Biological Psychology 83 (2010) 41–46

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

The effects of medial temporal lobe resections on verbal threat and fear conditioning

Fredrik Åhs [a,*], Örjan Frans [a], Bodil Tibblin [b], Eva Kumlien [b], Mats Fredrikson [a]

[a] Department of Psychology, Uppsala University, Box 1225, 751 42 Uppsala, Sweden
[b] Department of Neuroscience, Neurology, Uppsala University Hospital, 751 84 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 28 June 2007
Accepted 7 October 2009
Available online 27 October 2009

Keywords:
Amygdala
Anxiety
Startle
Electrodermal activity
Temporal lobectomy
Trace conditioning

ABSTRACT

A left hemisphere advantage in the processing of verbal threat has previously been reported, whereas both hemispheres seem equally important in fear conditioning. Here, we compared the effects of unilateral medial temporal lobe (MTL) resections on verbal threat as well as delay and trace fear conditioning. During verbal threat, right and left MTL-resections attenuated fear potentiated startle in comparison with controls. In contrast to previous studies, MTL-resections did not attenuate delay conditioning of skin conductance responses. Left and right resectioned patients did not differ in psychophysiological responses to verbal threat or delay fear conditioning. Trace conditioning was not observed in any group. Results suggest a bilateral MTL hemispheric involvement in the processing of verbal threat, whereas one intact hemisphere seems sufficient for delay conditioning.

1. Introduction

Fear and anxiety are adaptive responses to potentially dangerous stimuli. Anticipatory fear and anxiety responses can be evoked both by verbal instructions and by fear conditioning. During fear conditioning, fear reactions are conditioned to initially neutral cues that gain biological salience by being paired with an aversive event. A cognitive representation of the threat has been hypothesized to increase vigilance during instructed threat whereas cued fear conditioned reactions seem less dependent on cognitive representations (Funayama et al., 2001). The aim of the present study was to investigate the necessity of the anterior temporal lobe for autonomic reactivity evoked by shock anticipation and fear conditioning in patients with unilateral resections of the anterior medial temporal lobe (MTL) and healthy controls. The primary hypothesis was that verbal threat of shock would be dependent on the integrity of the left MTL, due to the preferential involvement of this hemisphere in language functions.

The neural circuitry of fear conditioning is well characterized and has been studied by pairing a neutral cue (conditioned stimulus, CS) to an aversive event (unconditioned stimulus, US) (LeDoux, 1998). There are two principal modes of acquiring conditioned fear which differ in the timing between the CS and US. The CS can overlap the US called delay conditioning, or there can be a time lag between the offset of the CS and the onset of the US referred to as trace conditioning. Delay conditioning is dependent on amygdala plasticity (LeDoux, 1998) whereas trace conditioning, in addition to the amygdala, has been attributed to hippocampal functioning (McEchron et al., 1998; Trivedi and Coover, 2006).

Previous studies of delay fear conditioning in patients with unilateral lesions to the MTL (LaBar et al., 1995; Peper et al., 2001; Weike et al., 2005) reported reduced conditioned responses as indexed by SCR when compared to a control group. Weike et al. (2005) also observed reduced startle potentiation to the reinforced stimulus in MTL-resectioned groups. However, no laterality effects have been established when comparing the right and left resectioned patients in the above studies. It is probable that damage to the amygdala and not the hippocampus accounts for the results in the studies by LaBar et al. (1995), Peper et al. (2001) and Weike et al. (2005) because a study comparing patients with selective bilateral damage to either the amygdala or the hippocampus only found reduced conditioned SCRs in patients with amygdala damage (Bechara et al., 1995). From these reports it seems plausible that the amygdala plays a role in human fear conditioning and that both hemispheres contribute equally to this form of learning.

Explicit knowledge of the stimulus contingencies has a positive effect on startle potentiation and skin conductance responses in delay conditioning (Grillon, 2002). Contingency awareness also has been shown to influence startle potentiation in trace fear conditioning (Weike et al., 2007). Due to the verbal nature of

* Corresponding author. Tel.: +46 18 4717843.
E-mail address: Fredrik.ahs@psyk.uu.se (F. Åhs).

