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Intact associative learning in patients with schizophrenia: Evidence from a Go/NoGo paradigm

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ABSTRACT

Objective: Schizophrenia is associated with deficits in executive control and associative learning. In the present study, we investigated the effect of associative learning during a Go/NoGo task in healthy controls subjects and patients with schizophrenia.
Methods: Thirty patients with schizophrenia and 30 age-and-gender matched healthy control subjects performed 15 blocks of training and 3 blocks of test trials. The trials consisted of responding to words denoting either living or non-living objects. In the training condition, subjects were instructed to respond by pressing the space bar (Go-task) to one of the word types (living or non-living objects), but not the other. In the test phase, the Go/NoGo mapping was reversed. Subjects were instructed to respond as quickly and as accurately as possible. Reaction times (RT) and accuracy were recorded for each trial and all subjects were debriefed upon completion of the test trials.
Results: Patients with schizophrenia had significantly longer Go RTs when compared to the control group, during both training and test trials. However, the two groups did not differ on any measure of associative learning.
Conclusions: Our findings suggest that associative learning is intact in schizophrenia patients during the performance of a relational Go/NoGo paradigm.

1. Introduction

Schizophrenia is a complex and debilitating psychiatric illness, affecting many aspects of cognition and social functioning (Kuperberg and Heckers, 2000). A central cognitive process disrupted in schizophrenia is executive control, i.e., a set of functions responsible for the integration of information to plan and support goal-directed behavior (Weisbrod et al., 2000). Response inhibition, one of the components of executive control (Barkley, 1997; Logan et al., 1997), is impaired in schizophrenia, as shown with stop-signal and Go/NoGo inhibition tasks (Badcock et al., 2002; Enticott et al., 2008; Kiehl et al., 2000).

Patients with schizophrenia also show abnormal associative learning, which could result in the impairment of executive control processes that depend on memory retrieval (Diwadkar et al., 2008; Elvevag et al., 2000; Lepage et al., 2006; Soriano et al., 2009). But studies of associative learning in schizophrenia (e.g., latent inhibition and Kamin blocking (Martins Serra et al., 2001) and classical conditioning (Jensen et al., 2008)) have traditionally not focused on executive control. The deficits in associative learning found in schizophrenia have been linked to

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anatomical and functional abnormalities of a fronto-hippocampal circuit (Diwadkar et al., 2008), whereas deficits of response inhibition have been linked to abnormalities of a fronto-striatal circuit (Blasi et al., 2006).

Here, we wanted to study the learning of a stimulus–response association and the strength of such binding during a subsequent reversal of the learned association in patients with schizophrenia. We employed a recently developed Go/NoGo paradigm (Verbruggen and Logan, 2008a). In this paradigm, subjects learned stimulus–response associations and the effectiveness of these learned associations was evaluated in the test phase of the paradigm in which the stimulus–response mapping was reversed. Our previous results show that healthy subjects learn stimulus–stop associations, as indicated by longer reaction times (RT) for old stimuli in the test phase, compared to learning a new set of stimulus–response pairings (Verbruggen and Logan, 2008a). Furthermore, our previous results show an increase in RTs for old stimuli in the test phase following the reversed mapping, compared to the same set of stimuli during training. The reversed mapping from the training phase to the test phase creates a mapping-switch cost which serves as an index of relational memory.

Since control processes rely on both executive processes and memory retrieval (Verbruggen and Logan, 2008b), this version of the Go/NoGo paradigm allowed us to assess whether patients with schizophrenia show an associative learning deficit that impacts their executive ability to inhibit responses. We hypothesized that patients are impaired in learning the stimulus-stop associations and that the mapping-switch cost of the reversed mapping in the test phase is decreased.

