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Title: Incidence of functional bi-temporal connections in the human brain in vivo and their relevance to epilepsy surgery

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Corresponding Author: Dr. Gonzalo Alarcon, MD, Ph.D.

Corresponding Author's Institution: King's College Hospital /Inst of Psychiatry

First Author: Diego Jiménez-Jiménez

Order of Authors: Diego Jiménez-Jiménez; Margely Abete-Rivas; David Martín-López ; María E Lacruz; Richard P Selway; Antonio Valentín; Gonzalo Alarcon, MD, Ph.D.

Abstract: The incidence of functional connections between human temporal lobes and their latencies were invistigated using intracranial EEG responses to electrical stimulation with 1 ms single pulses in 91 patients assessed for surgery for treatment of epilepsy. The areas studied were amygdala, hippocampus, parahippocampal gyrus, fusiform gyrus, inferior and mid temporal gyrus. Furthermore, we assessed whether the presence of such connecttions are related to seizure onset extent and postsurgical seizure control. Responses were seen in any region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes (N=60) and between both fusiform gyri in 7.1% (N=126). All other bi-lateral connections occurred in less than 5% of hemispheres. Depending on the structures, latencies ranged between 20 and 90 ms, with an average value of 60.2 ms. There were no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections. No difference was found in the proportion of patients showing bilateral or unilateral seizure onset among patients with and without contralateral temporal projections. The present findings corroborate that the functionality of bilateral temporal connections in humans is limited and does not affect the surgical outcome.

Incidence of functional bi-temporal connections in the human brain *in vivo* and their relevance to epilepsy surgery

DIEGO JIMÉNEZ-JIMÉNEZ[1,2,3], MARGELY ABETE-RIVAS[4], DAVID MARTÍN-LÓPEZ [1,2,5,6], MARÍA ELENA LACRUZ[1], RICHARD P. SELWAY[7], ANTONIO VALENTÍN[1,2&], GONZALO ALARCÓN[1,2,6&].

[1] Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience. King's College London, UK.

[2] Department of Clinical Neurophysiology, King's College Hospital NHS Trust, London, UK.

[3] School of Medicine, Universidad San Francisco de Quito, Quito, Ecuador.

[4] Departamento de Neurofisiología Clínica, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

[5] West Surrey Clinical Neurophysiology, St Peter's Hospital, Chertsey, UK

[6] Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain.

[7] Department of Neurosurgery, King's College Hospital, NHS Trust London, UK

[&]Drs A. Valentín and G. Alarcón are joint senior authors.

Corresponding author:
Dr Gonzalo Alarcon
Department of Clinical Neuroscience, PO Box 43
Institute of Psychiatry, King's College London
De Crespigny Park, London SE5 8AF
Email: gonzalo.alarcon@kcl.ac.uk
Telephone: 0207 848 5161; Fax: 0207 848 0988

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Abstract

The incidence of functional connections between human temporal lobes and their latencies were invistigated using intracranial EEG responses to electrical stimulation with 1 ms single pulses in 91 patients assessed for surgery for treatment of epilepsy. The areas studied were amygdala, hippocampus, parahippocampal gyrus, fusiform gyrus, inferior and mid temporal gyrus. Furthermore, we assessed whether the presence of such connecttions are related to seizure onset extent and postsurgical seizure control. Responses were seen in any region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes (N=60) and between both fusiform gyri in 7.1% (N=126). All other bi-lateral connections occurred in less than 5% of hemispheres. Depending on the structures, latencies ranged between 20 and 90 ms, with an average value of 60.2 ms. There were no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections. No difference was found in the proportion of patients showing bilateral or unilateral seizure onset among patients with and without contralateral temporal projections. The present findings corroborate that the functionality of bilateral temporal connections in humans is limited and does not affect the surgical outcome.

Keywords:

Limbic system - Contralateral temporal connections - Single pulse electrical stimulation - Seizure onset pattern - Epilepsy surgery.

Highlights:

- Hippocampus and amygdala have a low incidence of contralateral connections (5.0%).

- Fusiform gyrus showed the highest incidence of contralateral functional connections (≤7.1%).

- Bi-temporal connectivity is related neither to bilateral seizure onset nor postsurgical outcome.

1. Introduction[1]

Anatomical and neuroimaging studies have consistently shown structural connections between both temporal lobes. A component of the fornix crosses to the contralateral hippocampus constituting the hippocampal commissure (Catani, Dell'acqua, & Thiebaut de Schotten, 2013). A recent study with diffusion tensor imaging (DTI) has revealed that 56.7% of 52 healthy volunteers show contralateral temporal connections (Kwon & Jang, 2014). However, it remains unclear if human bilateral temporal connections are functional in vivo. Histopathological samples in normal subjects can identify ventral and dorsal hippocampal commissures, of which only the latter is well defined and sizable in humans (Gloor, Salanova, Olivier, & Quesney, 1993). Lesional and stimulation studies support that hippocampi on either hemisphere process memory independently of each other, suggesting that connections between both hippocampi may not be functionally relevant (Goldstein & Polkey, 1992; Lacruz et al., 2010).

Patients assessed with intracranial electrodes during presurgical assessment of epilepsy provide a unique opportunity to estimate the incidence of functional bi-

[1] Abbreviations:

SPES: Single Pulse Electrical Stimulation
DEE: Diffuse Electrodecremental Event pattern
FA: Fast activity pattern
FA-DEE: Fast activity-Diffuse Electrodecremental Event
SIOP: Sustained Ictal Onset Patterns
PED: Preceding Epileptiform Discharges

temporal connections in the human brain in-vivo. Indeed, electrical stimulation has failed to show functional connections between both hippocampi (Wilson, Isokawa, Babb, & Crandall, 1990), or has shown such connections in a small proportion of patients (Lacruz, Garcia Seoane, Valentin, Selway, & Alarcon, 2007; Lacuey et al., 2014).

Single Pulse Electrical Stimulation (SPES) is used routinely at our centre as part of presurgical assessment for epilepsy in order to identify the topography and extent of hyperexcitable cortex, which might be potentially epileptogenic. Briefly, SPES consists of recording intracranial EEG responses to cortical stimulation with a brief single electrical pulse. Two main types of cortical responses are evoked by the stimuli, early and late responses. Early responses are recorded in areas around the stimulated cortex but sometimes also at a distance, providing evidence of functional connections between stimulated cortex and the regions where early responses are recorded (Enatsu et al., 2012; Fish, Gloor, Quesney, & Olivier, 1993; Lacruz et al., 2010; Lacuey et al., 2014; Umeoka et al., 2009; Wilson et al., 1990). Late responses are reliable biomarkers of epileptogenic cortex (Flanagan, Valentin, Garcia Seoane, Alarcon, & Boyd, 2009; Valentin, Alarcon, Garcia-Seoane, et al., 2005; Valentin, Alarcon, Honavar, et al., 2005).

Approximately 33% of patients with temporal lobe epilepsy assessed for surgery with intracranial electrodes show bilateral changes at seizure onset, and some of such changes have implications for surgical outcome (Jiménez-Jiménez et al., 2014). However, the nature of those bilateral changes at seizure onset remains unclear. We hypothesise that, if bilateral changes at seizure onset are due to

synaptic transmission through anatomical pathways, they should be related to the presence of functional bilateral connections.

In the present study, we estimate the incidence and latencies of human functional contralateral temporo-temporal connections in-vivo in the largest series to date. Furthermore, this is the first study to address whether the presence of such connections is related to bilateral changes at seizure onset or to postsurgical seizure control.

2. Methods

2.1 Subjects

SPES recordings from all 269 patients who had intracranial electrodes implanted for pre-surgical evaluation at King's College Hospital between January 1999 and December 2013 were reviewed. The study included all 91 patients who had intracranial electrodes in both temporal lobes.

Patients were informed of the nature of the study and gave informed consent to undergo SPES. The ethical committee at King's College Hospital (99-017) approved the development of SPES. Single pulse electrical stimulation is now part of the clinical protocol for presurgical assessment of patients with epilepsy with intracranial recordings.

2.2 Electrode placement

The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp EEG recordings obtained with the Maudsley system (Alarcon et al., 2001; Fernandez Torre et al., 1999; Kissani, Alarcon, Dad, Binnie, & Polkey, 2001), neuropsychology (Akanuma et al., 2003) and neuroimaging. All patients with normal neuroimaging were assessed with intracranial electrodes. The selection criteria and implantation procedures have been described in detail elsewhere (Alarcon, 2012; Alarcon et al., 2006). Temporal depth (intracerebral) and subdural electrodes were used as shown in

figure 1 and described below. The anatomical locations were defined according to (Insausti et al., 1998).

