
Cerebellar Functional Abnormalities in Schizophrenia Are Suggested by Classical Eyeblink Conditioning

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Background: Previous research suggests that schizophrenia may result from disruptions in a cortico-cerebellar-thalamic-cortical circuit (CCTCC) producing a mental incoordination or "cognitive dysmetria." To further evaluate the cerebellar contribution to this disrupted circuitry, medication-free patients with schizophrenia completed classical eyeblink conditioning, a cerebellar-mediated learning task.

Methods: For classical eyeblink conditioning, 70 trials with a tone conditioned stimulus (CS) and air puff unconditioned stimulus (US) were presented to 15 patients with schizophrenia and 15 healthy control subjects. Acquisition rate for the conditioned response (CR) and response timing were compared between the two groups.

Results: Patients with schizophrenia displayed facilitated conditioning compared to control subjects based on a greater number of CRs during the session and a faster acquisition of the learned response.

Conclusions: Facilitated conditioning suggests that an enhanced excitability in the cerebellum occurs as part of a disrupted CCTCC in schizophrenia. The enhanced cerebellar-mediated associative learning may be maladaptive in the context of normal cerebro-cerebellar interactions, leading to the characteristic motor and mental incoordination of the disorder. Classical eyeblink conditioning may provide a useful model system for studying cerebellar involvement in the pathogenesis and treatment of schizophrenia. *Biol Psychiatry* 2000;48:204–209 © 2000 Society of Biological Psychiatry

Key Words: Schizophrenia, cerebellum, cerebellar circuits, classical eyeblink conditioning, associative learning, neuropsychology

Introduction

Although a heterogeneous disorder, accumulating evidence suggests that schizophrenia is a result of disrupted development in a cortico-cerebellar-thalamic-

cortical circuit (CCTCC) producing impairment in a fundamental cognitive process (Andreasen et al 1998). Cerebellar abnormalities within the CCTCC are suggested by the relationship of cerebellar morphology to symptoms and outcome (Wassink et al 1999), and by positron emission tomography (PET) studies showing cerebellar abnormalities at rest (Andreasen et al 1997) and during cognitive tasks (Andreasen et al 1996; Crespo-Facorro et al 1999; O'Leary et al 1996; Paulsen et al 1998; Wiser et al 1998). This evidence, in conjunction with research demonstrating a cerebellar role in nonmotor function (Houk and Wise 1995; Leiner et al 1986; Middleton and Strick 1994; Schmahmann 1991), indicates that schizophrenia may be the result of "cognitive dysmetria," a disorder of mental coordination resulting from a dysfunctional CCTCC (Andreasen et al 1996).

Despite the research evidence supporting the CCTCC model of cognitive dysmetria, the specific cerebellar functional abnormalities in schizophrenia have not been identified. One approach for evaluating cerebellar function is classical eyeblink conditioning, an associative motor learning task. Classical eyeblink conditioning involves the paired presentation of a neutral conditioned stimulus (CS), such as a tone, followed by an unconditioned stimulus (US), such as an air puff across the eye. The US evokes an unconditioned response (UR), which is the eyeblink. With repeated CS-US paired presentations the subject "learns" to blink prior to the US. This eyeblink is the conditioned response (CR) which, after a sufficient number of paired trials, is timed so that peak eyelid closure occurs near the onset of the US (Gormezano et al 1983). The neural circuitry underlying classical eyeblink conditioning essentially involves the cerebellum, as indicated in both animal (McCormick and Thompson 1984) and human (Daum et al 1993; Topka et al 1993) studies.

Based on the detailed understanding of the neurobiology of this type of associative learning, we undertook a study of eyeblink conditioning in medication-free patients with schizophrenia to identify specific cerebellar functional abnormalities underlying the disorder. We hypothesized that cerebellar abnormalities in schizophrenics would produce abnormal associative learning and poor timing of the eyeblink response, based on findings from an earlier study of adult psychiatric patients (Spain 1966).