2. Materials and method

2.1. Subjects

Thirty healthy control subjects and 30 schizophrenia patients participated for monetary compensation ($32). All subjects reported normal or corrected-to-normal vision and were native speakers of English. The two groups were matched for age, sex, and level of parental education but differed significantly in the level of subject education and estimated pre-morbid IQ (see Table 1). The patient group included 21 schizophrenia and 9 schizoaffective disorder diagnoses, with an average duration of illness of 19.8 ± 10.9 years for the group. The patients scored in the mild to moderate range on the Positive and Negative Symptom Scale (PANSS) and in the low range on the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) and Young Mania Rating Scale (YMRS) (Table 1). The mean daily chlorpromazine (CPZ) dose equivalent for 29 out of 30 patients was 519.9 mg ± 328.6 . One patient did not take any antipsychotic medication.

Table 1
Demographic and clinical information.

	Healthy control	Schizophrenia
Age	39.63 ± 12.30	40.20 ± 10.86
Sex	15 M, 15 F	15 M, 15F
Handedness	Right (24), Left (5), Amb (1)	Right (26), Left (3), Amb (1)
IQ [a]	111.53 ± 6.81	106.53 ± 8.23
Education [a]	15.80 ± 2.19	13.87 ± 2.80
Parental education	13.07 ± 3.07	13.09 ± 3.15
PANSS total	–	60.47 ± 15.63
PANSS: positive	–	17.00 ± 6.36
PANSS: negative	–	13.07 ± 5.81
PANSS: general	–	30.40 ± 7.35
SIGH-D	–	10.2 ± 6.78
YMRS	–	8.00 ± 8.21

[a] $p<0.05$.

2.2. Apparatus and stimuli

The experiment was run on a PC running Tscope, a C library for programming cognitive tasks (Stevens et al., 2006), and the stimuli were presented on a 17-in. LCD external monitor. Subjects made semantic judgments (living/non-living) about the referent words. A total of 80 unambiguous words (40 living and 40 non-living) were chosen from a list of 640 words used in a previous study (Arrington and Logan, 2004). The living and non-living words were matched for word length (4.7, 3–8 and 4.7, 3–7; mean, range) and frequency (16.5, 1–117 and 16.7, 1–120). The 80 words were used to create two sets of 40 words (20 living and 20 non-living). All stimuli were presented in a white lower case Courier font (size 36) on a black background.

2.3. Procedure

Subjects were seated in a private testing room and, after providing informed consent in a manner approved by the Vanderbilt University Institutional Review Board, were administered the Structured Clinical Interview for DSM-IV AXIS I Disorders (SCID), the Positive and Negative Syndrome Scale (PANSS), the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D), and the Young Mania Rating Scale (YMRS). None of the healthy control subjects had a history of major medical, neurological, or psychiatric illness.

Following the clinical interview, all subjects completed the experimental task. Subjects were instructed to press the space bar of a keyboard as quickly as possible when a Go stimulus (e.g., a 'living' word) was presented and refrain from pressing the spacebar when a NoGo stimulus (e.g., a 'non-living' word) was presented. Each trial started with the presentation of the word in the center of the screen for 1500 ms, followed by an inter-stimulus interval of 1000 ms. At the end of each block, the mean Go RT, the number of missed responses on Go trials, and the number of incorrect responses on NoGo trials were displayed for 10 s. Subjects were required to press the spacebar to proceed to the next block.

The task consisted of a training phase with 15 blocks of 40 trials and a test phase with 3 blocks of 80 trials. In each training block, the words from the first subset of 40 words were presented once in random order. The training phase was followed by a test phase in which the Go/NoGo mapping was reversed (e.g., 'living = Go' and 'non-living = NoGo' in the training phase was reversed to 'non-living = Go' and 'living = NoGo' in the test phase). In each test block, the first subset of 40 words (i.e., the old words, associated with

the old mapping instruction) and the second subset of 40 words (i.e., the new words) were presented once in random order. The Go/NoGo mapping was completely counterbalanced in both groups (i.e., for half of the subjects, 'living = Go' and 'non-living = NoGo' in the training phase, and 'living = NoGo' and 'non-living = Go' in the test phase; for the other half of the subjects, this mapping was reversed). All subjects received new instructions after the training phase, explaining the new Go/NoGo mapping rules.

