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Impaired fear conditioning in Alzheimer's disease

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Abstract

Classical conditioning of the fear response is a basic form of nondeclarative (nonconscious) memory that mediates both normal and pathological responses to aversive stimuli. Because fear conditioning critically depends on the amygdala, a medial temporal lobe structure that frequently undergoes significant pathological changes early in the course of Alzheimer's disease (AD), we hypothesized that fear conditioning would be impaired in patients with mild to moderate AD. We examined simple classical fear conditioning in a group of 10 patients with probable AD and 14 demographically matched, neurologically intact elderly controls. During conditioning, one stimulus (e.g. a green rectangle, the conditioned stimulus (CS+)), was paired with an aversive stimulus (a loud noise, the unconditioned stimulus (US)) using a partial reinforcement conditioning schedule. The opponent color (e.g. red rectangle), the CS−, was never paired with the US. The elderly controls acquired robust fear responses as demonstrated by their differential skin-conductance responses to the CS+ and CS−. In contrast, the AD group showed a marked impairment in conditioning, failing to exhibit significant conditioned fear responses. This failure to acquire conditioned responses could not be attributed to diminished responding by patients, relative to controls, to the aversive US. The results indicate that fear conditioning, an amygdala-dependent form of memory, is impaired in AD. These findings complement previous reports of impairments in declarative emotional memory in AD by demonstrating that a basic form of nondeclarative emotional memory is also impaired in AD.

Keywords: Conditioning; Amygdala; Memory; Aversive; Nondeclarative; Emotion

1. Introduction

The process by which a stimulus comes to elicit a conditioned aversive response through pairing with an aversive stimulus is referred to as fear conditioning [9,47]. Fear conditioning is an important basic learning mechanism in humans and non-human animals, allowing rapid behavioral adaptation to new threats [26,48]. In addition to this adaptive function, however, fear conditioning is also implicated in the mechanisms that underlie maladaptive, pathological fear responses such as those seen in anxiety disorders [17,32,33,36,48].

The basic neural mechanisms of fear conditioning appear to be relatively conserved across species [34]. The non-human animal model of fear conditioning has been extensively studied, and the mechanisms and pathways involved in fear conditioning have been mapped in detail. Fear conditioning is classified as a form of nondeclarative or nonconscious memory [54] because it can occur outside of awareness [19,35,48] and does not depend on the hippocampus and related structures that support forms of declarative or conscious memory such as recall and recognition [55,56].

Recent lesion and neuroimaging studies with humans suggest that the same brain networks are involved in fear conditioning as in experimental animals [5,10,30,31]. The basic fear conditioning circuit involves cortical sensory processing areas, the thalamus, and the amygdala [18,37]. Of these areas, the amygdala is thought to be the critical structure, in part because lesions to this area result in impairments in fear conditioning [17,35]. Because the basic mechanisms of fear conditioning are well understood, impairments observed in humans can be related to their neural basis.

It is currently unknown whether fear conditioning is affected in Alzheimer's disease (AD). In addition to the well-characterized declarative memory deficits in AD, classical conditioning of the eyeblink reflex has been found to be severely impaired in AD [60,61]. This deficit has been related to pathological changes in the hippocampal region, a region critical for this form of conditioning [57,61]. It is well-established that histopathological changes and atrophy frequently occur in the amygdala in early AD [6,13,25,41,57,58]. On the basis of MRI morphometry, the

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amount of amygdalar atrophy in early AD has been estimated at approximately 35%, although the degree of atrophy can be highly variable across cases [13,16,38,44,50,51]. Based on the pathological changes which typically occur in the amygdala in early AD, we predicted that fear conditioning would be impaired in patients who were in the early-stages of AD and had only mild cognitive impairments.