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Methods and Materials

Subjects

A total of 15 subjects with schizophrenia were recruited through the University of Iowa Mental Health Clinical Research Center for classical eyeblink conditioning. All subjects had an established diagnosis of schizophrenia based on the DSM-IV (American Psychiatric Association 1994) and structured interview with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992). All were assessed while medication free (no medications for the past 3 weeks), because of the potential effects of medication on eyeblink conditioning (Sears and Steinmetz 1990). A group of 15 healthy volunteers were recruited from the community as a comparison group. Volunteers were screened using an abbreviated version of the CASH to rule out a history of psychiatric disorder. The patient and control groups were comparable in gender (11 men, 4 women) and age (patient group age, mean (M) = 32.8 years, SD = 9.8, range = 20–49; control group age, M = 31.3 years, SD = 7.2, range = 21–41). All subjects had normal hearing (based on a hearing screen) and no identified neurological abnormalities.

Procedures

EYEBLINK CONDITIONING. For eyeblink conditioning, subjects wore headphones for delivery of the tone CS (75 dB, 1-kHz) and eyeglasses equipped to deliver the air puff US (5 psi) to the left eye. The eyeglasses also contained an infrared photobeam system for recording eyeblinks. Stimuli presentation was controlled by computer and the eyeblink response, recorded as eyeblink amplitude and latency, was digitized and stored for subsequent analysis. A total of 70 trials were presented to subjects during the acquisition phase of training. Every tenth trial was a CS-alone trial to evaluate the CR without the US. The remaining trials were CS-US paired presentations. The tone CS was presented for 500 ms and coterminated with the 100 msec US producing a 400 msec interstimulus interval (ISI) for delay conditioning. The interval between trials ranged from 8 to 16 sec (M = 12 sec). Following the 70 acquisition trials, subjects received 40 extinction trials consisting of unpaired CS and US presentations. During conditioning, subjects viewed a silent movie in order to maintain similar levels of attention and arousal across subjects. A background 65 dB white noise was provided between trials.

DATA ANALYSIS. A CR was counted if the eyeblink amplitude exceeded 10% of the subject's baseline UR amplitude (based on the mean UR amplitude for 10 US-alone trials presented prior to acquisition trials) and if the eyeblink response occurred between 200 and 400 msec after CS onset. Eyeblinks occurring prior to 200 msec after CS onset were counted as "alpha" responses (i.e., short-latency, tone-evoked nonassociative responses). Both an alpha response and CR were recorded for a trial if an alpha response was followed by eyelid opening and a second eyeblink (i.e., a "double-peaked" eyeblink response) during the 200–400 msec post-CS period.

Associative learning and timing of the classically conditioned eyeblink response were compared between groups using the percentage of CRs across the acquisition phase, the number of

trials needed to reach a learning criterion of 7 CRs across 10 trials, the average eyeblink latency, and the CR latency and amplitude for CS-alone trials. The mean percentage of CRs during acquisition and the mean number of trials needed to reach the 70% CR learning criterion were compared with one-tailed t tests (due to expectations of facilitated conditioning based on a previous study [Spain 1966]). The group difference in eyeblink onset latency was also compared using a two-tailed t test followed by an analysis of covariance to evaluate the latency difference between groups while controlling for differences in conditioning level (indicated by the percent CRs for each subject). Further analysis of the "topography" of the CR was completed by comparing CR latency and peak amplitude for CS-alone trials, where the performance of the CR is not altered by the presence of the US. Because differences in eyeblink responses could be due to nonassociative factors, we also evaluated group differences in the number of alpha responses (on trials without a CR) and UR latency on US-alone trials to determine if sensory- or motor-related factors could account for learning differences.

Results

Conditioned Responses

Patients with schizophrenia had a significantly higher percentage of CRs than control subjects during eyeblink conditioning trials ($t = 1.89$, $p_1 = .03$). The schizophrenia group had a mean of 63% CRs compared to 47% CRs for the control group. All subjects demonstrated extinction of the learned response, based on a decrease in CR amplitude during the extinction phase, indicating that group differences were learning related. Facilitated conditioning in schizophrenia was also not accounted for by differences in motor function based on performance of the UR. In fact, the UR latency (assessed on air-puff alone trials) was significantly longer in patients with schizophrenia ($M = 84$ msec) than control subjects ($M = 60$ msec; $t = 3.5$, $p_2 = .002$). Differences between groups in CRs also did not appear to be related to increased alpha responses, because there were no group differences ($t = 0.24$) in the number of these responses across trials (schizophrenia = 5.8%, control = 5.4%).