2.4. Statistical analysis

We used repeated measures analysis of variance (ANOVA) to determine main effects and interactions between the two groups in the test phase. Student *t*-tests were used to compare simple learning indices between the two groups. All statistical analyses were performed using SPSS 15.0 or 17.0 for Windows.

3. Results

The Go/NoGo paradigm outcome measures were calculated as described previously (Verbruggen and Logan, 2008a). The percentages of correct Go trials (i.e., Go trials on which a response was executed) for the control and patient groups were 99% and 97%, respectively, and were not further analyzed. Similarly, the probability of responding on a NoGo trial was very low (control and patient groups were 2.2% and 4.3%; main effect of group: $F(14,45) = 0.7$, $p = 0.7$) and was not further analyzed. Mean RTs for correct Go trials were calculated after removal of RTs longer than 2.5 *SDs* above the mean for each trial type.

Overall the schizophrenia group showed significantly longer Go RTs when compared to the control group in both the training phase (control = 537.0 ± 71.3; schizophrenia = 695.8 ± 128.0; main effect of group: $F(1,58) = 21.0$, $p < .001$) and the test phase (control = 586.0 ± 70.1; schizophrenia = 702.0 ± 108.7; main effect of group: $F(1,58) = 24.1$, $p < .001$) (Fig. 1). During training, both groups learned the association between stimulus and response, as shown by the decreasing RTs over the 15 blocks (control = 148.5 ± 94.4; schizophrenia = 118.4 ± 135.8; main effect of block: $F(1,58) = 7.1$, $p < .001$; group-by-block interaction, $F(1,58) = 0.4$, $p = 1.0$) (see Fig. 1).

For each group, we analyzed RT in the test phase by means of repeated measures ANOVA with 2 factors: stimulus type (old vs. new) and block (1–3). In the control group we found main effects of stimulus type ($F(1,29) = 11.3$, $p < .01$) and block ($F(2,58) = 7.0$, $p < .01$), and a stimulus type × block interaction ($F(2,58) = 12.5$, $p < .001$). In the patient group we found a main effect of block ($F(2,58) = 4.6$, $p < .05$) and a stimulus type × block interaction ($F(2,58) = 8.2$, $p < .01$). The stimulus × block interaction in both groups during the test phase results from the decrease of Go RTs for new but not old words across the three test blocks (see Fig. 1). The new words are not inhibited by the previously established associations during training, thus facilitating a decrease in Go RTs over the test phase. The new words were not associated with anything in the training phase and so show a learning effect similar to the one in the first three blocks of the training phase. The old words were associated with stopping in the training phase and retrieval of these associations counteracted learning of the new stimulus–response mapping during the test phase (Verbruggen and Logan, 2008a).

We compared RT in the test phase between the two groups by means of repeated measures ANOVA with 3 factors: group (healthy control vs. schizophrenia), stimulus (old vs. new) and block (1–3). We found a main effect of stimulus ($F(1,58) = 8.1$, $p < .01$), a main effect of block ($F(2,57) = 12.3$, $p < .001$) and a stimulus × block interaction ($F(2,57) = 15.5$, $p < .001$). Overall, the mean Go RT was longer in the schizophrenia group (control = 586.0 ± 70.1, schizophrenia = 702.0 ± 108.7; main effect of group: $F(1,58) = 24.1$, $p < .001$), however, there was no significant group × stimulus × block interaction ($F(2,57) = 1.2$, $p = 305$). This indicates that both groups show the same degree of associative learning in this Go/NoGo task.

This primary analysis of associative learning is supported by another test of learning in this study. The mapping-switch cost (defined as the difference in Go RT between the old words in test block 1 versus training blocks 13–15) did not differ significantly between the two groups (control = 73.1 ± 80.0 ms; schizophrenia = 54.6 ± 91.4 ms; $p = 0.407$). This finding is confirmed when using a repeated measures