0301-0511/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2009.10.002

contingency awareness, it was hypothesized that decreased awareness would be observed among subjects with left sided resections. It was further hypothesized that decreased contingency awareness in turn would affect trace fear conditioning more than delay conditioning in this group, because trace conditioning is more dependent on contingency awareness than delay conditioning (Carter et al., 2003).

Collectively, data support a possible bilateral involvement of anterior MTL structures in fear conditioning while results suggest a left hemisphere advantage in responding to verbal threat. Here, emotional behaviors were compared in subjects with resections to either the right or left anterior MTL due to medically intractable epilepsy. Startle potentiation was first measured during verbally instructed threat of electric shock. Delay and trace fear conditioning was then assessed. In addition to startle, skin conductance and shock expectancy were also measured during fear conditioning. Interactions were thus explored between resection side and emotional behavior during delay and trace fear conditioning as well as during shock anticipation with the aim to detect laterality differences in fear responses during verbal threat and cued fear.

2. Methods

2.1. Subjects

Thirty-three subjects who had undergone temporal lobe epilepsy surgery and 16 control subjects (mean age 35 ± 9.4 years, 8 women) were recruited. Nineteen subjects had resections to the left temporal lobe (left MTL-group, mean age 45 ± 9.7 years, 10 women) and 14 resections to the right temporal lobe (right MTL-group, mean age 44 ± 12.5 years, 8 women). Surgery was performed as an anterior medial temporal resection including amygdalohippocampectomy (Spencer et al., 1984) at one centre at Uppsala University Hospital. Mean age at epilepsy onset was 18.2 ± 10 years and 16.0 ± 10 years, and time since surgery at study participation was 8.2 ± 4.2 years and 6.6 ± 2.6 years in the left and right MTL-groups respectively. All demographic data are presented in Table 1. Five subjects (1 with left sided resections and 4 with right sided resections) were excluded from further analysis because of excessive amount of zero startle responses (>25%) during one or more than one of the conditions. The study was approved by the local ethics committee and all subjects signed informed consent.

2.2. Verbal threat

Subjects were seated in a comfortable armchair and were told to relax while 8 acoustic startle probes were delivered (baseline) with a mean inter-trial interval (ITI) of 18 s. During the verbal threat assessment (Anticipation) two electrodes for delivery of electric shock were applied to the right forearm and subjects were instructed that they were soon going to receive a shock but that they would first again hear noise bursts. After the instruction, 8 startle probes (mean ITI = 18 s) were delivered again. The shock level was then adjusted for each individual to be rated as "aversive but not painful".

2.3. Delay and trace fear conditioning

No explicit information about the CS–US relationship was given to the participants prior conditioning. The fear conditioning paradigm started with a habituation phase, where geometrical shapes consisting of a triangle, a circle and a square were shown on a computer screen 3 times each. No shocks were delivered during the habituation phase. An acquisition phase followed, where the delay conditioning stimulus (CSd+) always terminated with an electric shock delivered on the right forearm through two cup electrodes (Ag–AgCl). The trace conditioning stimulus (CSt+) was always followed by a 10 s trace interval before deliverance of electric shock. The CS− was never followed by an electric shock. Stimuli were shown 10 s with a 26 s mean ITI and were presented 6 times each. The electric shocks had a 0.5 s duration. A startle probe (see below) was presented on half of the CSd+, CSt+ and CS− presentations and half of the ITI's 5 s after onset. A startle probe was also delivered on half of the trace intervals 5 s after the CSt+ offset to measure conditioning during the trace interval. Conditioned stimuli were counterbalanced and presented in a pseudo-random order so that not more than 2 trials of the same CS were presented consecutively. Due to technical problems with the stimulus presentation software, data from the extinction phase were corrupted and could not be analyzed. See Fig. 1 for an illustration of the general out-line of the whole session together with of the individual CS−, CSd+ and CSt+ trials.