Acquisition Rate

Figure 1 displays the percentage of CRs for each group across the 70 acquisition trials with the mean percentage of CRs broken down into 10-trial blocks to illustrate group differences in CR acquisition. The schizophrenia group acquired CRs at a significantly faster rate than the control group ($t = 2.89$, $p_1 = .004$), based on the number of trials needed to reach a 70% CR learning criterion. The mean number of trials needed to reach learning criterion was 23.3 for the schizophrenia group and 44.4 for the control group.

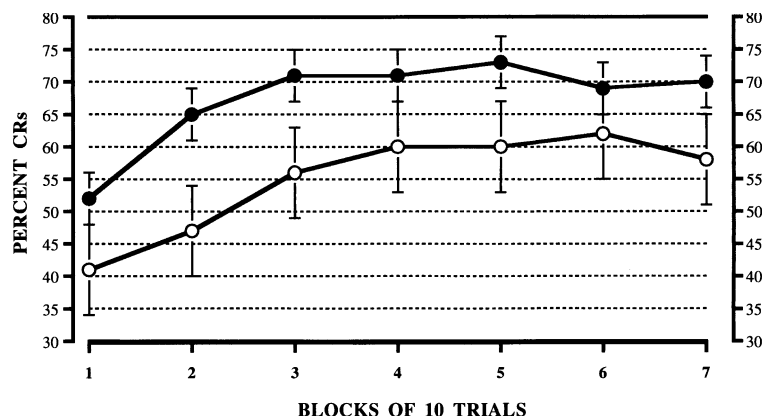


Figure 1. Percent conditioned responses (CRs) across 10-trial blocks for medication-free patients with schizophrenia (●) and healthy control subjects (○). Patients with schizophrenia displayed facilitated eyeblink conditioning based on the increased number of conditioned responses across the 70 trials. The bars represent the SEM for each block of trials.

Response Timing

The onset latency of eyeblinks relative to CS onset is displayed in Figure 2, where the 70 trials are displayed as 10-trial blocks. For the entire session the eyeblink onset latency for the schizophrenia group ($M = 336$ msec) was shorter than for control subjects ($M = 392$; $t = .205$, $p_2 = .04$). The analysis of covariance indicated that when group differences in conditioning level were taken into account the timing of the eyeblink was similar for both groups ($F = 0.64$, $p = .43$).

CS-Alone Trials

There were no significant differences ($t = 1.29$) in the CR latency during CS-alone trials between the schizophrenia ($M = 331$ msec) and control groups ($M = 356$ msec), in agreement with results of the analysis of covariance for response timing. CR amplitude, however, was significantly increased ($t = 3.19$, $p_{\alpha 2} = .001$) in schizophrenia ($M = 36.2$) compared to control subjects ($M = 23.6$).

Discussion

Results of this study indicate that medication-free patients with schizophrenia acquire the classically conditioned eyeblink response more rapidly than control subjects. The rapid acquisition was not due to differences in performance of the eyeblink motor response (based on UR latency) or nonassociative sensory processes (based on a comparison of alpha responses). Although the eyeblink onset latency was shorter for patients with schizophrenia, this difference was accounted for by the enhanced conditioning level in schizophrenia (as indicated by the increased number of CRs). The finding of facilitated classical eyeblink conditioning in schizophrenia supports the observations of a previous study (Spain 1966), where eyeblink conditioning was compared in 32 male schizophrenic patients and 24 control subjects. Our study extends these findings by including response timing as a conditioning variable, using a medication-free group of noninstitutionalized subjects, and by studying a group of pa-

