Epilepsy Research (2014) **108**, 327—330

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

SHORT COMMUNICATION

Effects of amygdala—hippocampal stimulation on synchronization

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Received 4 April 2013; received in revised form 17 October 2013; accepted 12 November 2013
Available online 7 December 2013

KEYWORDS
DBS;
Epilepsy;
Temporal lobe

Summary Changes in EEG synchronization, i.e., spatio-temporal correlation, with amygdala—hippocampal stimulation were studied in patients with temporal lobe epilepsy. Synchronization was evaluated for high frequency, 130 Hz, pseudo-monophasic or biphasic charge-balanced pulses. Desynchronization was most frequently induced by stimulation. There was no correlation between the changes in synchronization and the changes in interictal epileptiform discharge rates. Changes in synchronization do not appear yet to be a marker of stimulation efficiency in reducing seizures.

Introduction

Deep brain stimulation (DBS) of the amygdalo-hippocampal (AH) structure represents a potential therapeutic technique for patients with intractable epilepsy (Velasco et al., 2007; Boon et al., 2007; Boëx et al., 2011). Certain parameters of stimulation, such as stimulation frequency or waveform, can affect AH-DBS efficiency. These effects can be described by seizure frequency or interictal epileptiform discharge rates (IEDRs) (Boëx et al., 2007; Tyrand et al., 2012). In addition to these neurophysiological markers, changes in synchronization have also been used to analyze epileptic seizure dynamics (Schindler et al., 2007a,b; Jiruska et al., 2013 for a review). Regarding vagal nerve stimulation (VNS) or DBS in epilepsy, different methods for quantifying synchronization have been used, including correlation matrix of electroencephalography (EEG, Schindler et al., 2007c), gamma-band desynchronization expressed with phase-locking (Sohal and Sun, 2011) or phase lag index (Fraschini et al., 2013). The objective of the present study was to evaluate whether changes in synchronization, as assessed via correlation matrix, could be used as a neurophysiological marker of AH-DBS efficiency. We analyzed the changes in synchronization with different waveforms, i.e., pseudomonophasic or biphasic, applied with high frequency (130 Hz) AH-DBS in patients with temporal lobe epilepsy (TLE), to determine if the changes in synchronization could correlate with the effectiveness of stimulation with each waveform.

Methods

Patients

Twelve patients were enrolled in the study at the time of invasive pre-surgical evaluation (Table 1). Eleven of the

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http://dx.doi.org/10.1016/j.eplepsyres.2013.11.024

Table 1 Side of stimulation, seizure types and MRI of each patient: left (L); Right (R); complex partial seizure (CPS), secondary generalized seizure (SecGS), generalized tonic seizure (GTS); hippocampus sclerosis (HS), normal MRI (N) hippocampal sclerosis (HS), temporal lobe (TL). Changes in synchronization induced by the high frequency AH-DBS using biphasic or pseudomonophasic charge balanced pluses: desynchronization (D), synchronization (S), equivocal (E) and composite (C). Significant changes: ↑ increase, ↓ decrease, ↔ equivocal changes. Kolmogorov—Smirnov statistics in percent (i.e., maximum distance between empirical distribution functions, $p = 0.001$) indicated first for the average of the 5 smallest eigenvalues and second for the average of the 2 largest eigenvalues. NC: not conducted. M: channels of the intracranial EEG were not recorded.