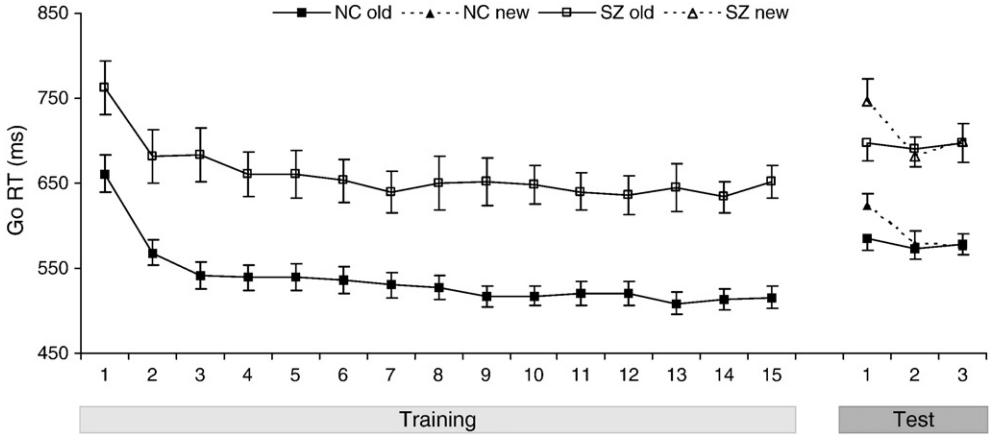

Fig. 1. Reaction time data: schizophrenia subjects.(SZ) have longer Go Reaction Time (RT) than normal control subjects (NC) during training of old and test for new and old words. Both groups show similar learning patterns for old and new words as well as similar mapping-switch cost from the training to the test phase.

ANOVA with phase (average RT in training blocks 13–15 vs. RT for old words in test block 1) and group as factors (main effect of phase ($F(1,58)=33.1$, $p<.001$); main effect of group ($F(1,58)=31.8$, $p<.001$); phase × group interaction ($F(1,58)=.7$, $p=.4$)). The mapping-switch cost in both groups was significantly different from zero (control: $t(29)=5.0$, $p<.001$; schizophrenia: $t(29)=3.3$, $p=.003$). Because the mapping-switch cost measures the strength of the stimulus–response associations formed during training, this provides further evidence for intact associative learning in patients with schizophrenia for this particular paradigm.

4. Discussion

We examined associative learning in schizophrenia during the performance of a recently developed Go/NoGo paradigm (Verbruggen and Logan, 2008a). In contrast to our hypothesis, we did not find evidence of impaired associative learning in our group of patients with schizophrenia. Both groups exhibited an ability to learn the stimulus–response associations during training and both showed the expected inhibition by previously established associations during the reversed mapping in the test phase.

Overall, the patient group had significantly longer Go RTs when compared to the control group in both the training and test phases. This longer response execution in patients with schizophrenia is consistent with prior research (Badcock et al., 2002; Heinz et al., 1998). The increased RTs in the schizophrenia group may result from an information processing deficit, which has been described previously as a central feature of cognitive dysfunction in schizophrenia (Dickinson et al., 2007). This slowing of RTs in schizophrenia subjects is thought to occur during the late stages of processing, following stimulus evaluation and preceding initiation of the response (Luck et al., 2009). This indicates that schizophrenia subjects need more time to process the association of a stimulus (e.g., a 'living word') with a response goal (e.g., 'Go'), leading to increased response latency. Furthermore, we found that performance improved during training, with the greatest decrease in Go RT observed in the beginning of the training phase. This is characteristic of learning curves in skill acquisition (Newell and Rosenbloom, 1981). Similar learning effects were observed for the new stimuli in the test phase: in both groups, Go RT decreased substantially from test blocks 1 to 3 for the new items, whereas the old items stayed relatively stable during the course of testing.

Our results suggest that associative memory in the context of this Go/NoGo paradigm is intact in schizophrenia. First, the initial learning of stimulus–response associations in the training phase was not impaired in the schizophrenia sample. This implies that the acquisition of associations is intact. Second, the mapping-switch cost of the reversed mapping was similar between the two groups. Had the patients with schizophrenia failed to establish adequate associations during training, then we would have expected a decrement in the mapping-switch cost.