2.3 Subdural electrodes:

Subdural electrodes consisted of strips and mats (AdTech Medical Instruments Corp., WI, USA). Each strip consisted of a single row of 4 to 8 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, and recessed approximately 0.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32 or 64 similar platinum electrodes with 10 mm centre-to-centre distances within rows. Subtemporal strips of electrodes were inserted through a lateral burr hole and slid under the temporal lobe. The position of each electrode was assessed according to CT or coregistered CT-MRI. Generally, the deepest electrodes in each strip (labelled as 1 and 2) were in contact with the parahippocampal gyrus, electrodes 3 and 4 in contact with the fusiform gyrus, electrodes 5 and 6 in contact with inferior temporal gyrus and electrodes 7 and 8 (most lateral) in contact with the mid temporal gyrus.

2.4 Intracerebral (depth) electrodes:

Multielectrode flexible bundles of depth electrodes (AdTech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. The electrode bundles contained 8 or 10 cylindrical 2.3 mm long platinum electrodes separated by 5 mm between centres of adjacent electrodes of the same bundle. Usually 3 depth electrode bundles were implanted via an orthogonal lateral

approach with the deepest electrodes (labelled as 1 and 2) at the amygdala, the anterior or posterior hippocampus according to MRI stereotactic target and the most superficial electrodes (labelled as 5 to 7) at the mid temporal gyrus.

2.5 EEG recordings

Recording of intracranial EEG started when the patient had recovered from electrode implantation, usually 24-48 hours after surgery. Cable telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 40 patients, the Telefactor Beehive-Beekeeper system (Astro-Med, RI, USA) was used. Data were digitized at 200 Hz and band pass filtered (high pass cut-off frequency at 0.3 Hz and low pass cut-off frequency at 70 Hz). The system input range was 2 mV and data were digitized with a 12 bit analog-to-digital converter (amplitude resolution of 0.488 μV). In the remaining 51 patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, United Kingdom). Data were digitized at 256 Hz and band pass filtered (0.05-70 Hz). The input range was 10 mV and data were digitized with a 22 bit analog-to-digital converter (an amplitude resolution of 0.153 μV). Data were recorded as common reference to Pz or to an intracranial electrode, and displayed in a variety of montages including various scalp, intracranial and average common references to identify the most inactive reference for review in each patient.

2.6 Experimental protocol

SPES was performed between adjacent electrodes using a constant-current neurostimulator approved for use in human subjects (Medelec ST10 Sensor, Oxford Instruments, UK or Leadpoint, Medtronic, UK). Electrical stimulation was

carried out with monophasic single pulses of 1ms duration and current intensity ranging between 4 and 8 mA (4 mA being the intensity most often used). Each pulse was delivered between pairs of contiguous electrodes, every 5 or 10 seconds and EEG responses to each pulse were recorded by the electrodes not used for stimulation. No permanent neurological or neuropsychological deficits have been observed associated with SPES. A more detailed description of the experimental protocol for SPES is described elsewhere (Valentín et al. 2002; A. Valentín et al. 2005; Antonio Valentín et al. 2005; Flanagan et al. 2009).

The term 'stimulus' or 'stimulation' will be used to designate each single pulse and the term 'series' will be used to designate a batch of several identical pulses applied to the same pair of electrodes, with the same polarity. Series usually comprised 10 stimuli. For each pair of adjacent electrodes, two separate stimulation series were carried out with opposite polarity. Series of opposite polarity might stimulate slightly different regions, since neuronal stimulation is assumed to be greatest at the cathode. The electrodes used for stimulation were not used for recording. In patients with subdural electrodes, all available electrodes were used to stimulate in at least one series. In patients with intracerebral recordings only pairs of electrodes located in grey matter (according to MRI obtained with the electrodes implanted) were used to stimulate. Throughout the paper, the term "contralateral" will refer to the temporal lobe contralateral to stimulation (i.e. the temporal lobe where responses were recorded).

The measured variables were: a) the presence or absence of early contralateral temporal responses when stimulating at each location; and b) the latency of contralateral responses. The presence of early responses is assumed to provide evidence of connections between the stimulated cortex and the areas where early responses are recorded. Responses to different stimulation locations within the same structure in the same hemisphere in the same patient were pooled together (counted only once for each direction).

2.7 Data analysis

In order to minimise stimulation artefact, responses to stimulation with opposite polarity through the same electrodes were averaged. Cortical responses were identified visually and were considered significant if their amplitude after averaging was at least twice the amplitude of the background activity during the 400ms previous to the stimulus artefact.

In each patient, contralateral (inter-hemispheric) connections were studied when each temporal lobe was stimulated. Thus, for any two regions in contralateral hemispheres, each patient provides two measures, one from right to left and one from left to right. The likelihood of finding functional connections between both regions was calculated as the proportion/percentage of connections found among the number of stimulated hemispheres where such connections could be tested (i.e. in subjects with electrodes implanted in both regions).

Latencies of responses evoked in contralateral structures were studied. Cortical contralateral responses following stimulation artefact were identified visually, and multiple cursors were scrolled through the traces to identify synchronous points and measure latency differences among cursors. Contralateral response latency was measured from the stimulation artefact to the first peak of the first identifiable deflection of the contralateral response. The presence of a response was checked in bipolar montage and in common reference montage with reference to the average of the electrodes from the same strip or bundle. Latencies were measured in the latter montage in order to avoid interference from remote references.

2.8 Seizure Onset Analysis

Seizure onset of all 40 patients who underwent resection was analysed. Ictal onset pattern was determined by visual analysis of the pruned ictal files of intracranial EEG recordings. The seizure onset patterns lasting for several seconds were classified as follows (Jiménez-Jiménez et al., 2014): a) Diffuse electrodemental event (DEE), b) Focal Fast activity (FA), c) sharp-waves, d) spike-waves, e) alpha activity, f) theta activity, and g) delta activity. When FA and DEE started within one second, this was classified as h) FA-DEE. These patterns will be generically designated as "sustained ictal onset patterns" (SIOP). Frequently, SIOPs were immediately preceded by a single epileptiform discharge (preceding epileptiform discharge, or PED), which can show a widespread or bilateral distribution. PEDs can precede any type of SIOP and consequently were analysed separately. The term "seizure onset patterns" will include SIOPs and

PEDs. A more detailed description of the seizure onset analysis is described elsewhere (Jiménez-Jiménez et al., 2014).

2.9 Surgical Procedures

Surgery included temporal resections only. Tissue was removed and pathology studies performed. En-bloc temporal lobectomies followed an anatomically standardised surgical techniques (Alarcon, 2009). En bloc temporal lobectomy was undertaken at King's College Hospital as originally described by Falconer (Falconer, 1971), later modified to achieve a more complete removal of the hippocampus by use of the principles described by Spencer (D. D. Spencer, Spencer, Mattson, Williamson, & Novelly, 1984). In effect, between 5.5 cm and 6.5 cm of temporal lobe was removed. In the dominant hemisphere, usually the left, all superior temporal gyrus except the anterior 2 cm was spared. Such a resection would have included at least 50% of the amygdala and 2–3 cm of parahippocampal gyrus and hippocampus. Electrocorticographic intraoperative recordings were carried out and the extent of the resection was occasionally modified according to electrocorticographic findings (Alarcon et al., 1997). Structural lesions shown on imaging were removed unless functional mapping suggested a significant risk of functional deficits. Post-operative imaging was performed in those patients where surgery failed.

2.10 Surgical outcome

Surgical outcome with regard to seizure control was determined at regular postoperative follow up assessments. Surgical outcome was coded according to Engel surgical outcome classification (Engel, Van Ness, Rasmussen, & Ojemann, 1993). Surgical outcome at the longest follow-up available was used for each

patient. For statistical analysis, only Engel classification was used. Grade I was considered as "good outcome" and grades II, III or IV as "poor outcome". Only those patients with at least one year of follow up were included in this analysis.

2.11 Surgical outcome analysis:

Two-tailed χ^2 testing with one degree of freedom and with Yate's correction was used to compare the proportion of patients with favourable outcome between the groups of patients showing contralateral connections temporal lobe connections. Existence of significant differences was assumed if $p<0.05$. Analysis was carried out with Graphpad.

(www.graphpad.com/quickcalcs/contingency1.cfm).

3. Results

3.1 Subjects and resections

Among the 91 patients included in the study, 45 (49.5%) were female and 46 (50.5%) were male. The median age of SPES assessment was 35.07 (minimum = 10 years; maximum = 29 years). Of the 91 patients, 40 (44.0%) underwent temporal lobe resection and among these, 34 had a follow up longer than 1 year. One hundred and fifty six seizures were studied from the 40 patients who underwent surgery. The median age at resection was 33.2 years (minimum = 15 years; maximum = 55 years).

