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Journal of Affective Disorders 86 (2005) 235–245

JOURNAL OF AFFECTIVE DISORDERS

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Research report

Impaired delay and trace eyeblink conditioning performance in major depressive disorder

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Received 30 June 2004; accepted 8 February 2005

Abstract

Background: Preliminary evidence obtained in our lab has revealed that depressive symptoms impair associative learning, as measured by acquisition of eyeblink classical conditioning (EBCC) tasks. The current study assesses EBCC acquisition in individuals with major depressive disorder (MDD).
Methods: The 17-item Hamilton Rating Scale for Depression (HAM-D_{17}) and the 30-item Inventory for Depressive Symptomatology, Self-Report (IDS-SR_{30}) were used to quantify severity of depressive symptoms. Participants received 60 trials each in delay 500, trace 500, and trace 1000 conditioning paradigms. A 150-ms, 5–7 psi air puff served as the unconditioned stimulus (US), and an 80-dB, 1-kHz tone as the conditioned stimulus (CS). Mean percent conditioned responses (CRs) served as the primary measure of task acquisition.
Results: The MDD group generated significantly fewer CRs on delay 500 and trace 500 tasks, and approached significance on the trace 1000 task compared to healthy controls. Furthermore, presentation of successive trials did not increase CR production in the depressed group, in contrast to progressive increases observed in the control group.
Limitations: The presentation of multiple EBCC tasks precludes some detailed analyses of task-specific performance. Future studies may also benefit from including sufficient numbers of subjects to assess differential characteristics of depression (e.g., length of episode, depressive subtype) and treatment effects.
Conclusions: These data suggest that MDD impairs acquisition of EBCC, providing behavioral support for cerebellar and hippocampal dysfunction in depression. Delineating the neural substrates involved in MDD may aid in future treatment approaches for this pervasive disorder.

Keywords: Eyeblink classical conditioning; Associative learning; Major depressive disorder; Affective disorders; Cerebellum; Hippocampus

1. Introduction

Eyeblink classical conditioning (EBCC), a well-defined associative learning paradigm, involves the

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doi:10.1016/j.jad.2005.02.006

cerebellum for intact conditioned response acquisition. Despite converging support for cerebellar dysfunction in depression (Escalona et al., 1993; Shah et al., 1992; Sweeney et al., 1998), few studies have examined EBCC in depressive disorders. Weckowicz et al. (1974) compared eyelid conditioning in two groups of depressed persons, but acquisition was not compared to controls. The comparison of EBCC between depressed persons and controls may provide behavioral indicators of cerebellar function in depression.

EBCC has been successfully used to assess associative learning in both animal and human models. Its flexibility and long history of physiological characterization (Anderson and Steinmetz, 1994; Kim and Thompson, 1997) make EBCC an ideal tool to indirectly investigate cerebellar dysfunction in depression. Despite previous identification of cerebellar projections to forebrain areas involved in emotion (Heath et al., 1980) and reports of considerable behavioral and cognitive changes associated with cerebellar damage (Schmahmann and Sherman, 1997), the cerebellum has only recently become a focal point for investigation in depressive disorders.

Evidence of cerebellar alterations in depression stems predominantly from neuroimaging studies that have detected significant differences in both cerebellar structure and function in depressed individuals (Bench et al., 1992; DelBello et al., 1999; Dolan et al., 1992; George et al., 1993; Soares and Mann, 1997). Structural imaging has indicated evidence of increased atrophy (Weinberger et al., 1982) and reductions in volume (Shah et al., 1992) in the cerebellar vermis, as well as smaller overall mean cerebellar volumes (Escalona et al., 1993) in depressed persons as compared to controls. Positron emission tomography (PET) studies with depressed individuals have reported increased rCMRglu bilaterally in the midline cerebellum (Kimbrell et al., 2002) and increased regional cerebral blood flow in the cerebellar vermis (Bench et al., 1992).

Behavioral approaches also provide converging evidence of cerebellar involvement in depression. For example, performance on a battery of oculomotor tasks indicated a disruption of frontostriatal circuitry and the cerebellar vermis in major depression (Sweeney et al., 1998). Collectively, these data compel further investigation of the involvement of the cerebellum in depression. EBCC may be an ideal, novel tool for this purpose.

Trace EBCC provides an additional opportunity to examine both hippocampal and cerebellar function in depression. Both animal and human models have demonstrated that CR acquisition in EBCC relies on the cerebellum (Canavan et al., 1994; Thompson et al., 1997), but damage to the hippocampal region causes deficits specific to trace conditioning (Gabrieli et al., 1995; Moyer et al., 1990). The hippocampal region has also been implicated in depressive pathophysiology (Mayberg, 1997; Seminowicz et al., 2004), although it is not frequently incorporated into pathophysiological models of depression. Mayberg (1997) discussed the involvement of the hippocampus and related areas in a tri-component model of depression and suggests that malfunction of this distributed network results in the manifestation of depression. Bremner et al. (2000) noted significant reductions in hippocampal volumes of depressed persons compared to controls, also suggesting hippocampal alteration in depression. Further, a review by Vaidya and Duman (2001) emphasized the role stress may play in damaging the hippocampi of depressed persons.