Our findings run contrary to our own hypothesis and to the existing literature on associative learning in schizophrenia. Impairments in making associations have been implicated in schizophrenia since Bleuler defined 'loosening of associations' as a hallmark feature of the disorder (Bleuler, 1911). Since then, researchers have reported abnormal associative learning in schizophrenia. Studies have provided evidence implicating an impairment in associative learning in schizophrenia and their first-degree relatives using latent inhibition and Kamin blocking tasks (Martins Serra et al., 2001). Others have used classical conditioning paradigms to demonstrate abnormal associative learning in schizophrenia (Jensen et al., 2008). Diwadkar et al. (2008), using an associative learning/memory task, showed that patients with schizophrenia had a slower rate of learning than control subjects. All of these studies provide evidence for an impairment in associative learning in schizophrenia.

In contrast to the studies reviewed above, we employed a novel version of a Go/NoGo paradigm to study associative learning in schizophrenia. Some investigators have explored response inhibition and executive control during Go/NoGo paradigms in schizophrenia (Kiehl et al., 2000; Weisbrod et al., 2000), but, to the best of our knowledge, such paradigms have not been used previously to examine associative learning in schizophrenia. The fact that our schizophrenia sample showed intact associative learning in the context of a Go/NoGo task might provide a clue towards understanding the neural basis of associative learning deficits in schizophrenia.

As noted above, we expected a weaker associative binding of the stimulus (e.g., a 'living word') to the response (e.g., 'Go') in the patient group, which would facilitate the "unlearning" of associations during the reversed mapping. We hypothesized that this is due to a specific associative learning deficit in a fronto-hippocampal circuit in schizophrenia (Diwadkar et al., 2008). However, it is likely that our task is testing several circuits involved in associative learning in schizophrenia. There is indeed emerging evidence that the learning of stimulus–response associations and the subsequent reversal during a test phase involve two neural circuits. For example, Casey et al. demonstrated the recruitment of both fronto-striatal and fronto-hippocampal circuits using fMRI during a stimulus–response compatibility task (Casey et al., 2002). Their results indicate that striatal circuitry is involved in indexing the extent of interference from a well learned stimulus–response association (Berns et al., 1997; Grafton et al., 1995; Rauch et al., 1998). In contrast, recruitment of a hippocampal circuit was involved in the explicit learning and retrieval of associations between a stimulus and a response. Our data are consistent with a normal interference effect in schizophrenia, but our experimental design (employing 15 training blocks) and the overall slowed RT in schizophrenia might not have allowed us to detect a potential hippocampal deficit in schizophrenia. Furthermore, task switching has been reported to be relatively unaffected in schizophrenia (Cools et al., 2000; Wylie et al., 2008), which could have made it more difficult to reveal an associative learning deficit during the test phase. Taken together, our finding of intact associative learning during a Go/NoGo task, in the context of associative memory impairments in other experimental paradigms, supports the notion that schizophrenia affects specific cognitive modules and neural circuits.

The current study has several limitations that need to be addressed with further research. We studied chronic patients, treated with antipsychotic medication, and we cannot exclude an effect of medication, as was seen in previous studies

of the Kamin blocking effect (Jones et al., 1992). Another limitation is that we did not identify study subjects based on their current degree of psychopathology (such as negative or positive symptoms). Additionally, the task took approximately 45 min to complete, which may have contributed to attentional or motivational confounds. However, any of these confounding variables is unlikely sufficient to explain our finding of normal associative learning in this sample of subjects with schizophrenia. Furthermore, there could be an associative learning deficit in schizophrenia that is not captured with our experimental paradigm. The training phase is extensive and might reduce the sensitivity of our associative learning measurements. Future studies with shorter training periods could explore the efficacy and strength of the learned associations, which might increase the sensitivity of the test.

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Contributors

Authors S.H., G.L. and F.V. designed the study and wrote the protocol. Author A.W. collected all data. Authors S.H., S.K, A.W. and N.W. completed all data analysis and wrote the manuscript, with help from G.L. and F.V. All authors contributed to and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest.

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