3.2 Intracranial electrodes

3.2.1 Subdural electrodes:

Among all 91 patients, 61 patients (67.0%) had only subdural strips, which included bilateral subtemporal strips in all cases. In addition to the subtemporal strips, 12 patients (13.2%) had one additional unilateral frontal strip, 4 patients (4.4%) had one additional unilateral frontal mat, 3 patients (3.3%) had one additional occipital strip, 1 patient (1.1%) had an additional unilateral frontal mat and a subdural occipital strip, and 1 patient (1.1%) had an additional unilateral frontal strip and one occipital strip.

3.2.2 Depth electrodes:

Among all 91 patients, 28 patients (30.8%) had depth electrodes bilaterally implanted in the temporal lobes. In addition to the temporal electrodes, 4

patients (4.4%) had one subdural frontal strip, 3 patients (3.3%) had one subdural occipital strip, and 2 patients (2.2%) had one unilateral depth frontal.

3.2.3 Subdural and Depth electrodes:

Two patients (2.2%) had a combination of temporal subdural and depth electrodes.

3.3 Presence of contralateral temporal connections

The number and percentage of temporal lobes presenting contralateral temporal responses are shown in Table 1. Responses were seen in a region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes (*N*=60) (Figure 2) and between fusiform gyri in 7.1% (*N*=126) (Figure 3). All other connections were seen less than 5% of hemispheres as in figure 4.

3.4 Latencies of contralateral temporal connections

Depending on the structures, latencies ranged between 20 and 90 ms, with an average value of 60.2 ms. Table 2 shows the latencies of contralateral connections.

3.5 Seizure Onset Patterns

Table 3 shows the incidence of each SIOP for the 40 patients who underwent surgery. Patients have been divided into those with and without contralateral

temporal connections. Overall, the most common SIOP was FA, which was seen in 14 patients (35.0%), followed by DEE seen in 7 patients (17.65%) and FA-DEE in 5 patients (12.5%). No difference was found in the proportion of patients showing a specific SIOP among patients with and without contralateral temporal projections.

Among the 28 patients without contralateral connections, PEDs were present in 16 patients, were focal in 3 patients, widespread (unilateral involvement of more than one temporal structure) in 12 patients and bilateral in 1 patient. Among the 12 patients with contralateral connections, PEDs were present in 6 patients, were focal in 2 and widespread in 4 patients. Interestingly, no patient with contralateral connections showed bilateral PEDs.

No difference was found in the proportion of patients showing PED or in PED extension among patients with and without contralateral temporal projections.

Table 4 shows the anatomical structure showing seizure onset and PEDs. A substantial proportion of patients showed a lobar onset involving more than one structure. Among the remaining patients, the majority of seizures arose from the hippocampus and parahippocampal gyrus. The largest proportion of PEDs showed a widespread distribution, involving more than one structure. No difference was found among patients with and without contralateral temporal projections, in the proportion of patients showing seizure onset or PED at each location.

3.6 Prognostic value of contralateral temporal lobe connections

Surgical outcome from all 34 patients who underwent resection and had a follow up period longer than one year after a temporal resection is summarised in Table 5. Overall, 38.28% of patients remained seizure free after surgery. The median follow up was 21.00 months (minimum = 12 months; maximum = 144 months). Among the 34 patients, 12 showed contralateral temporal connections (30%).

Among the 26 patients without contralateral temporal connections, 10 (38.46%) had Engel Class I whereas among the 8 patients with contralateral temporal lobe connections 3 (37.5%) had Engel Class I. There is no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections.

4. Discussion

Our findings confirm that the functionality of bilateral temporal connections is limited. Only 5 % of amygdala project to the contralateral amygdala. Similarly, 5% of hippocampus is connected to the contralateral hippocampus and 3.9% to the mid temporal gyrus. The highest contralateral temporal projections arise from both fusiform gyri (7.1%) (Figure 4). These findings are consistent with previous reports from smaller series (Fish et al., 1993; Lacruz et al., 2007; Lacuey et al., 2014; Umeoka et al., 2009; Wilson et al., 1991). Our findings are also consistent with the notion that the temporal lobes on either hemisphere process memory independently (Lacruz et al., 2010). This is in contrast with what occurs with other parts of the limbic system. For instance, the cingular gyrus shows profuse functional connections with contralateral frontal cortex (Lacruz et al., 2007; Rosenzweig, Beniczky, Brunnhuber, Alarcon, & Valentin, 2011; Valentin et al., 2011). The shortest inter temporal latency was between amygdalae, possibly reflecting the shorter distance or callosal propagation. Overall we have found latencies for contralateral bi-temporal connections within the range previously reported (Lacruz et al., 2007; Umeoka et al., 2009), and shorter than those reported from the temporal lobes (Lacruz et al., 2007).

The absence of functional connections between hippocampi is puzzling, as there is ample evidence for the presence of anatomical connections (Lacuey et al., 2014; Lieb & Babb, 1986; Lieb, Engel, & Babb, 1986; Wilson et al., 1990; Wilson et al., 1991). There are of two commissural systems in primates, responsible of

connecting contralateral hippocampi structures: a) the ventral hippocampal commissure, which interconnects both hippocampi; b) the dorsal hippocampal commissure interconnecting both entorhinal cortices. Neurophysiological and neuropathological methods suggest that the ventral hippocampal commissure has virtually disappeared in humans, while the dorsal hippocampal commissure, which interconnects both entorhinal cortices, appears to remain functional (Gloor, 1997; Gloor et al., 1993; Umeoka et al., 2009). We have found that the fusiform gyrus is the temporal structure with the highest proportion of contralateral temporal projections, supporting that the dorsal hippocampal commissure is the most relevant pathway in humans. We found minimal connectivity (5% of temporal lobes) between both amydagalae, in concordance with a previous report using PET (Irwin et al., 2004).

The functionality of bilateral temporal connections affects neither the presence of bilateral changes at seizure onset nor seizure control after surgery. This suggests that the presence of bilateral changes at seizure onset may not be due to rapid propagation through the pathways studied. The absence of relation between bitemporal connections and seizure control after surgery further suggests that seizure propagation may not preferentially occur along these synaptic pathways, and consequently, severance of such pathways may not be necessary to achieve favourable outcome. However, analysis of seizure spreading in patients implanted with intracranial electrodes has suggested that the different commissures may be involved in ictal propagation to the contralateral hippocampi (Gloor et al., 1993; S. S. Spencer, Williamson, Spencer, & Mattson,

1987). It is possible that seizures may propagate through anatomical pathways that may not be relevant in normal function.

In conclusion, the present study is novel in two respects:

1) Our series is substantially larger (91 patients) than any previous report. Because the connections described are so infrequent, their presence cannot be estimated in small series. Therefore reporting a large series like ours is crucial for such estimation.

2) This is the first study to address whether the presence of bilateral temporal connections is related to bilateral seizure onset patterns and/or to postsurgical seizure control, which has obvious clinical implications.

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Incidence of functional bi-temporal connections in the human brain *in vivo* and their relevance to epilepsy surgery

Diego Jiménez-Jiménez[1,2,3], Margely Abete-Rivas[4], David Martín-López [1,2,5,6], María Elena Lacruz[1], Richard P. Selway[7], Antonio Valentín[1,2&], Gonzalo Alarcón[1,2,6&].

[1] Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience. King's College London, UK.

[2] Department of Clinical Neurophysiology, King's College Hospital NHS Trust, London, UK.

[3] School of Medicine, Universidad San Francisco de Quito, Quito, Ecuador.

[4] Departamento de Neurofisiología Clínica, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

[5] West Surrey Clinical Neurophysiology, St Peter's Hospital, Chertsey, UK

[6] Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain.

[7] Department of Neurosurgery, King's College Hospital, NHS Trust London, UK

[&]Drs A. Valentín and G. Alarcón are joint senior authors.

Corresponding author:
Dr Gonzalo Alarcon
Department of Clinical Neuroscience, PO Box 43
Institute of Psychiatry, King's College London
De Crespigny Park, London SE5 8AF
Email: gonzalo.alarcon@kcl.ac.uk
Telephone: 0207 848 5161; Fax: 0207 848 0988

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Abstract

The incidence of functional connections between human temporal lobes and their latencies were invistigated using intracranial EEG responses to electrical stimulation with 1 ms single pulses in 91 patients assessed for surgery for treatment of epilepsy. The areas studied were amygdala, hippocampus, parahippocampal gyrus, fusiform gyrus, inferior and mid temporal gyrus. Furthermore, we assessed whether the presence of such connecttions are related to seizure onset extent and postsurgical seizure control. Responses were seen in any region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes (N=60) and between both fusiform gyri in 7.1% (N=126). All other bi-lateral connections occurred in less than 5% of hemispheres. Depending on the structures, latencies ranged between 20 and 90 ms, with an average value of 60.2 ms. There were no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections. No difference was found in the proportion of patients showing bilateral or unilateral seizure onset among patients with and without contralateral temporal projections. The present findings corroborate that the functionality of bilateral temporal connections in humans is limited and does not affect the surgical outcome.