The main goal of the present study was to compare the performance of persons with major depressive disorder (MDD) to controls on acquisition of EBCC. To our knowledge, this is the first study attempting to compare these behavioral indicators of cerebellar and hippocampal integrity between clinically depressed persons and healthy controls.

2. Methods

2.1. Participants

Participants were recruited as outpatients from the Mood Disorders Research Program and Clinic at UT Southwestern Medical Center and from psychology courses at UT Dallas. Informed consent was obtained from 52 individuals subsequently evaluated for potential participation. Participants ranged from 18 to 45 years of age and were required to be free of psychoactive medications for at least 2 weeks (5 weeks for fluoxetine) prior to and during all testing. Subjects taking medication at the time of testing that could significantly impair learning or memory (e.g., cold medicine, sleep aids) were excluded. Subjects

were also excluded if evidence indicated the presence of a significant general medical or psychiatric condition (other than MDD for depressed participants), including substance or alcohol dependence or abuse. Subjects completed the Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) to assess cognitive status. Subjects with MMSE scores ≤27 were to be excluded from further participation; however, no subjects received a score <28.

Psychiatric history was evaluated for both groups based on a telephone screen evaluation, the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997). Depressed persons met DSM-IV (American Psychiatric Association, 1994) criteria for MDD, and the presence of other diagnoses in either group resulted in exclusion as described above. The HAM-D_{17} (17-item version) (Hamilton, 1967) served as the primary measure of depressive symptom severity. Participants also completed the Inventory for Depressive Symptomatology, Self-Report (IDS-SR_{30}) (Rush et al., 1996). Depressed subjects required scores ≥18 on the IDS-SR_{30} and ≥15 on the HAM-D_{17} for inclusion, whereas control subjects required scores ≤10 on the IDS-SR_{30} and ≤7 on the HAM-D_{17}.

An anxiety score was calculated based on individual item scores from the IDS-SR_{30}. Items used from the IDS-SR_{30} were those correlated with the anxiety factor reported in a factor analysis conducted by Rush et al. (1996), including sleep onset insomnia, feelings of anxiety or tension, psychomotor agitation, somatic complaints (e.g., aches and pains), sympathetic arousal (e.g., bodily symptoms), panic and/or phobic symptoms, and gastrointestinal symptoms, for a total of 21 possible points. The Depressive Retardation Rating Scale (DRRS) (Widlocher and Ghozlan, 1989) was administered to assess the presence and severity of clinical psychomotor retardation.

Of the 52 participants initially assessed, 14 were excluded for the following reasons: 4 had comorbid psychiatric or medical conditions, 5 scored outside the appropriate assessment ranges, 3 were unable to complete all assessments, and 2 could not complete the EBCC tasks. Table 1 summarizes baseline demographic and assessment data for the remaining 38 participants (depressed, $N=20$; control, $N=18$).

2.2. Eyeblink classical conditioning (EBCC) tasks

The EBCC setup used in this study consisted of hardware and software developed by Thompson and colleagues (Thompson et al., 1994; Akase et al., 1994) to track eyeblink responses and control timing of presentation of CS and US stimuli. An adjustable headset fitted with an LED and phototransistor sends eyeblink information to a custom detector circuit, the output of which is digitized and stored.

Table 1
Demographics and baseline characteristics

	Depressed ($N=20$)	Control ($N=18$)	F	p
	Mean ± S.D.	Mean ± S.D.		
Age	29.8 ± 7.3	27.6 ± 6.3		
Gender (M/F)	6:14	4:14		
Education	14.3 ± 1.8	15.4 ± 1.9		
MMSE	29.0 ± 0.9	29.1 ± 0.9	0.3	0.6
Symptom Severity Measures				
IDS-SR_{30}	34.5 ± 9.6	6.1 ± 2.6	170.1	<0.0001
HAM-D_{17}	23.2 ± 4.9	3.9 ± 1.8	234.5	<0.0001
Anxiety	8.5 ± 2.6	2.2 ± 1.2	92.0	<0.0001
DRRS	12.5 ± 4.1	2.6 ± 2.1	83.1	<0.0001
Baseline Conditioning Characteristics				
Peak amplitude (mV)	3081.9 ± 545.6	3292.5 ± 328.9	2.0	0.16
Peak latency (ms)	93.2 ± 29.8	75.5 ± 2.75	3.6	0.07
Blink frequency (number of blinks)	3.5 ± 1.5	3.3 ± 1.5	0.14	0.71

MMSE, Mini Mental State Examination; IDS-SR_{30}, 30-item Inventory of Depressive Symptomatology; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; DRRS, Depressive Retardation Rating Scale.

