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Review

Electrical stimulation of the piriform cortex for the treatment of epilepsy: A review of the supporting evidence

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ABSTRACT

In this review, we consider how the piriform cortex is engaged in both focal and generalized epilepsy networks and postulate the various neural pathways that can be effectively neuromodulated by stimulation at this site. This highlights the common involvement of the piriform cortex in epilepsy. We address both current and future preclinical studies of deep brain stimulation (DBS) of the piriform cortex, with attention to the critical features of these trials that will enable them to be of greatest utility in informing clinical translation. Although recent DBS trials have utilized thalamic targets, electrical stimulation of the piriform cortex may also be a useful intervention for people with epilepsy. However, more work is required to develop a solid foundation for this approach before considering human trials.

1. Introduction

The piriform cortex has received renewed attention in recent years with regard to its role in epilepsy. While olfactory auras have been a known epileptic symptom, more recent studies have shown the piriform cortex as a common hub of activity in focal epilepsy [1–3]. It is a highly susceptible site for electrical kindling and generation of seizures [4–6]. In recent clinical trials, the anterior and centromedian nuclei of the thalamus have undergone deep brain stimulation (DBS) for refractory epilepsies with promising results [7,8]. In focal epilepsy, several preclinical studies of DBS have already been conducted on the piriform cortex utilizing various animal models [5,9–11]. In generalized epilepsy, the piriform cortex displays significant connections to several brain regions which are critically involved [12,13], although there is yet to be a DBS study conducted using an animal model of genetic generalized epilepsy. Neuromodulation for epilepsy has a long experimental history, but only recently has DBS shown to be a viable treatment option because of an improved understanding of epileptogenic networks and advancements in medical devices. However, how DBS should be best applied, in terms of appropriate selection of animal models, specification of the DBS target site, and stimulation parameters are open questions that are critical to answer before progressing to human trials of piriform cortex DBS. The piriform cortex may therefore, be another DBS target for the treatment of both cases of focal and generalized epilepsies.

1.1. Piriform cortex anatomy and subdivisions

The piriform cortex is located between the frontal and temporal lobes (Fig. 2). While relatively small in humans, it is a large structure in a rat brain. The piriform cortex exhibits a three-layered structure, remarkably similar to that of the hippocampus, with highly interconnected pyramidal cells, inhibitory gamma-Aminobutyric acid (GABAergic) interneurons, and a horizontal arrangement of fiber projections [1]. The piriform cortex has been subdivided in several different ways. In humans, the piriform cortex is commonly subdivided into frontal and temporal regions, in relation to these lobes of the brain. In the rodent, the piriform cortex is divided into anterior and posterior parts, based upon the thickness of cell layer III and the presence of the overlying olfactory tract (Fig. 1) [4]. A "central piriform cortex" region has been proposed by the group Löscher et al. defined as the transition zone between these sections as well as the disappearance of the lateral olfactory tract and an increase in cell layer III and the ventral endopiriform nucleus [2,4]. The "area tempestas" is positioned deep to the anterior piriform

Abbreviations: DBS, deep brain stimulation; LFS, low-frequency stimulation; HFS, high-frequency stimulation; GABA, gamma-Aminobutyric acid; GAERS, Genetic Absence Epilepsy Rats from Strasbourg; WAG/Rij, Wistar Albino Glaxo and Rijswijk.

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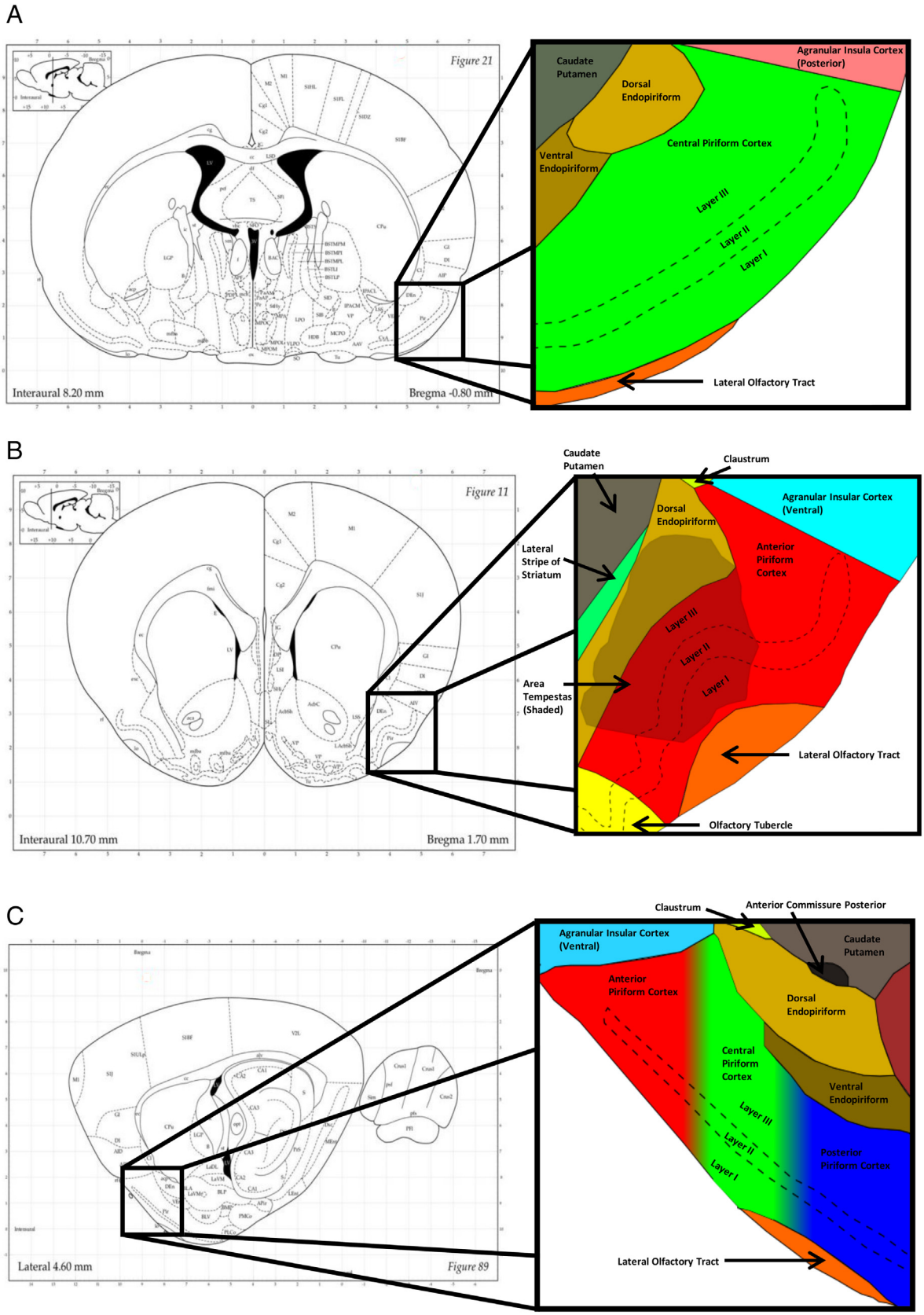

Fig. 1. A) Rodent central piriform cortex (Coronal); B) Rodent anterior piriform cortex (Coronal); C) Rodent central piriform cortex (Sagittal); area tempestas shading defined by the description in Wahnschaffe & Löscher [14].
Figures adapted from Paxinos and Watson [101] with permission.