Keywords:

Limbic system - Contralateral temporal connections - Single pulse electrical stimulation - Seizure onset pattern - Epilepsy surgery.

Highlights:

- Hippocampus and amygdala have a low incidence of contralateral connections (5.0%).

- Fusiform gyrus showed the highest incidence of contralateral functional connections (≤7.1%).

- Bi-temporal connectivity is related neither to bilateral seizure onset nor postsurgical outcome.

1. Introduction[1]

Anatomical and neuroimaging studies have consistently shown structural connections between both temporal lobes. A component of the fornix crosses to the contralateral hippocampus constituting the hippocampal commissure (Catani, Dell'acqua, & Thiebaut de Schotten, 2013). A recent study with diffusion tensor imaging (DTI) has revealed that 56.7% of 52 healthy volunteers show contralateral temporal connections (Kwon & Jang, 2014). However, it remains unclear if human bilateral temporal connections are functional in vivo. Histopathological samples in normal subjects can identify ventral and dorsal hippocampal commissures, of which only the latter is well defined and sizable in humans (Gloor, Salanova, Olivier, & Quesney, 1993). Lesional and stimulation studies support that hippocampi on either hemisphere process memory independently of each other, suggesting that connections between both hippocampi may not be functionally relevant (Goldstein & Polkey, 1992; Lacruz et al., 2010).

Patients assessed with intracranial electrodes during presurgical assessment of epilepsy provide a unique opportunity to estimate the incidence of functional bi-

[1] Abbreviations:

SPES: Single Pulse Electrical Stimulation
DEE: Diffuse Electrodecremental Event pattern
FA: Fast activity pattern
FA-DEE: Fast activity-Diffuse Electrodecremental Event
SIOP: Sustained Ictal Onset Patterns
PED: Preceding Epileptiform Discharges

temporal connections in the human brain in-vivo. Indeed, electrical stimulation has failed to show functional connections between both hippocampi (Wilson, Isokawa, Babb, & Crandall, 1990), or has shown such connections in a small proportion of patients (Lacruz, Garcia Seoane, Valentin, Selway, & Alarcon, 2007; Lacuey et al., 2014).

Single Pulse Electrical Stimulation (SPES) is used routinely at our centre as part of presurgical assessment for epilepsy in order to identify the topography and extent of hyperexcitable cortex, which might be potentially epileptogenic. Briefly, SPES consists of recording intracranial EEG responses to cortical stimulation with a brief single electrical pulse. Two main types of cortical responses are evoked by the stimuli, early and late responses. Early responses are recorded in areas around the stimulated cortex but sometimes also at a distance, providing evidence of functional connections between stimulated cortex and the regions where early responses are recorded (Enatsu et al., 2012; Fish, Gloor, Quesney, & Olivier, 1993; Lacruz et al., 2010; Lacuey et al., 2014; Umeoka et al., 2009; Wilson et al., 1990). Late responses are reliable biomarkers of epileptogenic cortex (Flanagan, Valentin, Garcia Seoane, Alarcon, & Boyd, 2009; Valentin, Alarcon, Garcia-Seoane, et al., 2005; Valentin, Alarcon, Honavar, et al., 2005).

Approximately 33% of patients with temporal lobe epilepsy assessed for surgery with intracranial electrodes show bilateral changes at seizure onset, and some of such changes have implications for surgical outcome (Jiménez-Jiménez et al., 2014). However, the nature of those bilateral changes at seizure onset remains unclear. We hypothesise that, if bilateral changes at seizure onset are due to

synaptic transmission through anatomical pathways, they should be related to the presence of functional bilateral connections.

In the present study, we estimate the incidence and latencies of human functional contralateral temporo-temporal connections in-vivo in the largest series to date. Furthermore, this is the first study to address whether the presence of such connections is related to bilateral changes at seizure onset or to postsurgical seizure control.

2. Methods

2.1 Subjects

SPES recordings from all 269 patients who had intracranial electrodes implanted for pre-surgical evaluation at King's College Hospital between January 1999 and December 2013 were reviewed. The study included all 91 patients who had intracranial electrodes in both temporal lobes.

Patients were informed of the nature of the study and gave informed consent to undergo SPES. The ethical committee at King's College Hospital (99-017) approved the development of SPES. Single pulse electrical stimulation is now part of the clinical protocol for presurgical assessment of patients with epilepsy with intracranial recordings.

2.2 Electrode placement

The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp EEG recordings obtained with the Maudsley system (Alarcon et al., 2001; Fernandez Torre et al., 1999; Kissani, Alarcon, Dad, Binnie, & Polkey, 2001), neuropsychology (Akanuma et al., 2003) and neuroimaging. All patients with normal neuroimaging were assessed with intracranial electrodes. The selection criteria and implantation procedures have been described in detail elsewhere (Alarcon, 2012; Alarcon et al., 2006). Temporal depth (intracerebral) and subdural electrodes were used as shown in

figure 1 and described below. The anatomical locations were defined according to (Insausti et al., 1998).

2.3 Subdural electrodes:

Subdural electrodes consisted of strips and mats (AdTech Medical Instruments Corp., WI, USA). Each strip consisted of a single row of 4 to 8 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, and recessed approximately 0.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32 or 64 similar platinum electrodes with 10 mm centre-to-centre distances within rows. Subtemporal strips of electrodes were inserted through a lateral burr hole and slid under the temporal lobe. The position of each electrode was assessed according to CT or coregistered CT-MRI. Generally, the deepest electrodes in each strip (labelled as 1 and 2) were in contact with the parahippocampal gyrus, electrodes 3 and 4 in contact with the fusiform gyrus, electrodes 5 and 6 in contact with inferior temporal gyrus and electrodes 7 and 8 (most lateral) in contact with the mid temporal gyrus.

2.4 Intracerebral (depth) electrodes:

Multielectrode flexible bundles of depth electrodes (AdTech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. The electrode bundles contained 8 or 10 cylindrical 2.3 mm long platinum electrodes separated by 5 mm between centres of adjacent electrodes of the same bundle. Usually 3 depth electrode bundles were implanted via an orthogonal lateral

approach with the deepest electrodes (labelled as 1 and 2) at the amygdala, the anterior or posterior hippocampus according to MRI stereotactic target and the most superficial electrodes (labelled as 5 to 7) at the mid temporal gyrus.

2.5 EEG recordings

Recording of intracranial EEG started when the patient had recovered from electrode implantation, usually 24-48 hours after surgery. Cable telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 40 patients, the Telefactor Beehive-Beekeeper system (Astro-Med, RI, USA) was used. Data were digitized at 200 Hz and band pass filtered (high pass cut-off frequency at 0.3 Hz and low pass cut-off frequency at 70 Hz). The system input range was 2 mV and data were digitized with a 12 bit analog-to-digital converter (amplitude resolution of 0.488 μV). In the remaining 51 patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, United Kingdom). Data were digitized at 256 Hz and band pass filtered (0.05-70 Hz). The input range was 10 mV and data were digitized with a 22 bit analog-to-digital converter (an amplitude resolution of 0.153 μV). Data were recorded as common reference to Pz or to an intracranial electrode, and displayed in a variety of montages including various scalp, intracranial and average common references to identify the most inactive reference for review in each patient.

2.6 Experimental protocol

SPES was performed between adjacent electrodes using a constant-current neurostimulator approved for use in human subjects (Medelec ST10 Sensor, Oxford Instruments, UK or Leadpoint, Medtronic, UK). Electrical stimulation was

carried out with monophasic single pulses of 1ms duration and current intensity ranging between 4 and 8 mA (4 mA being the intensity most often used). Each pulse was delivered between pairs of contiguous electrodes, every 5 or 10 seconds and EEG responses to each pulse were recorded by the electrodes not used for stimulation. No permanent neurological or neuropsychological deficits have been observed associated with SPES. A more detailed description of the experimental protocol for SPES is described elsewhere (Valentín et al. 2002; A. Valentín et al. 2005; Antonio Valentín et al. 2005; Flanagan et al. 2009).