For EBCC tasks, a 150-ms, 5–7 psi air puff (compressed nitrogen) applied to the left lateral cornea served as the unconditioned stimulus (US). The air puff was administered via tubing attached to the headset worn by the subject. An 80-dB, 1-kHz tone conditioned stimulus (CS) was administered binaurally through headphones, with tone presentation and generation gated by a LabLinc V85-05 module (Coulbourn Instruments, Allentown, PA). Equipment was calibrated and sanitized prior to each use.

Prior to testing, subjects were seated in a comfortable chair, fitted with the EBCC headgear and headphones, and read a set of instructions advising them that they would hear tones and feel mild puffs of air in their left eye. They were instructed to blink as they desired and to remain as still as possible during testing. Subjects viewed a silent comedy film displayed on a monitor throughout the entire experimental procedure.

After fitting the headgear, 10 air puff-only trials were administered to familiarize the subject with the air puff US and for adjustment of the equipment as necessary for optimal detection. These trials also allowed for standardization of the quality of eyeblink responses (i.e., amplitude and latency measures) and assessment of baseline eyeblink frequency.

2.3. Conditioned learning paradigms

Following the 10 air puff-only trials, three conditioned learning paradigms were presented. Delay 500 conditioning consisted of a 650 ms CS, paired with the US during the last 150 ms. Trace 500 conditioning consisted of a 100 ms CS, followed by a 500 ms inter-stimulus trace interval, and then by a 150 ms US (i.e., non-overlapping but paired stimuli). Trace 1000 conditioning had the same parameters as trace 500 conditioning, but the trace interval was 1000 ms long. EBCC tasks were administered in a counterbalanced fashion between subjects.

For each of the three tasks, a total of six blocks of 10 trials (i.e., 60 trials per task) were administered. The 10th trial of each block consisted of a CS-only presentation. Conditioned responses occurring on such trials were referred to as Pavlovian CRs. The observation (or lack thereof) of Pavlovian CRs is another indicator of the strength of the association between the US and CS. Intertrial intervals (ITIs) averaged 8 s for all paradigms (see Carrillo et al., 1997). Subjects' blink responses were monitored during each trial for 1000 ms prior to CS onset, and continually thereafter for 2500 ms, in order to fully characterize both spontaneous and evoked eyeblink behavior. Blinks that occurred prior to CS onset were characterized as spontaneous responses (Gormezano, 1966). Blinks were characterized as alpha responses (Gormezano, 1966) if they occurred in the first 100 ms of the CS presentation, and such responses were not counted as CRs. Conditioned responses were counted, however, if they occurred following an alpha response.

A CR was defined as a response occurring 100 ms or later from the onset of the CS and before the onset of the US. In the case of CS-only trials, responses were counted as Pavlovian CRs if they occurred prior to the time the US would have been presented (i.e., "late" CRs were not evaluated). Total numbers of CRs were calculated for all paradigms using a conservative criterion (i.e., an amplitude more than four standard deviations above baseline; see Thompson et al., 1992). In addition, the number of trials required to reach a criterion of 40% CRs within each paradigm was calculated for each subject. This criterion measure is frequently used as a more sensitive measure of the rate of acquisition than an overall conditioning performance measure (see Thompson et al., 1996; Gormezano, 1966; Graves and Solomon, 1985).

Additionally, CRs were characterized as adaptive or nonadaptive. CRs that returned to baseline after US onset were characterized as adaptive, since they illustrate the ability to successfully prohibit air puffs from hitting the eye. CRs that returned to baseline before US onset were characterized as nonadaptive. Nonadaptive CRs can show evidence of learning, but do not prevent the aversive effects of the US. Production of adaptive responses demonstrates the most proficient acquisition of the task.

2.4. Statistical analyses

Baseline measures obtained during the US-only presentations were evaluated using one-way analyses of variance (ANOVAs) for blink frequencies, unconditioned response (UR) peak amplitudes, and UR peak latencies. ANOVAs also assessed spontaneous blink

and alpha response generation during the active conditioning tasks.

A multivariate analysis of variance (MANOVA) was conducted with group (depressed or control) as the between factor, and total mean percent CRs for each task type–delay 500, trace 500, or trace 1000–as dependent variables. Similarly, a group × order analysis was conducted to assess potential differences on total mean percent CRs produced on the first, second, and third EBCC tasks presented to subjects. A repeated-measures ANOVA was conducted for mean percent adaptive CRs on the first task presented for each of the six blocks of trials. Because task presentation was counterbalanced, adaptive CRs were chosen since they assess task-specific timing to avoid the US. The repeated-measures analysis was conducted only for the first task in order to eliminate influence from previously administered tasks. The primary variable of interest in these analyses was total mean percent CRs. MANOVAS were also computed for each paradigm with the following EBCC measures: nonadaptive, adaptive, and total mean percent CRs, the number of trials to reach a 40% CR criterion, and number of Pavlovian CRs produced.

Regression analyses were conducted to assess the involvement of depression severity, anxiety, and psychomotor retardation on EBCC performance. Regression analyses were conducted between scores on the IDS-SR_{30}, HAM-D_{17}, the anxiety measure and the DRRS and total mean percent CRs for each of the three EBCC tasks. Significance levels were set at $p \leq 0.05$ for all analyses. Parameter values are reported below as mean ± standard deviation.