Patients	Stimulated side	Seizure types	MRI	Biphasic	Pseudomonophasic
S1	L	CPS	N	NC	D ↑ 32 ↓ 31
S2[a]	R	CPS; SecGS	N	NC	D ↔ ↓ 27
S2[b]				NC	D ↑ 52 ↓ 30
S3	R	GTS	No HS	NC	S ↓ 67 ↔
S5	L	CPS; SecGS	L FHS	D ↔ ↓ 51	NC
S6	L	CPS	R HS	D ↑ 60 ↓ 02	NC
S7	R	CPS; SecGS	R periventrical heterotopies	D ↑ 45 ↓ 13	NC
S9	L	CPS; SecGS	L HS; R TL atrophy	D ↑ 79 ↓ 80	M
S10	L	CPS; GTS	L HS; Cortical dayplasia	C ↓ 88 ↓ 44 (sleep)	D ↑ 12 ↓ 19
S12	R	CPS; GTC	R HS; Amygdala atrophy	S ↓ 40 ↔	E ↔ ↔
S15[a]	R	CPS	N	S ↑ 81 ↔	D ↑ 98 ↓ 24
S15[b]				D ↑ 100 ↔	D ↑ 97 ↔
S17[a]	R	CPS; GTS	R HS	D ↔ ↓ 46	D ↑ 25 ↓ 11
S17[b]				D ↑ 11 ↔	S ↓ 13 ↑ 04
S18[a]	L	CPS	Neocortical TL atrophy	E ↔ ↔	E ↔ ↔
S18[b]				D ↑ 48 ↓ 36	D ↑ 08 ↓ 02

[a] Phase width of 0.21 ms.
[b] Phase width of 0.45 ms.

patients also participated in the study reported by Tyrand et al. (2012). Patient Pt8 was left out of the present study because he was implanted with a single depth electrode which is insufficient to derive synchronization. In addition to the patients described in this previously study, patient S18 was also enrolled in our study (patient characteristics: 59-year-old female; right hand dominancy; drug resistant complex partial seizures; age of epileptic onset: 11 months; left hippocampal sclerosis and left cortico-subcortical temporal atrophy; left and right temporal IEDs; intracranial iEEG: left amygdala—hippocampus > right; ictal onset: amygdala and left hippocampus; and stimulation: left hippocampus). The study was conducted according to the recommended ethical guidelines of the Declaration of Helsinki and was approved by the Ethical Committee of the University Hospital of Geneva. All subjects provided informed consent.

Stimulation parameters

Synchronization was analyzed on the same group of patients and using the same stimulation parameters as those described by Tyrand et al. (2012). High frequency stimulation, i.e., 130 Hz, was applied for periods of two consecutive hours. At maximum two periods of two consecutive hours of stimulation was applied per day, and at max over two days. Charge-balanced, bipolar electrical stimulation was applied to the estimated epileptogenic zone (i.e., the first contact involved in seizures). Two different waveform stimuli were evaluated: the standard charge-balanced pseudomonophasic (Soletra neurostimulators, M37021, Medtronic, Minneapolis, MN, USA) and the biphasic charge-balanced pulses (Grass S88X with the opto-isolator SIU-BI, Astro-Med, West Warwick, RI, USA). With the Soletra neurostimulators, the first phase is cathodic (negative), and its width is the one used as a stimulation parameter in the literature. The second phase, anodic (positive), is long width and low amplitude, depending on the cathodic phase width, in order to ensure charge balancing. The biphasic pulses have symmetrical amplitude and duration.

Changes in synchronization

Synchronization was calculated from the correlation matrix of normalized iEEG (Müller et al., 2005). This method was chosen because it has been applied in the context of DBS stimulation, allowing comparison to previous results (Schindler et al., 2007c). Phase locking was also used in DBS (Sohal and Sun, 2011), but phase computation is subject to scepticism as EEG recordings are referenced to a common electrode (Guevara et al., 2005). The matrix is an instantaneous correlation of each pair of iEEG channels within a sliding time window. The temporal evolution of the average of the smallest and largest eigenvalues of the correlation matrix was computed (Schindler et al., 2007c). The smallest eigenvalues reflected an evolution that concerned only a subset of channels, whereas the largest eigenvalues reflected an evolution of the entire iEEG. To qualify the changes in synchronization induced by the electrical stimulation, the eigenvalues were compared between those computed from the iEEG of the 2-h