The term 'stimulus' or 'stimulation' will be used to designate each single pulse and the term 'series' will be used to designate a batch of several identical pulses applied to the same pair of electrodes, with the same polarity. Series usually comprised 10 stimuli. For each pair of adjacent electrodes, two separate stimulation series were carried out with opposite polarity. Series of opposite polarity might stimulate slightly different regions, since neuronal stimulation is assumed to be greatest at the cathode. The electrodes used for stimulation were not used for recording. In patients with subdural electrodes, all available electrodes were used to stimulate in at least one series. In patients with intracerebral recordings only pairs of electrodes located in grey matter (according to MRI obtained with the electrodes implanted) were used to stimulate. Throughout the paper, the term "contralateral" will refer to the temporal lobe contralateral to stimulation (i.e. the temporal lobe where responses were recorded).

The measured variables were: a) the presence or absence of early contralateral temporal responses when stimulating at each location; and b) the latency of contralateral responses. The presence of early responses is assumed to provide evidence of connections between the stimulated cortex and the areas where early responses are recorded. Responses to different stimulation locations within the same structure in the same hemisphere in the same patient were pooled together (counted only once for each direction).

2.7 Data analysis

In order to minimise stimulation artefact, responses to stimulation with opposite polarity through the same electrodes were averaged. Cortical responses were identified visually and were considered significant if their amplitude after averaging was at least twice the amplitude of the background activity during the 400ms previous to the stimulus artefact.

In each patient, contralateral (inter-hemispheric) connections were studied when each temporal lobe was stimulated. Thus, for any two regions in contralateral hemispheres, each patient provides two measures, one from right to left and one from left to right. The likelihood of finding functional connections between both regions was calculated as the proportion/percentage of connections found among the number of stimulated hemispheres where such connections could be tested (i.e. in subjects with electrodes implanted in both regions).

Latencies of responses evoked in contralateral structures were studied. Cortical contralateral responses following stimulation artefact were identified visually, and multiple cursors were scrolled through the traces to identify synchronous points and measure latency differences among cursors. Contralateral response latency was measured from the stimulation artefact to the first peak of the first identifiable deflection of the contralateral response. The presence of a response was checked in bipolar montage and in common reference montage with reference to the average of the electrodes from the same strip or bundle. Latencies were measured in the latter montage in order to avoid interference from remote references.

2.8 Seizure Onset Analysis

Seizure onset of all 40 patients who underwent resection was analysed. Ictal onset pattern was determined by visual analysis of the pruned ictal files of intracranial EEG recordings. The seizure onset patterns lasting for several seconds were classified as follows (Jiménez-Jiménez et al., 2014): a) Diffuse electrodemental event (DEE), b) Focal Fast activity (FA), c) sharp-waves, d) spike-waves, e) alpha activity, f) theta activity, and g) delta activity. When FA and DEE started within one second, this was classified as h) FA-DEE. These patterns will be generically designated as "sustained ictal onset patterns" (SIOP). Frequently, SIOPs were immediately preceded by a single epileptiform discharge (preceding epileptiform discharge, or PED), which can show a widespread or bilateral distribution. PEDs can precede any type of SIOP and consequently were analysed separately. The term "seizure onset patterns" will include SIOPs and

PEDs. A more detailed description of the seizure onset analysis is described elsewhere (Jiménez-Jiménez et al., 2014).

2.9 Surgical Procedures

Surgery included temporal resections only. Tissue was removed and pathology studies performed. En-bloc temporal lobectomies followed an anatomically standardised surgical techniques (Alarcon, 2009). En bloc temporal lobectomy was undertaken at King's College Hospital as originally described by Falconer (Falconer, 1971), later modified to achieve a more complete removal of the hippocampus by use of the principles described by Spencer (D. D. Spencer, Spencer, Mattson, Williamson, & Novelly, 1984). In effect, between 5.5 cm and 6.5 cm of temporal lobe was removed. In the dominant hemisphere, usually the left, all superior temporal gyrus except the anterior 2 cm was spared. Such a resection would have included at least 50% of the amygdala and 2–3 cm of parahippocampal gyrus and hippocampus. Electrocorticographic intraoperative recordings were carried out and the extent of the resection was occasionally modified according to electrocorticographic findings (Alarcon et al., 1997). Structural lesions shown on imaging were removed unless functional mapping suggested a significant risk of functional deficits. Post-operative imaging was performed in those patients where surgery failed.

2.10 Surgical outcome

Surgical outcome with regard to seizure control was determined at regular postoperative follow up assessments. Surgical outcome was coded according to Engel surgical outcome classification (Engel, Van Ness, Rasmussen, & Ojemann, 1993). Surgical outcome at the longest follow-up available was used for each

patient. For statistical analysis, only Engel classification was used. Grade I was considered as "good outcome" and grades II, III or IV as "poor outcome". Only those patients with at least one year of follow up were included in this analysis.

2.11 Surgical outcome analysis:

Two-tailed χ^2 testing with one degree of freedom and with Yate's correction was used to compare the proportion of patients with favourable outcome between the groups of patients showing contralateral connections temporal lobe connections. Existence of significant differences was assumed if $p<0.05$. Analysis was carried out with Graphpad.

(www.graphpad.com/quickcalcs/contingency1.cfm).

3. Results

3.1 Subjects and resections

Among the 91 patients included in the study, 45 (49.5%) were female and 46 (50.5%) were male. The median age of SPES assessment was 35.07 (minimum = 10 years; maximum = 29 years). Of the 91 patients, 40 (44.0%) underwent temporal lobe resection and among these, 34 had a follow up longer than 1 year. One hundred and fifty six seizures were studied from the 40 patients who underwent surgery. The median age at resection was 33.2 years (minimum = 15 years; maximum = 55 years).

3.2 Intracranial electrodes

3.2.1 Subdural electrodes:

Among all 91 patients, 61 patients (67.0%) had only subdural strips, which included bilateral subtemporal strips in all cases. In addition to the subtemporal strips, 12 patients (13.2%) had one additional unilateral frontal strip, 4 patients (4.4%) had one additional unilateral frontal mat, 3 patients (3.3%) had one additional occipital strip, 1 patient (1.1%) had an additional unilateral frontal mat and a subdural occipital strip, and 1 patient (1.1%) had an additional unilateral frontal strip and one occipital strip.

3.2.2 Depth electrodes:

Among all 91 patients, 28 patients (30.8%) had depth electrodes bilaterally implanted in the temporal lobes. In addition to the temporal electrodes, 4

patients (4.4%) had one subdural frontal strip, 3 patients (3.3%) had one subdural occipital strip, and 2 patients (2.2%) had one unilateral depth frontal.

3.2.3 Subdural and Depth electrodes:

Two patients (2.2%) had a combination of temporal subdural and depth electrodes.

3.3 Presence of contralateral temporal connections

The number and percentage of temporal lobes presenting contralateral temporal responses are shown in Table 1. Responses were seen in a region of the contralateral temporal lobe when stimulating temporal regions in 30 patients out of the 91 (32.96%). Bi-hippocampal or bi-amygdalar projections were seen in only 5% of temporal lobes (*N*=60) (Figure 2) and between fusiform gyri in 7.1% (*N*=126) (Figure 3). All other connections were seen less than 5% of hemispheres as in figure 4.

3.4 Latencies of contralateral temporal connections

Depending on the structures, latencies ranged between 20 and 90 ms, with an average value of 60.2 ms. Table 2 shows the latencies of contralateral connections.

3.5 Seizure Onset Patterns

Table 3 shows the incidence of each SIOP for the 40 patients who underwent surgery. Patients have been divided into those with and without contralateral

temporal connections. Overall, the most common SIOP was FA, which was seen in 14 patients (35.0%), followed by DEE seen in 7 patients (17.65%) and FA-DEE in 5 patients (12.5%). No difference was found in the proportion of patients showing a specific SIOP among patients with and without contralateral temporal projections.

Among the 28 patients without contralateral connections, PEDs were present in 16 patients, were focal in 3 patients, widespread (unilateral involvement of more than one temporal structure) in 12 patients and bilateral in 1 patient. Among the 12 patients with contralateral connections, PEDs were present in 6 patients, were focal in 2 and widespread in 4 patients. Interestingly, no patient with contralateral connections showed bilateral PEDs.

No difference was found in the proportion of patients showing PED or in PED extension among patients with and without contralateral temporal projections.

Table 4 shows the anatomical structure showing seizure onset and PEDs. A substantial proportion of patients showed a lobar onset involving more than one structure. Among the remaining patients, the majority of seizures arose from the hippocampus and parahippocampal gyrus. The largest proportion of PEDs showed a widespread distribution, involving more than one structure. No difference was found among patients with and without contralateral temporal projections, in the proportion of patients showing seizure onset or PED at each location.

