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Connections of the limbic network: A corticocortical evoked potentials study

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ABSTRACT

Papez proposed a network for higher brain function, which is termed the limbic network. However, the *in vivo* human limbic network has not been established. We investigated the connectivity of the human limbic system using corticocortical evoked potential (CCEP). This retrospective analysis included 28 patients with medically intractable focal epilepsy who underwent stereoelectroencephalography (SEEG) and CCEP. Alternating 1 Hz electrical stimuli were delivered to parts of the limbic system [anterior and posterior hippocampus, temporal pole, parahippocampal gyrus (PHG), amygdala, anterior (ACG) and posterior cingulate gyrus (PCG), medial and lateral orbitofrontal cortex (OF)]. A total of 40–60 stimuli were averaged in each trial to obtain CCEP responses. CCEP distributions were evaluated by calculating the root mean square (RMS) of CCEP responses. Anterior hippocampal stimulation elicited prominent CCEP responses in medial and lateral temporal structures, PCG, medial OF and insula over the ipsilateral hemisphere. Posterior hippocampal stimulation induced CCEP responses in the ipsilateral medial and lateral temporal structures and PCG. The findings also revealed connections from temporal pole to the ipsilateral medial temporal structures, and connections from PHG to the ipsilateral hippocampus and PCG. The amygdala projected to broad areas including the ipsilateral medial and lateral temporal structures, medial and lateral frontal areas, the cingulate gyrus, insula and inferior parietal lobule. ACG and PCG showed connections to the ipsilateral medial fronto-parietal areas and connections to bilateral medial temporo-parieto-occipital and lateral parieto-occipital areas, respectively. Medial and lateral OF stimulation induced responses in the adjacent cortices. This study revealed that various regions within the limbic network are intimately connected in reverberating circuits and are linked to specific ipsilateral and contralateral regions, which may reflect distinct functional roles.

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1. Introduction

Papez (1937) proposed a system involved in emotion and episodic memory, which is composed of the hypothalamus, hippocampus, mammillary body, thalamus, cingulate gyrus, parahippocampal gyrus (PHG) and the entorhinal cortex. Thereafter, Maclean (1949, 1952) introduced the neurophysiological and neuroanatomical concept of "the limbic system". He added the orbitofrontal cortex and amygdala, and named this group of structures the "limbic system". These structures have interconnections constituting a harmonious mechanism which may elaborate the functions of emotion and memory. These previous reports contribute to understanding of the mechanisms of human higher function. Scoville and Milner (1957) described a profound and selective impairment in human memory after bilateral surgical removal of the medial temporal lobe. It has also been reported that medial temporal lobe damage causes memory impairment in cases of viral encephalitis (Damasio, Eslinger, Damasio, Van Hoesen, & Cornell, 1985), posterior cerebral artery occlusion (Benson, Marsden, & Meadows, 1974), and Alzheimer's disease (Hyman, Van Hoesen, Damasio & Barnes, 1984). These studies of human amnesia have identified the anatomical components of memory in the limbic network. However, despite these reports, little information is available regarding the connections within the limbic network; specifically the *in-vivo* anatomo-neurophysiological connectivity of the human limbic network has not been established. Understanding this network would be useful not only for understanding human higher brain functions, such as memory, recognition, and emotion, but also for elucidating the pathophysiology of neurological and psychiatric disorders, such as Alzheimer's disease and focal epilepsy involving various components of the limbic system, anxiety disorders and affective disorders. The investigations in limbic epilepsy can be misleading because the seizure onset is located in an anatomically deep region and the complicated spread pattern can give rise to atypical seizure semiologies and EEG findings (Engel & Williamson, 2008). Therefore knowledge of the limbic network is important for the presurgical evaluation of patients with pharmacoresistant epilepsy arising within the limbic system.

Electrical stimulation was recently introduced as an *in-vivo* test to track the various human brain networks (Lacruz, Garcia Seoane, Valentin, Selway, & Alarcon, 2007; Matsumoto et al. 2004; Rosenberg, Mauguiere, Catenoix, Faillenot, & Magnin, 2009; Wilson, Isokawa, Babb, & Crandall, 1990). We developed a methodology, termed corticocortical evoked potential (CCEP), to study human brain networks *in-vivo* (Matsumoto et al. 2004).

In this study, we aimed to identify the functional connectivity of the limbic network, using CCEP methods in patients implanted with stereoelectroencephalography (SEEG) electrodes.

2. Patients and methods

2.1. Patients

This retrospective analysis included 28 patients (13 females) with medically intractable focal epilepsy who underwent SEEG evaluation at Cleveland Clinic Epilepsy Center since 2009. Twenty-four patients were right-handed and four were left-handed. In these patients, functional MRI revealed right language dominance in two patients and bilateral language dominance in one patient. Their age ranged from 15 to 68 years old (median 30 years old) and age at seizure onset ranged from 6 months to 65 years old (median 13 years old). All these patients underwent CCEPs with stimulation of parts of the limbic system [anterior and posterior hippocampus, temporal pole, PHG, amygdala, anterior (ACG) and posterior cingulate gyrus (PCG), medial and lateral orbitofrontal cortex (OF)] as a part of their routine invasive clinical neurophysiological analysis for various clinical purposes such as understanding ictal propagation or interictal epileptiform discharge distribution.

The following regions were stimulated for CCEP analysis. The right anterior hippocampus was stimulated in eight patients and left anterior hippocampus in six. The right and left posterior hippocampus was stimulated in six and five patients, respectively. The right temporal pole was stimulated in five patients and left temporal pole in two patients. The right PHG was stimulated in three patients and four locations on the left in three patients (One patient had two stimulation sites in left PHG stimulation). The right amygdala was stimulated in two patients. There were five stimulation sites in the right ACG in four patients, three stimulation sites in left ACG in three patients, seven stimulation sites in right PCG in seven patients and eight stimulation sites in left PCG in seven patients (One patient had two stimulation sites in right ACG stimulation and one patient had two stimulation sites in left PCG stimulation). The medial OF was stimulated in 10 locations in five patients on the right and four locations in three patients on the left (One patient had four stimulation sites and two patients had two stimulation sites in right medial OF stimulation and one patient had two stimulation sites in left medial OF stimulation). The right lateral OF was stimulated in seven locations in five patients and seven locations on the left in six patients (Two patients had two stimulation sites in right lateral OF stimulation and one patient had two stimulation sites in left lateral OF stimulation).

The number of recording electrodes in each area is shown in Tables 1–4. This study was approved by the Institutional Review Board Committee of Cleveland Clinic (IRB#12-857).

2.2. Implantation of SEEG electrodes

Implantation targets were determined based on a clinically-generated pre-implantation hypothesis for the localization of the epileptogenic zone. The depth electrode targeting and trajectory were determined using standard stereotactic software (iPlan; BrainLAB, Feldkirchen, Germany) or a robotic system (ROSA; Medtech, Montpellier, France). The planned trajectory was reviewed to verify that no vessels or other important structures would be at risk of injury, and was modified if necessary. Under general anesthesia, the electrodes were inserted one by one in an orthogonal or oblique fashion, in relation to the midline vertical plane. The number of implanted SEEG electrodes ranged between 11 and 17 (median 13) per patient. The electrodes consisted of 10–12