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SINGLE PULSE ELECTRICAL STIMULATION OF THE HIPPOCAMPUS IS SUFFICIENT TO IMPAIR HUMAN EPISODIC MEMORY

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Abstract—We have used the single pulse electrical stimulation (SPES) technique to investigate whether more localized stimulation of the hippocampus can affect human episodic memory. A recognition memory test including words, object drawings, abstract drawings and unfamiliar faces was performed without stimulation (baseline) or synchronized with single 1 ms electrical pulses applied to the left, right or both hippocampi in 12 epileptic patients investigated with bilateral depth electrodes. No differences were found in memory performance between baseline and unilateral stimulation, either in the total score or in material-specific scores. In contrast, bilateral stimulation was associated with a pronounced decrease in the median of total memory scores (57%), and of material-specific sub-scores for words (38%), geometrical drawings (81%) and faces (100%). Additional study of stimulation at presentation of stimuli (encoding) versus the recognition memory (retrieval) test phase, showed reduction in memory only at encoding. The results provide causal evidence that the hippocampi are necessary for supporting episodic memory. The induction of memory deficits by bilateral stimulation with parameters that do not induce effects when applied unilaterally suggests that recognition memory can be processed independently by the hippocampus on either hemisphere.

Key words: single pulse electrical stimulation, hippocampal formation, memory deficit, episodic memory, temporal lobe.

Present knowledge on the anatomical structures involved in human memory largely derives from the study of memory deficits induced by brain lesions or surgical resections, and more recently from functional neuroimaging studies. It appears that medial temporal structures, in particular the hippocampal region, including the hippocampus, the adjacent perirhinal, entorhinal and parahippocampal cortices, are critical for the formation of declarative memory (Squire and Zola-Morgan, 1991). Bilateral lesions involving medial temporal structures are associated with severe memory deficits and global, predominantly anterograde amnesia (Scoville and Milner, 1957; Zola-Morgan et al., 1986; Rempel-Clower et al., 1996; Stefanacci et al., 2000). By contrast, unilateral temporal lobectomies which include medial temporal structures induce much milder memory deficits which appear to be material specific: left lesions can selectively impair verbal memory (Milner, 1958; Weingartner, 1968) whereas right lesions seem to impair non-verbal memory (Kimura, 1963; Jones-Gotman, 1986a,b; Abrahams et al., 1997; Bohbot et al., 1998; Spiers et al., 2001; Stepankova et al., 2004). Memory deficits associated with such unilateral lesions tend not to cause pronounced everyday memory impairment (Goldstein and Polkey, 1992; Lacruz et al., 2004). Rare cases of amnesia after a unilateral temporal resection have been reported, presumably due to pre-existence of a contralateral temporal lesion (Baldwin, 1956). Functional magnetic resonance imaging (fMRI) has recently emerged as a useful technique to identify brain areas associated with memory function, but there is some difficulty in determining whether activation patterns are causally related to memory function or secondarily activated as an epiphenomenon from memory processing.

Attempts to study hippocampal function by exploring the effects of lesions on memory have certain limitations, as lesions restricted to this region are rare. Focal unilateral electrical stimulation offers an alternative method for investigating the effects of disruption of hippocampal function. Effectively, it can provide a transient lesion, disrupting neural function around the stimulating electrodes while current is applied, and the effect of suppression of function can be compared against a baseline state without stimulation (baseline). Studies on the cognitive effects of electrical stimulation of the human hippocampus are scarce because they are ethically acceptable only in very specific circumstances, such as during the evaluation of epileptic patients with intracranial electrodes. Feindel and Penfield found arrest of memory encoding when stimulating near the human hippocampus (Feindel and Penfield, 1954). However, disruption of memory performance with unilateral electrical stimulation of human medial temporal structures only occurred in a minority of patients and required the induction of epileptiform discharges (afterdischarges) by the stimulus (Bickford et al., 1958; Halgren and Wilson, 1985). Nevertheless, temporary amnesia could be induced in most patients when stimulating medial temporal structures bilaterally with trains of electrical pulses lasting 3–50 s

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Abbreviations: d', discrimination score; fMRI, functional magnetic resonance imaging; FSIQ, full-scale intelligence quotient; PIQ, performance intelligence quotient; SPES, single pulse electrical stimulation; VIQ, verbal intelligence quotient.

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(Brazier, 1966; Chapman et al., 1967; Ervin et al., 1969). Thus, these early studies suggested that in order to demonstrate an effect on episodic memory, stimulation had to be either unilateral with afterdischarges or bilateral. Such studies, whilst providing further support for hippocampal involvement in memory are subject to the issue of how widely afterdischarges can propagate, preventing localization of the associated disruption in neural function (Alarcon et al., 1994). Later studies provided evidence that electrical stimulation of medial temporal structures at a level below that required for eliciting afterdischarges can induce material-specific deficits in recognition memory tests, either by stimulating unilaterally at a single site (Lee et al., 1988, 1990; Coleshill et al., 2004) or bilaterally at multiple sites (Halgren et al., 1985).