3.6 Prognostic value of contralateral temporal lobe connections

Surgical outcome from all 34 patients who underwent resection and had a follow up period longer than one year after a temporal resection is summarised in Table 5. Overall, 38.28% of patients remained seizure free after surgery. The median follow up was 21.00 months (minimum = 12 months; maximum = 144 months). Among the 34 patients, 12 showed contralateral temporal connections (30%).

Among the 26 patients without contralateral temporal connections, 10 (38.46%) had Engel Class I whereas among the 8 patients with contralateral temporal lobe connections 3 (37.5%) had Engel Class I. There is no statistical difference in the proportion of patients showing Engel Class I between patients with and without contralateral temporal connections.

4. Discussion

Our findings confirm that the functionality of bilateral temporal connections is limited. Only 5 % of amygdala project to the contralateral amygdala. Similarly, 5% of hippocampus is connected to the contralateral hippocampus and 3.9% to the mid temporal gyrus. The highest contralateral temporal projections arise from both fusiform gyri (7.1%) (Figure 4). These findings are consistent with previous reports from smaller series (Fish et al., 1993; Lacruz et al., 2007; Lacuey et al., 2014; Umeoka et al., 2009; Wilson et al., 1991). Our findings are also consistent with the notion that the temporal lobes on either hemisphere process memory independently (Lacruz et al., 2010). This is in contrast with what occurs with other parts of the limbic system. For instance, the cingular gyrus shows profuse functional connections with contralateral frontal cortex (Lacruz et al., 2007; Rosenzweig, Beniczky, Brunnhuber, Alarcon, & Valentin, 2011; Valentin et al., 2011). The shortest inter temporal latency was between amygdalae, possibly reflecting the shorter distance or callosal propagation. Overall we have found latencies for contralateral bi-temporal connections within the range previously reported (Lacruz et al., 2007; Umeoka et al., 2009), and shorter than those reported from the temporal lobes (Lacruz et al., 2007).

The absence of functional connections between hippocampi is puzzling, as there is ample evidence for the presence of anatomical connections (Lacuey et al., 2014; Lieb & Babb, 1986; Lieb, Engel, & Babb, 1986; Wilson et al., 1990; Wilson et al., 1991). There are of two commissural systems in primates, responsible of

connecting contralateral hippocampi structures: a) the ventral hippocampal commissure, which interconnects both hippocampi; b) the dorsal hippocampal commissure interconnecting both entorhinal cortices. Neurophysiological and neuropathological methods suggest that the ventral hippocampal commissure has virtually disappeared in humans, while the dorsal hippocampal commissure, which interconnects both entorhinal cortices, appears to remain functional (Gloor, 1997; Gloor et al., 1993; Umeoka et al., 2009). We have found that the fusiform gyrus is the temporal structure with the highest proportion of contralateral temporal projections, supporting that the dorsal hippocampal commissure is the most relevant pathway in humans. We found minimal connectivity (5% of temporal lobes) between both amydagalae, in concordance with a previous report using PET (Irwin et al., 2004).

The functionality of bilateral temporal connections affects neither the presence of bilateral changes at seizure onset nor seizure control after surgery. This suggests that the presence of bilateral changes at seizure onset may not be due to rapid propagation through the pathways studied. The absence of relation between bitemporal connections and seizure control after surgery further suggests that seizure propagation may not preferentially occur along these synaptic pathways, and consequently, severance of such pathways may not be necessary to achieve favourable outcome. However, analysis of seizure spreading in patients implanted with intracranial electrodes has suggested that the different commissures may be involved in ictal propagation to the contralateral hippocampi (Gloor et al., 1993; S. S. Spencer, Williamson, Spencer, & Mattson,

1987). It is possible that seizures may propagate through anatomical pathways that may not be relevant in normal function.

In conclusion, the present study is novel in two respects:

1) Our series is substantially larger (91 patients) than any previous report. Because the connections described are so infrequent, their presence cannot be estimated in small series. Therefore reporting a large series like ours is crucial for such estimation.

2) This is the first study to address whether the presence of bilateral temporal connections is related to bilateral seizure onset patterns and/or to postsurgical seizure control, which has obvious clinical implications.

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5. Figures

5.1 Figure 1

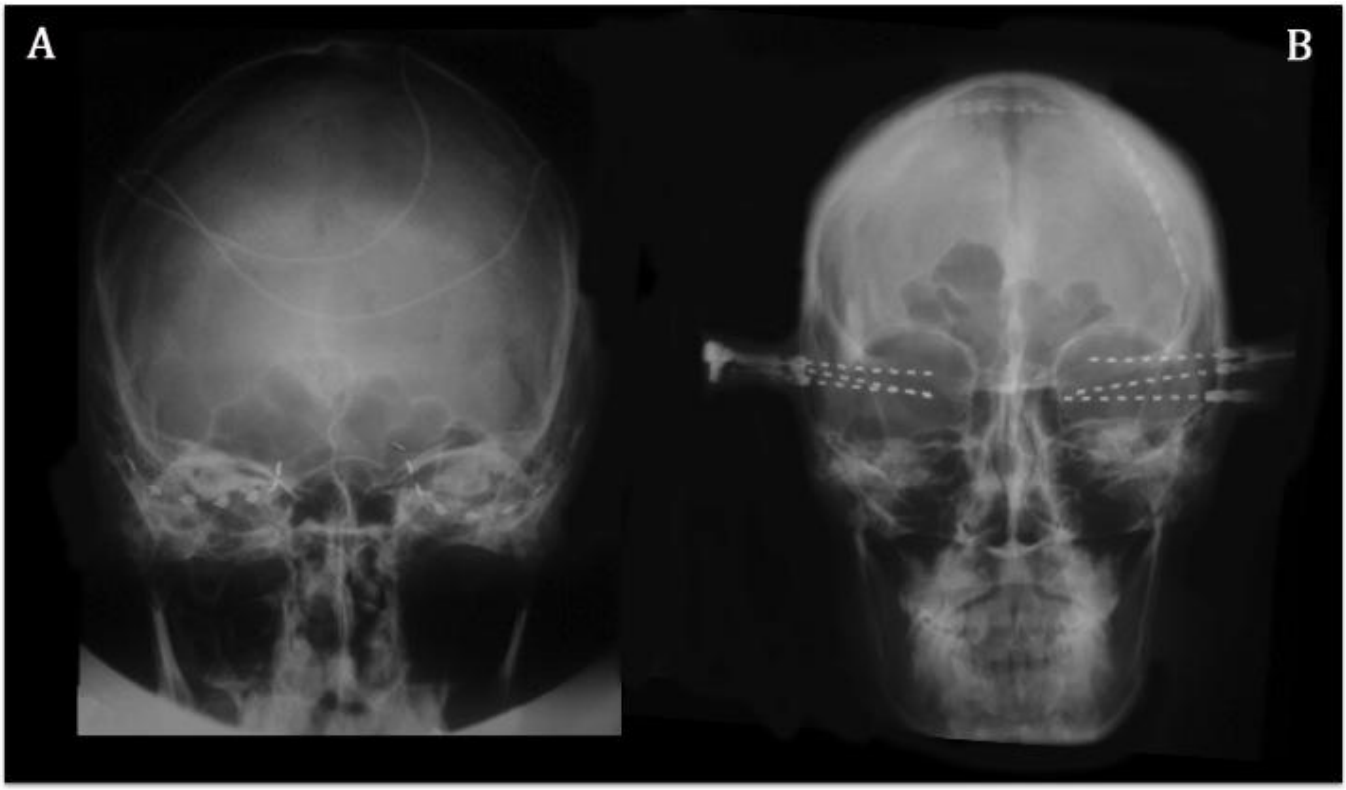

Figure 1. Two examples of typical bilateral subtemporal strips (A) and depth electrode (B) implantations. A) Subtemporal strips are slid under the under-surface of the temporal lobes and record from the lateral cortex, fusiform gyrus and parahippocampal gyrus. B) On each temporal lobe, three depth electrode bundles are implanted stereotactically targeting at the amygdala, anterior and posterior hippocampus. For each bundle, the depth electrode records from one of these structures, and the more superficial electrodes record from the mid temporal gyrus.