3. Results

Baseline measures of response amplitudes and latencies indicated no significant differences between groups for peak response amplitude, peak response latency, or blink frequency. Specific values for these measures are presented in Table 1.

An overall MANOVA conducted for group × EBCC task type indicated a significant main effect difference between groups across the three EBCC tasks (Wilks' $\lambda = 0.779$, $F(3,31) = 2.9$, $p < 0.05$). In order to determine which specific tasks differed, a series of ANOVAs were conducted. These analyses revealed significant main effects of group for delay 500 conditioning ($F(1,33) = 8.5$, $p < 0.01$; depressed: 29.8 ± 29.8; control: 60.7 ± 26.6) and trace 500 conditioning ($F(1,33) = 5.1$, $p < 0.04$; depressed: 48.3 ± 31.1; control: 72.7 ± 23.1), and a trend toward significance for trace 1000 conditioning ($F(1,33) = 3.9$, $p < 0.06$; depressed: 48.1 ± 30.8; control: 67.9 ± 28.6). Age was introduced as a covariate in these analyses (i.e., a MANCOVA and ANCOVAs were computed). Neither a significant main effect of age nor interactions with age emerged from these analyses; therefore, subsequent analyses of EBCC variables did not include age. Mean percent CRs generated by both groups on each of the EBCC tasks are presented in Fig. 1 (top).

The group × task order MANOVA did not reach statistical significance, although it did approach it (Wilks' $\lambda = 0.796$, $F(3,31) = 2.6$, $p < 0.07$). This is likely due to a significant order effect found with the trace 1000 task on a group × task order ANOVA ($F(2,29) = 4.3$, $p < 0.03$). Both control and depressed groups were more likely to perform better on the trace 1000 task when it was the first task presented, as opposed to the second (Fisher's PLSD, $p < 0.01$). Regardless, the group effect was maintained ($F(1,29) = 4.5$, $p < 0.05$). No order effect was found for the group × order ANOVAs on delay or trace 500 conditioning. ANOVAs conducted by group with each task order individually yielded significant findings for task 1 ($F(1,33) = 4.8$, $p < 0.04$; depressed: 44.3 ± 31.1; control: 70.7 ± 25.8) and task 2 ($F(1,33) = 7.9$, $p < 0.01$; depressed: 38.1 ± 31.6; control: 66.1 ± 22.7), and approached significance with task three ($F(1,33) = 4.1$, $p < 0.06$; depressed: 42.8 ± 32.6; control: 64.6 ± 30.1). Fig. 1 (bottom) depicts both groups' mean percent conditioned responses for each order of task presentation.

A repeated-measures ANOVA analyzing mean percent adaptive CRs over six blocks (of 10 trials each) on the first task revealed significant main effects for group ($F(1,36) = 5.9$, $p < 0.02$) and time ($F(5,180) = 2.3$, $p < 0.05$). In order to better understand the differences between groups, simple effects analyses for each group were conducted using one-way ANOVAs. The control group produced significantly more CRs over time ($F(5,85) = 2.8$, $p < 0.02$), but the depressed group did not ($F(5,95) = 0.5$, $p < 0.79$). Learning curves (Fig. 2) illustrate the increase in

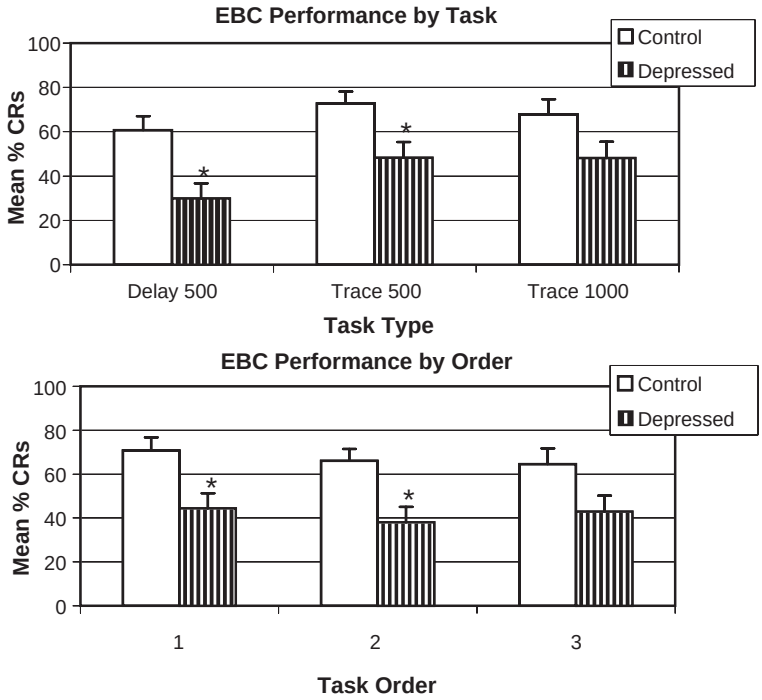

Fig. 1. Top: Total mean percent conditioned responses (CRs) on each EBCC task. The depressed group generated significantly fewer CRs than the control group on the delay and trace 500 tasks (indicated by asterisks), and approached significance on the trace 1000 task. Bottom: Total mean percent conditioned responses (CRs) for each order of presentation of the EBCC tasks. The depressed group generated significantly fewer CRs than the control group on the first and second tasks, and approached significance on the third task.