2.4. Startle

Electromyography (EMG) registration was performed using Psylab (Contact Precision Instruments inc., London, UK). Two Ag–AgCl electrodes were used, one placed under the pupil, the other 1–2 cm lateral to the first (Blumenthal et al., 2005). The ground electrode was placed on the forehead. For half of the patients in each resectioned group, the electrodes were placed under the right eye. For the other half electrodes were placed under the left eye. In the control group, 9 persons had the electrodes placed under the right and 7 under the left eye. This way the MTL-patients could be grouped into one group with the electrode placement contralateral to the resection (right resection-left eye and left resection-right eye) and one group with electrode placement ipsilateral to the resection (right resection-right eye and left resection-left eye) to investigate possible differences in ipsilateral and contralateral potentiation of the startle blink reflex with respect to the laterality of the resection. White noise with 100 ms duration and near instantaneous rise time, delivered binaurally through head phones, was used as startle probes. Intensity of the startle probe was gradually increased during a work-up procedure until subjects reported the sound level to be tolerable and not painful. This subjective intensity criterion was used to correct for individual differences in sound level sensitivity and because of ethical considerations. Startle probe intensities (0–100 arbitrary units) did not differ between MTL-groups and controls (mean ± SD MTL-groups: 57.38 ± 31.05 arbitrary units; controls: 52.81 ± 31.57 arbitrary units; t_{35} = 0.44, p = 0.66).

EMG data were collected using 100 Hz sampling rate. Data were low pass filtered at 500 Hz, high pass filtered at 30 Hz, and rectified prior to A/D conversion. Response amplitude was quantified as the maximum response in a time window 20–120 ms after stimulus onset subtracted from a baseline defined as the mean value 100–0 ms prior to stimulus onset. Responses are reported in microvolts. The Kruskal–Wallis test was used to evaluate differences in the number of zero responses between groups and the Wilcoxon signed rank test between conditions. Differences in response probability were not found to be different between conditions or groups with all χ^2 and Z statistics showing p values >0.05.

2.5. Skin conductance responses

Skin conductance was recorded during trace and delay fear conditioning with two Ag–AgCl electrodes filled with isotonic electrolytic gel using Psylab (Contact Precision Instruments Inc., London, UK) using 100 Hz sampling rate. The signal was high pass filtered at 0.1 Hz. Responses were quantified by subtracting the maximum value 1000–4500 ms post-stimulus onset from the mean skin conductance level 500–0 ms preceding onset. To reduce deviance from normality and influence of extreme values, responses were square root transformed prior to statistical analysis.

2.6. Contingency learning

Subjects rated the probability that a shock would follow after the presentation of each CS during delay and trace conditioning immediately following the study in a post-experiment interview. Ratings were performed using a 0–100 scale where 0 represented certainty that no shock would follow the CS and 100 represented certainty that a shock would follow. A rating of 50 indicated uncertainty as to whether a shock would occur or not. A post hoc procedure was used in order not to prime subjects to search for patterns in the presentations of CSs and shocks during conditioning. Ratings are missing for 2 subjects in the left MTL-group who were excluded from the analysis of shock expectancy data.

2.7. Statistical analysis

The mean startle responses during anticipation were subtracted from the mean of the 8 startle responses during baseline to determine startle potentiation. During delay fear conditioning, startle potentiation was defined as the mean startle responses during CSd+ subtracted from the mean ITI startle response. During trace fear conditioning, the mean startle response during the CSt+ as well as the mean startle response during the trace interval was each subtracted from the mean ITI startle response. For SCR data from the acquisition phase, the averages of the 4 last responses for each CS-type were used to reflect conditioned learning. All between-

Table 1
Demographic and neuropsychological data for patients with unilateral resections to the temporal lobe. Means (SD).

	Affected hemisphere	
	Left	Right
n	18	10
Age (years)	45.5 (9.9)	43.9 (13.2)
Age of epilepsy onset (years)	17.7 (8.7)	16.8 (13.6)
Time since surgery (years)	8.2 (4.4)	6.5 (2.8)
Clinical outcome (Engel I/II/III)	10/3/5	9/1/0
Verbal IQ (WAIS)	93.3 (11.5)	103.2 (9.3)[a]
Performance IQ (WAIS)	104.3 (14.3)	109.7 (13.2)[a]

[a] Data are missing for 2 subjects.