that immediately precedes the cognitive testing. We hypothesize that direct social interaction may be very effective in recruiting the PFC network even in those individuals who have been shown to be impaired in activating PFC systems. One by-product of activating the PFC networks in response to social information processing may be a temporary facilitation in all functions that depend on this network including WM. This hypothesis remains to be tested with the functional neuroimaging methods including the fMRI.

General discussion

In the present study, we have begun to examine potential effects of socio-affective factors in WM using a circumscribed set of strategies. We found that WM deficit in schizophrenia can be reduced, at least temporarily, by manipulating the social context of the task. However, there are many unanswered questions.

One important issue concerns the hemispheric specialization for affective valence. Left PFC is associated with positive affect and approach behavior, whereas right PFC activation is linked to negative affect and withdrawal (Davidson, 1995). Thus, depending on the mood state, different components of WM should be enhanced or reduced. Recent studies report that positive/approach affect improved verbal WM whereas negative/withdrawal affect was linked to enhancement of spatial WM (Gray et al., 2002; Gray, 2001; Perlstein et al., 2002). We examined spatial WM in our study and according to Davidson's model, negative affect should facilitate spatial WM. However, we specifically avoided inducing negative mood in our subjects by using positive reinforcements and mildly pleasant film clips. Yet, we observed a facilitation of spatial WM, especially in schizophrenic patients. One possibility is that the results reported by Gray et al. (2002) and Perlstein et al. (2002) may not generalize to all types of emotions and to individuals who have reduced hemispheric asymmetry. First, an earlier study by Arnsten and Goldman-Rakic (1998) directly contradicts the hypothesis that negative affect should be associated with better spatial WM performance. Stressful, unpleasant noise impaired spatial WM (Arnsten and Goldman-Rakic, 1998). Second, schizophrenia is associated with reduced hemispheric asymmetry, both functional and structural (see Sommer et al., 2001 for a quantitative review; Fallgatter and Strik, 2000). A recent fMRI study of verbal and spatial WM is especially illuminating. Walter et al. (2003) reported an absence of prefrontal lateralization in schizophrenic patients. While normal controls showed greater activation of the right PFC

during a spatial WM task and that of the left PFC during a verbal WM task, schizophrenic patients failed to show such functional lateralization (Walter et al., 2003). Hence, it is not clear whether the hemispheric specialization for affective valence and that for verbal vs spatial processing are intact in schizophrenic subjects even when handedness is controlled for.

To summarize, in three exploratory experiments, we found that social information processing may facilitate WM function especially in those who have known WM deficits. Schizophrenia patients have severe deficits in WM, which in turn may limit their potential for successful cognitive rehabilitation and integration into society (Green, 1996). The current trend in developing new antipsychotic drugs is to target cognitive deficits but no drug has proved to be very effective in improving cognitive functions. Clozapine worsens WM at least temporarily (Meltzer and McGurk, 1999) and at best, risperidone has a modest effect on verbal WM (Green et al., 1997). Other investigators have attempted to improve WM by introducing cognitive exercises (Wexler et al., 2000). These exercises typically involve practicing targeted functions on computers. Some success has been reported (Bell et al., 2003) but the effects are quite modest even after lengthy and intensive training.

One factor that is common to the pharmaceutical and cognitive training strategies is that both aim to improve cognitive functions with minimal social interactions and implicit in both strategies is to minimize the cost involved in the personnel. However, if social information processing is effective in activating and facilitating PFC networks, it would be important to develop and refine methods with which we might be able to "boost" neural circuits that benefit specific functions and to yoke such strategies to the ongoing pharmacotherapy or cognitive rehabilitation training.

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