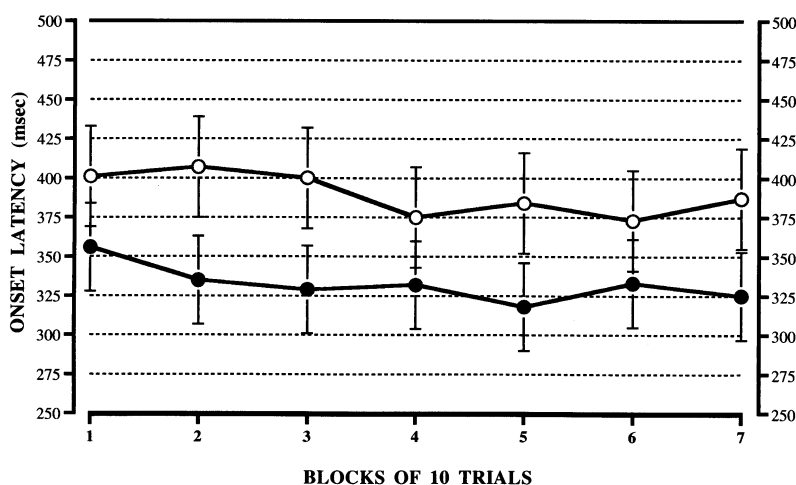


Figure 2. Eyeblink onset latencies (latency to the eyeblink following conditioned stimulus [CS] onset) for medication-free patients with schizophrenia (●) and healthy control subjects (○). Patients with schizophrenia displayed earlier onset of the conditioned responses, reflecting facilitated conditioning. With learning, the eyeblink occurs before the unconditioned stimulus onset (i.e., 400 msec following CS onset). The bars represent the SEM for each block of trials.

tients rigorously diagnosed using relatively narrow modern diagnostic criteria.

The purpose of this study was to identify classical eyeblink conditioning abnormalities in schizophrenia that may relate to cerebellar dysfunction, based on our understanding of the neural circuitry underlying learning of the eyeblink response. Extensive animal and human studies indicate that the cerebellum is essentially involved in eyeblink conditioning with critical sites of plasticity including the cerebellar cortex and deep cerebellar nuclei (Thompson et al 1997). Information regarding the CS and US reach the cerebellum via mossy and climbing fibers, respectively, contacting both the deep nuclei and Purkinje cells in the cerebellar cortex. This cerebellar circuitry supports associative learning (i.e., the subject “learns” that the CS signals the US) and appears to be functionally enhanced in schizophrenia.

Mechanisms Underlying Facilitated Conditioning

The neural mechanisms that may be associated with facilitated conditioning in schizophrenia have not been identified. One possibility is that eyeblink conditioning is enhanced through increased brainstem excitation, such as may occur in association with basal ganglia lesions (Daum et al 1996). Abnormalities in frontostriatal pathways, indicated by decreased blood flow, have been identified in schizophrenia in conjunction with increased cerebellar blood flow (Andreasen et al 1997). This paradoxical relationship could account for enhanced cerebellar-mediated associative learning in the context of the general cognitive deficits (presumably involving cerebral cortex) that is observed in schizophrenia (Mohamed et al 1999). This pattern of facilitated cerebellar function with impaired forebrain function parallels an early model described by Hughlings-Jackson (1931), who suggested that the symptoms of schizophrenia result from both “disease” and a “release” phenomena occurring in connected brain regions. Increased brainstem arousal, such as through this type of mechanism, could account for facilitated conditioning. Further studies of eyeblink conditioning that include measures of arousal during conditioning will be important for examining the relationship of arousal and learning in schizophrenia and, potentially, the underlying brainstem–cerebellar functional abnormalities.

A second possibility is that the enhanced cerebellar-mediated associative learning capacity is due to an abnormality in cerebellar development. This type of abnormality is consistent with evidence that schizophrenia is a neurodevelopmental disorder (Woods 1998). Classical eyeblink conditioning has been studied in mutant mice allowing for analysis of the effects of cerebellar maldevelopment on learning. A variety of developmental abnormalities im-

pairing eyeblink conditioning have been described in mutant mice, such as Purkinje cell loss (Chen et al 1996) and absent brain-derived neurotrophic factor (Bao et al 1998). In contrast, facilitated eyeblink conditioning occurs in a knockout mouse deficient in the γ isoform of protein kinase C (PKC γ ; Chen et al 1995). This mouse fails to eliminate multiple climbing fiber–Purkinje cell synapses during development and, as a result, Purkinje cells are innervated by multiple climbing fibers in the adult (in contrast to the normal pattern of single climbing fiber innervation [Kano et al 1995]). The facilitated conditioning in the PKC γ mouse may be due to an enhanced “teaching” input to the cerebellum that is provided by increased climbing fiber innervation of Purkinje cells (Chen et al 1995). The supranormal error correction system resulting from multiple climbing fiber innervation may enhance long-term depression in cerebellar cortex, a potential mechanism of cerebellar learning, and increase excitability in the deep nuclei based on a reduction of cerebellar cortical inhibition (Ito 1989). Despite this enhanced associative motor learning, the PKC γ mouse is impaired in motor coordination. Thus, this mouse model parallels findings in schizophrenia where facilitated conditioning (observed in this study) occurs in the context of motor incoordination (Vrtunski et al 1989).