5.2 FIGURE 2

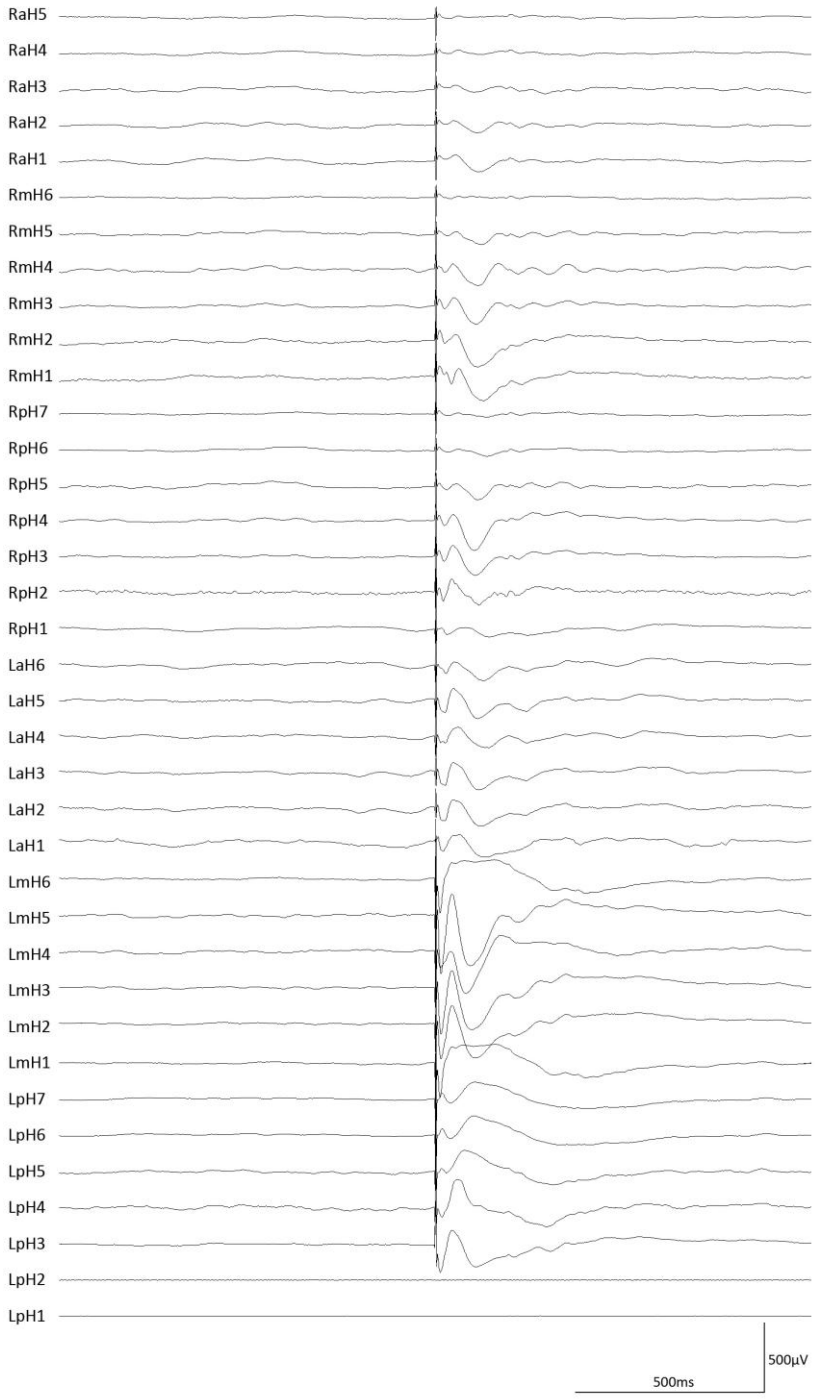

Figure 2. Example of contralateral hippocampal response evoked by single pulse electrical stimulation. The patient had bilateral depth electrodes implanted. When stimulating through electrodes 1 and 2 of the left posterior temporal bundle (LpH1-LpH2) there is a response in the contralateral hippocampus (RpH4-RpH2, RmH4-RmH1, RaH1-RaH2) suggesting the presence of functional connections between both hippocampi. The flat horizontal lines show the stimulating electrodes (LpH1-LpH2). For each depth electrode bundle, electrode 1 was the most distal electrode to the insertion burr hole (i.e. the deepest electrode). Recordings are shown in common reference montage. RaH, Right anterior Hippocampus; RpH, Right posterior Hippocampus; RmH, Right middle Hippocampus; LaH left anterior Hippocampus; LmH, Left middle Hippocampus.

5.3 FIGURE 3

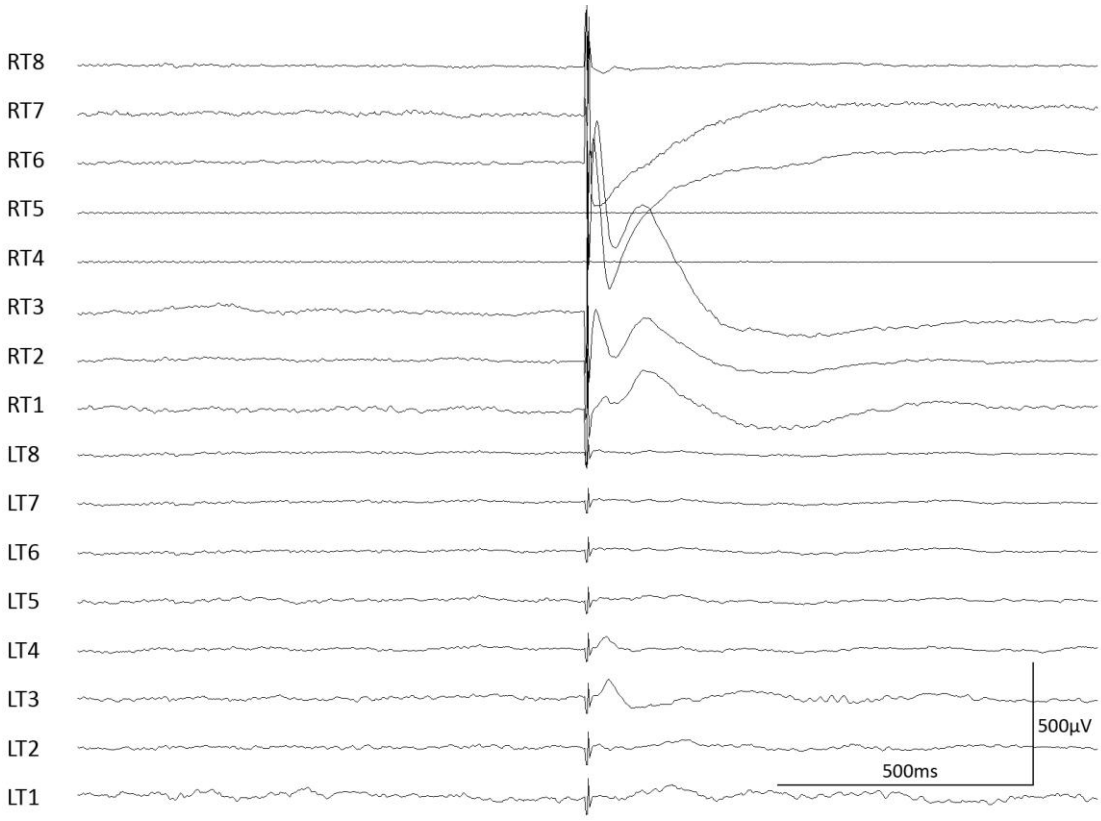

Figure 3. Example of contralateral response at the left fusiform gyrus evoked by single pulse electrical stimulation of the right fusiform gyrus. The patient had bilateral subtemporal electrodes implanted. When stimulating through electrodes 5 and 4 of the right temporal bundle (RT5-RT6), there is a response in the contralateral temporal lobe (LT4-LT3), suggesting the presence of contralateral functional connections between both fusiform gyri. The flat horizontal lines show the stimulating electrodes. Recording shown in common average reference. For each strip, electrode 1 was the most distal electrode to the insertion burr hole. RT= Right temporal. LT= Left temporal.