We investigated the status of fear conditioning in AD by comparing the performance of 10 patients with mild-to-moderate probable AD to 14 demographically matched, neurologically intact elderly control subjects. Fear conditioning was assessed by measuring skin-conductance responses (SCRs), an index of autonomic arousal. Following an initial familiarization phase, one of two color stimuli was repeatedly paired with an aversive unconditioned stimulus (a loud noise), a procedure that typically results in robust acquisition of fear responses to the paired color stimulus in unimpaired subjects. After this acquisition phase, extinction of the conditioned response (i.e. decrement in the conditioned fear response following repeated nonreinforcement) was examined by repeatedly presenting the color stimuli without the unconditioned stimulus. Of primary interest was whether the AD patients would be impaired in their acquisition of the conditioned fear response relative to the elderly control subjects.

2. Method

2.1. Subjects

Ten patients with probable AD (four men and six women) completed the experiment. An additional six probable AD and five healthy elderly participants were excluded because they failed to meet the inclusion criteria for this study. All patients were enrolled in the National Institute on Aging supported Emory Alzheimer's Disease Center. They were diagnosed by neurologists and neuropsychologists using criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [40]. The patients were classified as mildly to moderately demented according to their scores on the mini-mental state exam (MMSE), mean score = 19.8 points (range = 14–24) [21]. Scores on additional tests assessing dementia and depression were available for 9 of the 10 patients. The mean score on the Mattis Dementia Rating Scale [39] was 111.8 points, with all but one patient scoring in the mild to moderate range (range = 109–129; one patient scoring 62), and the mean score on the Clinical Dementia Rating Scale [27] was 0.8, with all but one patient scoring in the mild to moderate range (range = 0.5–1.0; 2.0 for the same patient outlier). The mean score on the Geriatric Depression Scale [8] was 7.6 (range = 1–19). The AD group had a mean age of 70.0 years (range = 56–81 years) and had 15.0 years (range = 9–19 years) of education. Six patients were taking Aricept for cognitive impairment and four were taking selective serotonin reuptake inhibitor medication.

A total of 14 demographically matched healthy elderly individuals (11 females and 3 males) also completed the experiment (elderly control group, ELD). Elderly subjects were recruited from a pool of community-dwelling volunteers and had a mean age of 66.2 years (range = 57–80 years) and 15.3 years (range = 10–18 years) of education. These subjects had an average score of 29.1 points (range = 28–30) on the MMSE.

There were no significant differences ($P > 0.05$) between the patients and controls in age, education, or in the distribution of gender. There was no previous history of neurologic disease (e.g. strokes, seizures), neuropsychiatric disorders, or substance abuse in either group. This study was reviewed and approved by the Emory University School of Medicine Human Investigations Committee. All subjects gave informed consent prior to the start of the experiment.

2.2. Inclusion/exclusion criteria

Fear conditioning is typically assessed in humans through SCRs, measured in microSiemens units of electrical conductance [5,30,31]. The SCR is a change in the skin's electrodermal conductance associated with an event. SCRs provide an index of emotional arousal and can thus be used to measure the magnitude of an aversive response. During fear conditioning, SCRs which are initially elicited by an unconditioned stimulus (US) such as a loud noise gradually begin to be elicited by a previously neutral stimulus (CS+) paired with the US.

Pilot testing indicated that elderly control subjects who exhibited low SCRs to the US showed little acquisition of fear conditioning. This is consistent with the well-established finding that the acquisition of conditioned fear responses depends on the presence of adequate unconditioned responses to the US [53]. Therefore, a minimal criterion for unconditioned responding to the US was established for purposes of subject inclusion based on these pilot data. Subjects who failed to show a minimum mean square-root transformed SCR of 0.5 microSiemens across the first four unconditioned noise stimuli were not included further in the data analysis. The total number of subjects excluded on the basis of these criteria was six AD patients and five controls. Approximately 25% of the adult population under 25 does not show measurable SCRs to any physical stimuli [59]. In addition, electrodermal nonresponsiveness increases with advancing age, in part due to diminished eccrine gland activity in the skin [22,52].

All subjects were screened for color-blindness and severe hearing impairment. Color-blindness was assessed with the Ishihara color test [28] presented on a color computer monitor. None of the subjects exhibited evidence of color-blindness. Hearing acuity was assessed with a hand-held audiometer (Oto Screen I, Handtronix Inc., Logan, UT).