adaptive CR production over time in the control group and the flat curve of the depressed group, reflecting absence of learning. Surprisingly, the group × time interaction was not significant ($F(5,180)=1.6$, $p<0.17$). However, it is plausible that the similarity in group performance over the first 3–4 blocks of trials could account for this finding.

MANOVAs were also conducted for each EBCC task to assess potential group differences on non-adaptive, adaptive, and total mean percent CR

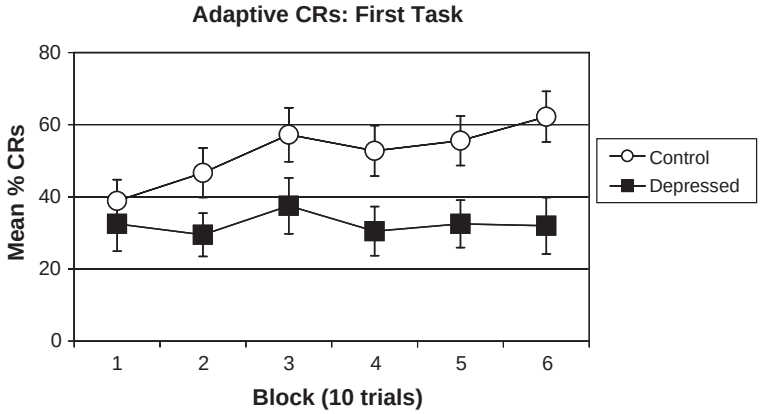

Fig. 2. Learning curves based on mean percent adaptive conditioned responses during the first task presented. The control group showed increasingly more CRs produced throughout the task, whereas the depressed group showed no change from baseline CR production.

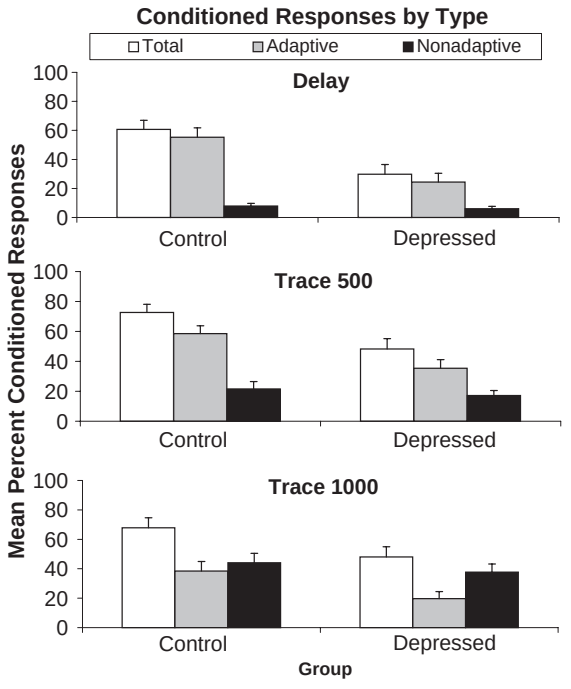

Fig. 3. Total, adaptive, and nonadaptive mean percent conditioned responses (CRs) for each EBCC task. Although the depressed group produced fewer total CRs, those that they did generate were qualitatively similar to the control group for the delay and trace 500 tasks (i.e., both groups generated mostly adaptive CRs). However, in the trace 1000 task, the control group produced similar numbers of adaptive and nonadaptive CRs, whereas the depressed group produced more nonadaptive than adaptive CRs.

production, trials-to-criterion of 40%, and number of Pavlovian CRs. These analyses did not reach statistical significance, although the MANOVAs for both delay and trace 500 conditioning approached significance (delay: Wilks' $\lambda = 0.680$, $F(6,30) = 2.36$, $p < 0.06$; trace 500: Wilks' $\lambda = 0.796$, $F(6,29) = 1.2$, $p < 0.07$; trace 1000: Wilks' $\lambda = 0.807$, $F(6,27) = 1.08$, $p < 0.40$). However, individual ANOVAs revealed significant differences on several variables that warrant mention.

Fig. 3 depicts the percentages of total, adaptive, and nonadaptive conditioned responses on each task. As noted, depressed persons produced fewer total CRs (either adaptive or nonadaptive) on all tasks. ANOVAs revealed no significant differences on nonadaptive CR production, but significant group differences on adaptive CR production (delay: $F(1,35) = 11.84$, $p < 0.01$; trace 500: $F(1,34) = 7.59$, $p < 0.01$; trace 1000: $F(1,32) = 5.54$, $p < 0.03$).