Relevance for Schizophrenia

In addition to identifying deviant cerebellar function in schizophrenia, the findings of facilitated conditioning may have relevance for understanding the symptoms of the disorder. Facilitated conditioning has not been typically observed in studies of other disorders of brain development. For example, delay eyeblink conditioning has been reported to be normal (or impaired under certain conditions) in persons with mental retardation of unknown etiology (Ohlrich and Ross 1968) and in Down syndrome and Fragile X syndrome (Woodruff-Pak et al 1994). Interestingly, facilitated conditioning has been reported in autism (Sears et al 1994), a developmental disorder with behavioral characteristics similar to the negative symptoms in schizophrenia. Schizophrenia and autism may also share similar patterns of cerebellar functional abnormalities. Neuroimaging studies using PET indicate increased cerebellar metabolism at rest in both schizophrenia (Andreasen et al 1997) and autism (Chugani et al 1997), suggesting that both disorders may share a common increased excitability in the cerebellar circuitry.

Our research group has proposed that schizophrenia may result from “cognitive dysmetria” (Andreasen et al 1996), a disturbance of cerebellar–forebrain interaction resulting in poor mental coordination, similar to the motor incoordination resulting from cerebellar lesions (Schmah-

mann 1991). Evidence for disruption in the motor component of the cerebrocerebellar system is suggested by slowed reaction time (Shakow and Huston 1936) and motor incoordination (Vrtunski et al 1996). The specific abnormalities in mental coordination are not identified, but could involve a variety of processes including timing, sequencing, and modifying responses based on corrective feedback. Findings of our study suggest that the mental incoordination may relate to abnormalities in the associative learning function served by the cerebellum.

Although intuitively, enhanced cerebellar plasticity may be expected to lead to improved cognition, it may alternatively lead to abnormal cerebellar–forebrain interactions. The normal role of the cerebellum in refining the compound movements controlled by cerebral cortex (Ito 1984) may be disrupted because of altered interactions of the cerebellum and forebrain regions. Thus, the enhanced associative learning in the cerebellum may not be adaptive for the generation of coordinated mental and motor responses. An associative learning abnormality of this type may produce improper connections of perceptions and associations leading to delusions and hallucinations (Andreasen et al 1999). Likewise, aberrant associations in the language system may lead to disconnected speech and “thought disorder.” Associative learning, based on these examples, could be considered an essential mechanism of brain plasticity underlying a variety of cognitive functions. Alternatively, the associative learning abnormality may not be causative but may be a result of cerebellar dysfunction associated with a variety of separate cognitive and affective abnormalities (Schmahmann 1991). Further research on the relationship of eyeblink conditioning to symptoms and neuropsychological function may indicate the significance of facilitated conditioning in schizophrenia.

Eyeblink conditioning may also provide a useful model for studying medication effects in schizophrenia. Haloperidol, for example, has been shown in the rabbit preparation to alter the sensory threshold for processing the CS and to decrease deep cerebellar neural activity (Sears and Steinmetz 1990). This finding suggests that one beneficial effect of haloperidol may result from a decrease in excitability in the deep cerebellar nuclei and a reduction in the hypothesized cerebellar hyperexcitability in schizophrenia. Thus, the more “normalized” cerebellar function that may occur with haloperidol may produce more adaptive responses and improved mental coordination by reducing the discrepancy between cerebellar and forebrain function. Evaluating eyeblink conditioning in subjects with schizophrenia while on medication can further test this model.

Conclusions

Patients with schizophrenia display facilitated eyeblink conditioning suggesting enhanced cerebellar-mediated as-

sociative learning. This enhanced associative learning may be abnormal in the context of typical cerebellar–forebrain interactions and disrupt the CCTCC, leading to cognitive dysmetria, a disturbance in mental coordination hypothesized to underlie schizophrenia. Future research using classical eyeblink conditioning will be helpful in understanding the relationship of cerebellar dysfunction to the deficits and symptoms of schizophrenia. Eyeblink conditioning may also provide a useful animal model for studying the etiology and treatment of the disorder.

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