Figure 4

5.4 FIGURE 4

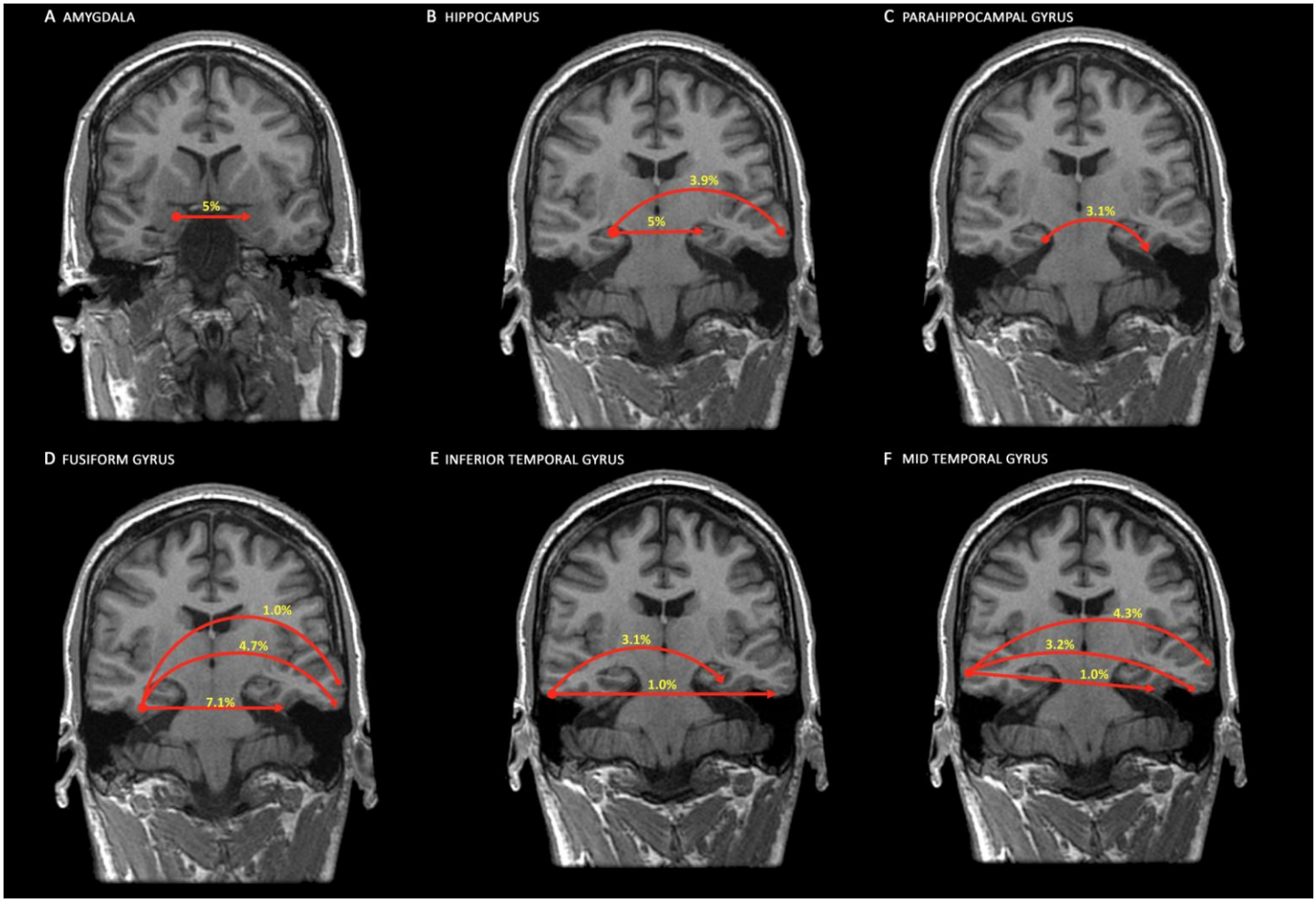

Figure 4. Coronal MRI showing void flows from the stimulation site to all identified contralateral temporal responses. The stimulated site is shown next to panel letter. The percentages of hemispheres presenting each projection are shown in yellow. Arrows go from stimulated site to the regions showing responses. Data from all hemispheres from all patients are pooled together as going from right to left. A) Contralateral projections from the amygdala. B) Contralateral projections from the hippocampus. C) Contralateral projections from the parahippocampal gyrus. D) Contralateral projections from fusiform gyrus. E) Contralateral projections from the inferior temporal gyrus. F) Contralateral projections from the mid temporal gyrus.

6. TABLES

6.1 TABLE 1

Table 1. Incidence of contralateral responses to stimulation of temporal lobes.

		Regions showing responses									
		Amygdala		Hippocampus		Fusiform gyrus		Inferior temporal gyrus		Mid temporal gyrus	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Stimulated Regions	Amygdala	3/60	5.0	0/60	0.0	X	X	X	X	0/60	0.0
	Hippocampus	0/60	0.0	3/60	5.0	X	X	X	X	5/126	3.9
	Parahippocampal Gyrus	X	X	X	X	4/126	3.1	0/126	0.0	0/126	0.0
	Fusiform gyrus	X	X	X	X	9/126	7.1	6/126	4.7	2/126	1.0
	Inferior temporal gyrus	X	X	X	X	4/126	3.1	2/182	1.0	0/182	0.0
	Mid temporal gyrus	0/126	0.0	0/126	0.0	2/126	1.0	6/182	3.2	8/182	4.3
	Total	3	5.0	3	5.0	19	13.3	14	8.9	15	5.3

n = number of temporal lobes where connection was present;
N = number of temporal lobes where connections were studied.
X = not tested.

6.2TABLE 2

Table 2. Latency (ms) of contralateral temporal connections. N= number of temporal lobes stimulated, n=number of temporal lobe with connection.

Stimulated area	Contralateral response	n/N	Median	Minimum	Maximum
Amygdala	Amygdala	3/60	45.75	35.00	70.60
Hippocampus	Hippocampus	3/60	53.61	40.0	58.38
Mid temporal gyrus	Mid temporal gyrus	5/60	61.03	48.0	64.40
Parahippocampal Gyrus	Fusiform gyrus	4/126	57.63	20.0	84.21
Fusiform gyrus	Fusiform gyrus	9/126	62.15	40.0	86.99
	Inferior temporal gyrus	8/126	58.50	45.65	70.66
	Mid temporal gyrus	2/126	74.41	59.09	89.74
Inferior temporal gyrus	Fusiform gyrus	4/126	74.88	59.66	85.00
	Inferior temporal gyrus	6/126	58.66	53.73	63.6
Mid temporal gyrus	Fusiform gyrus	2/126	60.61	60.00	61.22
	Inferior temporal gyrus	6/126	63.64	55.00	73.77
	Mid temporal gyrus	8/182	59.94	45.00	77.72

6.3TABLE 3

Table 3. Presence and percentage of each SIOP in patients with and without contralateral connections.

SIOP	Alpha		DEE		Delta		FA		FA-DEE		Sharp - wave		Sharps		Spike - wave		Theta		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Patients with connections	1	2.5	2	5.0	0	0.0	4	10.0	1	2.5	1	2.5	1	2.5	1	2.5	1	2.5	12	30.0
Patients without Connections	0	0.0	2	12.5	1	2.5	10	25.0	4	10.0	1	2.5	1	2.5	3	7.5	3	7.5	28	70.0
Total	1	2.5	7	17.5	1	2.5	14	35.0	5	12.5	2	5.0	2	5.0	4	10.0	4	10.0	40	100.0

6.4TABLE 4

Table 4. Number and percentage of anatomical occurrence of SIOP and PED in patients with and without contralateral temporal lobe connections

SIOP	Hippocampus		Parahippocampus Gyrus		Fusiform gyrus		Inferior Temporal gyrus		Lobar		Total	
	n	%	n	%	n	%	n	%	n	%	N	%
Patients with connections	3	25.0	3	25.0	1	8.3	0	0.0	5	41.7	12	100.0
Patients no connections	3	10.7	2	7.1	3	10.7	4	14.3	16	57.1	28	100.0
Total (n=40)	6	15.0	5	12.5	4	10.0	4	10.0	21	52.5	40	100.0
PED	**Hippocampus**		**Parahippocampus Gyrus**		**Fusiform gyrus**		**Inferior Temporal gyrus**		**Widespread unilateral**		**Total (excluding bilateral)***	
	n	%	n	%	n	%	n	%	n	%	N	%
Patients with connections	0	0.0	2	3.3	0	0.0	0	0.0	4	66.7	6	100.0
Patients with no connections	1	6.3	1	6.3	1	6.3	0	0.0	12	75	16	100.0
Total (n=40)	1	4.5	3	13.6	1	4.5	0	0.0	17	77.2	22	100.0

SIOP= Sustained ictal onset pattern
PED= Preceding epileptiform discharge
***= One patient with no connections had bilateral PED and no patient with connections showed bilateral PED**

6.5 TABLE 5

Table 5. Number and percentage of patients with each outcome grade in patients with and without acontralateral temporal lobe connections. Roman numbers refer to Engel surgical outcome classification.

Engel Class	I		II		III		IV		Total	
	n	%	n	%	n	%	n	%	N	%
Patients with connections	10	38.5	4	15.4	7	26.9	5	19.2	26	100.0
Patients with no connections	3	37.5	2	25.0	0	0.0	3	37.5	8	100.0
TOTAL (n=34)	13	38.2	6	17.6	7	20.6	8	23.5	34	100.0