The number of trials needed to reach a 40% mean percent CR production criterion, illustrated in Fig. 4 (top), was significantly different between groups on the delay ($F(1,35) = 8.64$, $p < 0.01$; depressed: 53.9 ± 12.4; control: 41.3 ± 13.7) and trace 500 ($F(1,33) = 4.69$, $p < 0.04$; depressed: 45.6 ± 14.9; control: 35.7 ± 12.2) EBCC tasks, but not the trace 1000 task. Because the greatest number of trials possible with which to achieve the criterion is equal to the total number of trials presented (in this case 60), the number 61 was conservatively used in the above analyses for those subjects who never achieved the criterion. Group differences are not obvious when comparisons are made only between those who

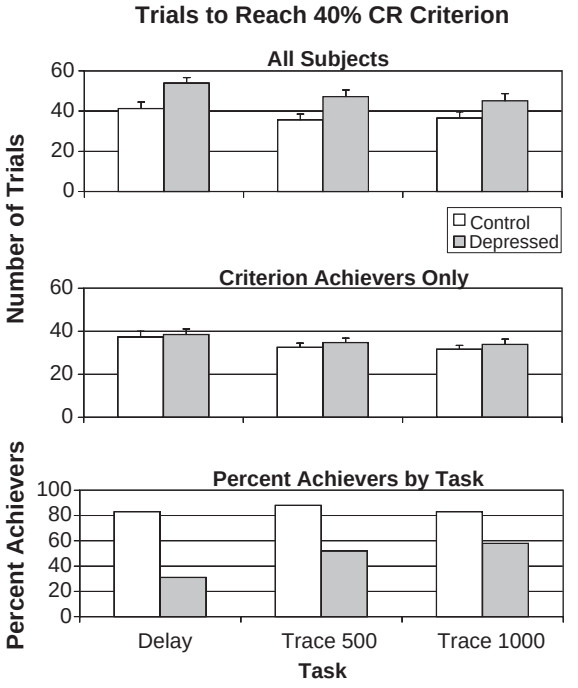

Fig. 4. Number of trials required by each group to reach a criterion of 40% conditioned responses. Top: When all subjects are included, regardless of whether or not criterion was met, it appears that there are significant group differences in the number of trials needed for depressed persons to achieve criterion. A conservative value of 61 (one more than possible to meet the criterion) was assigned to those who did not reach the criterion within 60 trials. Middle: There are no group differences in the number of trials needed to reach the criterion when only those who achieved the criterion are assessed. This suggests that depressed learners perform as well as control learners; however, there is a significantly lower percentage of depressed learners, accounting for the perceived differences in the top graph (Bottom).

attained the criterion, as illustrated in the middle graph of Fig. 4. However, the bottom graph of Fig. 4 shows that a much higher percentage of subjects in the control group reached the criterion than in the depressed group. Thus, depressed persons who achieved the criterion did so in an equivalent number of trials to those in the control group, although there were significantly fewer persons in the depressed group who achieved the criterion.

As described previously, CRs produced on CS-only trials, Pavlovian CRs, are believed to reflect the strength of association between the air puff US and tone CS (i.e., the more Pavlovian CRs produced, the stronger the association). The depressed group produced significantly fewer Pavlovian CRs on all tasks than did the control group (delay: $F(1,35)=15.43$, $p<0.01$; trace 500: $F(1,35)=6.20$, $p<0.02$; trace 1000: $F(1,33)=5.11$, $p<0.03$). These data again indicate that depressed participants did not acquire EBCC tasks as well as controls.

Table 2 shows model R^2 values for measures of depression severity, anxiety, and psychomotor retardation and mean percent conditioned responses for each of the EBCC tasks. As demonstrated in the table, several regression analyses reached statistical significance, particularly with delay and trace 500 EBCC measures. Both self-reported and clinician-rated depressive symptomatology predicted CR generation on delay (IDS-SR_{30}: $R^2=0.17$, $p<0.01$; $HRSD_{17}$: $R^2=0.18$, $p<0.01$) and trace 500 (IDS-SR_{30}: $R^2=0.13$, $p<0.02$; $HRSD_{17}$: $R^2=0.13$, $p<0.03$) conditioning, but not trace 1000 conditioning (IDS-SR_{30}: $R^2=0.07$, $p<0.12$; $HRSD_{17}$: $R^2=0.10$, $p<0.07$). Only mean percent CRs for delay conditioning were significantly predicted by anxiety scores ($R^2=0.17$, $p<0.01$), although the analysis approached significance for trace 500 conditioning ($R^2=0.10$, $p<0.06$). In contrast, DRRS scores significantly predicted mean percent CRs on all three EBCC tasks.