One difficulty in assessing the effects of electrical stimulation on human memory derives from the fact that most studies have been performed using repetitive stimulation at relatively high frequency, typically at 50 or 60 Hz, applied for several seconds around the time of item presentation. This is a rather non-physiological stimulation, where cortical networks are bombarded by new stimuli before returning to their resting state. In addition, it is difficult to evaluate the topography of responses to each pulse due to interference by repetitive stimulation artifacts, and to the amalgamation of responses from successive pulses. Consequently, the extent of propagation of electrical activity induced by repetitive stimulation remains unknown. An alternative is the use of single pulse electrical stimulation (SPES), a safe technique to identify human epileptogenesis used routinely in our centre during presurgical assessment with intracranial electrodes (Valentin et al., 2002, 2005a,b). In addition to its role in identifying epileptogenesis, SPES provides a method to interfere with neuronal function while allowing recording of cortical responses to stimulation. Since single 1 ms electrical pulses induce 100–300 ms cortical responses at most stimulated sites, it can be assumed that single pulses behave as a brief localized reversible lesion, lasting for a few hundreds of milliseconds. We have studied the relevance of the human hippocampus to memory by using a computer-controlled recognition memory test while single 1 ms pulses applied to the left, right or both hippocampi were either absent (baseline) or synchronized with the presentation of items. In order to maximize the effects, stimulation was initially applied during encoding and retrieval tasks.

EXPERIMENTAL PROCEDURES

Subjects

Main experimental protocol (see below Design and procedure). The study included 12 consecutive English-speaking epilepsy patients admitted for video-telemetry monitoring with intracranial depth electrodes at King's College Hospital who fulfilled the following inclusion criteria: (a) patients had bilaterally symmetrically implanted electrodes in the hippocampus, corroborated by MRI or X-ray; (b) clear early responses elicited by SPES applied to each hippocampus, which confirmed that hippocampal structures were stimulated; (c) unilateral stimulation was applied to each hippocampi, (d) Intelligence quotient (IQ) 70 or above; (e) age 16 or above.

Additional experimental protocols (see below Design and procedure). The study included 13 (of which five also underwent the main experimental protocol) English-speaking epilepsy patients admitted for video-EEG monitoring with intracranial electrodes between 2003 and 2010 at King's College Hospital who fulfilled the following inclusion criteria: (a) patients had implanted electrodes in or outside the hippocampus, corroborated by MRI or X-ray; (b) clear early responses elicited by SPES applied to each target region, which confirmed that the target regions were indeed stimulated; (c) IQ 70 or above; (d) age 16 or above.

All patients were fully informed of the nature of the research and gave informed consent according to the Declaration of Helsinki. The experimental procedure was approved by the Local Research Ethics Committee of King's College Hospital (reference number 01-03-004).

Electrode implantation

Main experimental protocol (see below Design and procedure). Bilateral intracerebral (depth) electrodes (supplied by AdTech Medical Instruments Corp., WI, USA) were implanted in the 12 patients. The type, number and location of the electrodes were determined by the suspected location of the epileptogenic zone in each patient, according to previous findings from clinical history, neuroimaging, neuropsychology and electroencephalographic (EEG) recordings. The selection criteria and implantation procedure have been described elsewhere (Elwes, 2000).

Intracerebral (depth) electrodes were multicontact flexible bundles of depth electrodes which were implanted stereotactically under MRI guidance in both hemispheres. The electrodes consisted of 6–10 cylindrical 2.3 mm long platinum contacts separated by 5 mm between centers of adjacent electrodes of the same bundle. On each side, anterior temporal electrodes were placed orthogonally through the lateral temporal cortex. The tip was positioned in the inferior amygdala and more proximal contacts were in contact with the hippocampal head, temporal white matter and lateral temporal cortex. Positioning of electrodes was confirmed by post-implantation MRI (Fig. 1). Contacts located at the hippocampal head were used to stimulate.

Additional experimental protocols (see below Design and procedure). Stimulation of extra-hippocampal structures was carried out via depth electrodes similar to those described above or via subdural strip electrodes. Each subdural strip consisted of a single row of eight platinum disk electrodes spaced at 10 mm between centres. The disks were embedded in a 0.7 mm thick polyurethane strip which overlapped the edges leaving a diameter of 2.3 mm exposed, recessed approximately 0.1 mm from the surface plane.

Stimulation protocol

Stimulation was performed between adjacent electrodes using one or two constant-current neurostimulators approved for use in human subjects (Medelec ST10 Sensor, Oxford Instruments, UK). Stimulation was carried out with monophasic constant-current single pulses of 1 ms duration and current intensity ranging between 4 and 6 mA. Several intensities were tried at 6 mA or below before carrying out the memory tests. If patients reported a facial feeling or twitching associated to each pulse, intensity was reduced until patients did not notice the pulses. The highest intensity at which patients did not notice stimulation pulses was used. In conditions other than baseline, one pulse was delivered every 5 s time locked to a memory item (see below). Only one polarity was used for stimulation. During stimulation, EEG responses were recorded by the electrodes not used for stimulation. For the main