Table 2
Model R^2 values for measures of depression severity, anxiety, and psychomotor retardation

Task[a]	IDS-SR_{30}		HAM-D_{17}		Anxiety		DRRS	
	R^2	p	R^2	p	R^2	p	R^2	p
Delay	0.17	0.01	0.18	0.01	0.17	0.01	0.20	0.01
Trace 500	0.13	0.02	0.13	0.03	0.10	0.06	0.10	0.05
Trace 1000	0.07	0.12	0.10	0.07	0.05	0.22	0.13	0.04

[a] Total Mean % CRs. IDS-SR_{30}, 30-item Inventory of Depressive Symptomatology, Self-Report; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression,; DRRS, Depressive Retardation Rating Scale.

The presence of two outlying groups–depressed learners and control nonlearners–lowered R^2 values, even on those analyses that reached statistical significance. Whereas it is often noted that a subgroup of normal controls fail to learn EBCC tasks, we did not anticipate finding a subgroup of depressed learners. Regression plots showing mean percent CR production on delay conditioning predicted from IDS-SR_{30}, $HRSD_{17}$, anxiety, and DRRS scores are shown in Fig. 5. These data are representative of the other significant regression findings and illustrate the presence of the two outlying groups mentioned above—depressed learners and control nonlearners.

The characteristics of CRs must be considered when assessing the possible reasons for the observance of group differences on EBCC measures. Group means for CR peak amplitudes, CR peak latencies and alpha response generation are presented in Table 3. No significant group differences emerged, with the exception of the peak amplitude for trace 500 conditioning ($F(1,33)=10.40$, $p<0.01$). A diminution of the response in the depressed group was suspected, but examination of the response from the control group suggests that the control group's responses were more robust on this task in comparison to the other two EBCC tasks, which likely accounted for this finding.

4. Discussion

This study is the first known demonstration of impairment in EBCC associated with major depressive disorder. Depressed persons showed significant reductions in mean percent conditioned response generation on delay and trace 500 EBCC measures in comparison to controls. The depressed group also generated fewer CRs on the trace 1000 task, although the analysis did not reach statistical significance. In addition, the associative strength between the US and CS was weaker in the depressed group than in the control group on all three conditioning measures, reflected in fewer Pavlovian CRs produced by the depressed group. Furthermore, adaptive CR production did not increase in the depressed group through-

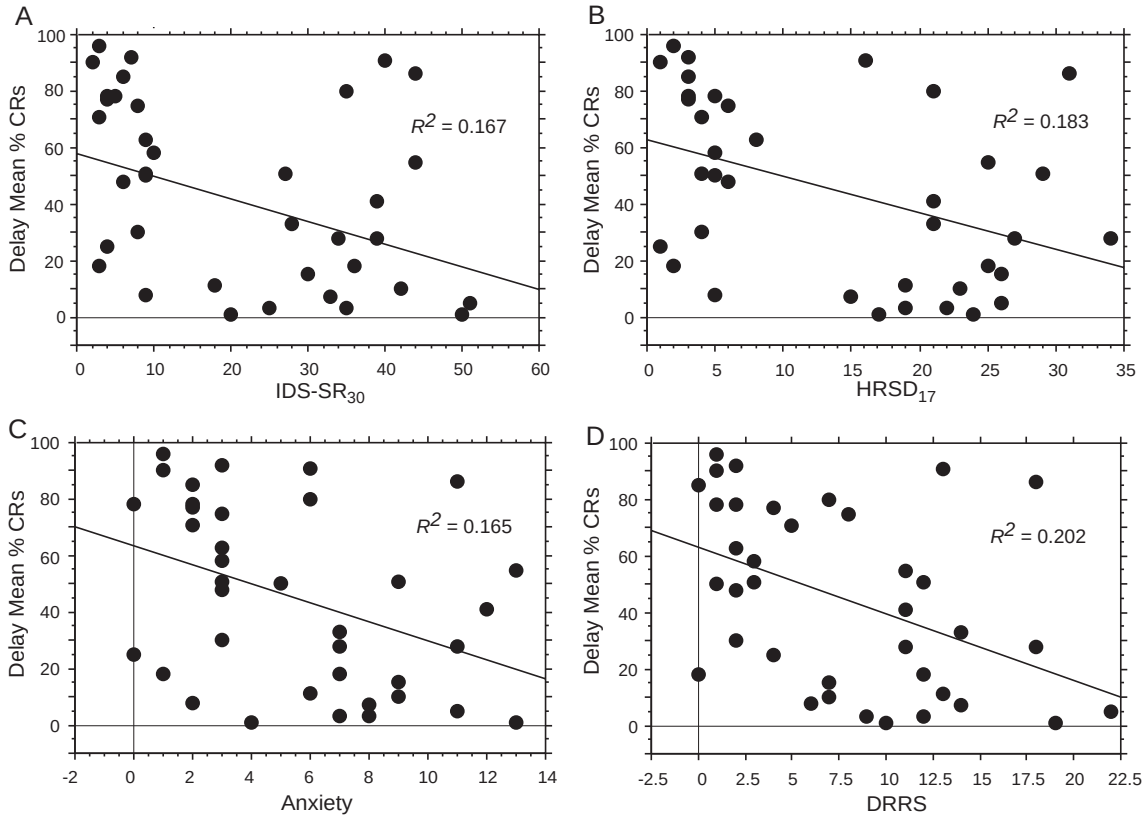

Fig. 5. Regression plots predicting mean percent CRs on delay conditioning from the IDS-SR_{30} (A), HAM-D_{17} (B), Anxiety Score (C), and DRRS (D). The presence of two outlying groups is illustrated in all depictions, but particularly in the plots with severity measures (A and B). All analyses were significant ($p < 0.05$).

out the course of the first task. These data provide behavioral support for cerebellar and hippocampal dysfunction in clinically depressed persons.

Table 3
CR Characteristics from paired conditioned stimulus-unconditioned stimulus presentations

	Peak amplitude (mV)	Peak latency (ms)	Alpha responses (number of blinks)
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Delay			
Control	3487.7 ± 887.1	355.9 ± 57.3	3.8 ± 2.8
Depressed	2990.6 ± 822.3	344.5 ± 68.1	2.5 ± 2.8
Trace 500			
Control	3738.5 ± 469.1	396.2 ± 66.3	4.1 ± 4.2
Depressed	2843.1 ± 712.4	374.0 ± 99.5	2.5 ± 2.8
Trace 1000			
Control	2987.1 ± 818.9	560.0 ± 115.6	3.4 ± 3.0
Depressed	2749.2 ± 824.1	578.3 ± 90.9	3.8 ± 2.9

The observed performance decrements in the depressed group do not appear to be related to differences in response generation. Baseline measures of unconditioned response peak amplitudes and spontaneous blink frequency were not significantly different between the two groups. However, group differences in peak latencies approached significance and there was considerably more variability in the peak latencies of the depressed group than those of the control group, suggesting the need for further assessment in depressed populations. The topography of CRs and URs are different enough that the observed learning differences are likely not attributable to a delayed onset of the CR in the depressed group, but that possibility should be further investigated.

Interestingly, conditioned response amplitudes were significantly different between the depressed and control groups only on the trace 500 task. The

depressed group showed fairly consistent CR amplitudes, all of which were lower than those observed in controls. It is likely that the more robust CR amplitudes for the control group during trace 500 conditioning accounted for the significance of group differences on that task. However, these data also suggest a need for further investigation of response characteristics.

In this study, both depressed and control subjects produced more adaptive than nonadaptive responses, illustrating that both groups could successfully avoid the aversive US; the depressed group, however, did so less frequently. It is possible that the depressed group simply needed more trials to reach the same level of learning as the control group. This is unlikely given the number of trials presented for each task and the absence of an order effect in which the third task presented would show a higher percentage of CR production. However, because three different tasks were used in this study, the effect of increased numbers of trials within the same paradigm could not be directly assessed. Future assessments of EBCC in depression would benefit by employing a single task per study and increasing the number of trials presented for that task to ascertain whether or not depressed individuals may eventually reach the level of CR production generated by controls.

Of particular interest in this investigation was the identification of a subset of depressed persons who performed comparably to controls on the EBCC tasks, suggesting that the overall deficit observed in the depressed group is not applicable to all depressed persons. Furthermore, depressed learners were not restricted to those with the mildest depressive symptoms, but rather some of the most depressed persons in this study could be characterized as "depressed learners." Characteristics that may be associated with the observed variability in EBCC performance in the depressed group should be assessed in future investigations, including age of onset, length of illness, number of depressive episodes, depressive subtypes, quality of life measures, and demographic variables.

Limitations of the study include a small sample size and completion of multiple paradigms by each participant. In addition, analyses of individual EBCC responses (i.e., nonadpative, adaptive, trials to 40% criterion, and number of Pavlovian CRs) should be interpreted with caution due to the multiple comparisons made and the absence of an overall group difference in MANOVA analyses. These data, however, suggest the need for future investigation of these characteristics in persons with depression.

Despite the fact that patients with depression frequently report difficulties with learning, memory, and concentration, little is known about how to remedy these impairments and few treatment protocols for depression directly address these problems. Current approaches to the study of cognition and depression have produced equivocal answers to the question of what specific types of cognitive processes are affected by depressive disorders. EBCC may provide a novel and non-invasive approach to understanding these difficulties in depressive disorders, and when used in conjunction with other cognitive assessments, may provide a more complete understanding of the nature of cognitive dysfunction associated with depression.

Acknowledgements

The authors would like to thank W. Jay Dowling, PhD, Hervé Adbi, PhD, and Bert Moore, PhD, for their contributions to this project, and Bruce Grannemann, MS, for statistical support. The authors also thank David Savage and Melissa Haldeman for technical and secretarial support and Eric Nestler, M.D., PhD, Lou and Ellen McGinley Distinguished Professor and Chairman, Department of Psychiatry, University of Texas Southwestern Medical Center, for administrative support. This study was conducted as part of the doctoral dissertation requirement at the University of Texas at Dallas.

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