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PERSISTENT GENITAL AROUSAL DISORDER ASSOCIATED WITH FUNCTIONAL HYPERCONNECTIVITY OF AN EPILEPTIC FOCUS

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Abstract—Persistent Genital Arousal Disorder (PGAD) refers to the experience of persistent sensations of genital arousal that are felt to be unprovoked, intrusive and unrelieved by one or several orgasms. It is often mistaken for hypersexuality since PGAD often results in a high frequency of sexual behaviour. At present little is known with certainty about the etiology of this condition. We described a woman with typical PGAD symptoms and orgasmic seizures that we found to be related to a specific epileptic focus. We performed a EEG/MEG and fMRI spontaneous activity study during genital arousal symptoms and after the chronic administration of 300 mg/day of topiramate. From MEG data an epileptic focus was localized in the left posterior insular gyrus (LPIG). FMRI data evidenced that sexual excitation symptoms with PGAD could be correlated with an increased functional connectivity (FC) between different brain areas: LPIG (epileptic focus), left middle frontal gyrus, left inferior and superior temporal gyrus and left inferior parietal lobe. The reduction of the FC observed after antiepileptic therapy was more marked in the left than in the right hemisphere in agreement with the lateralization identified by MEG results. Treatment completely abolished PGAD symptoms and functional hyperconnectivity. The functional hyperconnectivity found in the neuronal network including the epileptic focus could suggest a possible central mechanism for PGAD.

Key words: posterior insular cortex, magnetoencephalography, fMRI, epilepsy, functional connectivity.

Persistent Genital Arousal Disorder (PGAD), first described in 2001 as "persistent sexual arousal syndrome" (Leiblum and Nathan, 2001), results in a spontaneous and persistent genital arousal with or without orgasm, with genital engorgement, unrelated to feelings of sexual desire. This condition is distressing and is characteristically accompanied by the sensation of intrusiveness of sensorial arousals and by a variety of negative feelings including frustration, guilt and anxiety (Basson et al., 2003). To date, the etiology of PGAD is controversial and debated. Since the first description of the syndrome, many case-studies have been published, each with unique associated conditions: increased soy intake (Amsterdam et al., 2005), brain cancer (Krychman et al., 2004), increased atrial natriuretic peptide (Goldmeier et al., 2006), blood dyscrasias (Medina, 2002) or antidepressant drugs use or withdrawal (Goldmeier et al., 2006; Mahoney and Zarate, 2007). Many cases appeared to be idiopathic (Nappi et al., 2005) and sympathetic abnormalities were found to correlate with the increased sexual arousal (Van den Hout and Barlowd, 2000); nonetheless PGAD is mostly attributed to psychological mechanisms (Leiblum and Chivers, 2007). Only one study speculated that there might be a neurological epileptic basis for PGAD (Goldstein et al., 2006): PGAD appeared as a consequence of CNS lesions. However there was no subsequent support for this ictal hypothesis.

Persistent feelings of sexual excitation are not described as associated with epileptic (ictal) sexual manifestation (Rémillard et al., 1983; Reading and Will, 1997; Betts and Crawford, 1998; Schenck et al., 2007). Other sexual manifestations instead, such as genital or sexual automatisms, genital sensations or sexual aura can be symptoms of complex partial seizures (Bancaud et al., 1971; Stoffels et al., 1980; Dobesberger et al., 2004; Janszky et al., 2004; Mascia et al., 2005; Aull-Watschinger et al., 2008) and reflex epilepsy can be triggered by orgasm (Ozkara et al., 2006). Sexual auras characterized by erotic pleasant feelings or thoughts with or without sexual arousal and orgasm are also associated with temporal lobe epilepsy (TLE) and have been reported to occur predominantly in women (Currier et al., 1971; Rémillard et al., 1983; Toone, 1991; Freeman and Schachter, 1995; Janszky et al., 2004). Genital sensations like numbness, tingling, vaginal feeling with compulsion to masturbate, pain or unpleasant sensation in the genitals are considered somatosensory auras and indicate an epileptic focus in the post-central gyrus, interhemispheric fissure and perisylvian region (Ruff, 1980). No firm conclusions can be drawn about lateralization of sexual ictal manifestations: sexual auras in men and women with an epileptic focus in tem-

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Abbreviations: BOLD, blood oxygen level-dependent; ECD, equivalent current dipole; EEG, electroencephalography; FC, functional connectivity; FMRI, functional magnetic resonance imaging; IC, independent component; LFEF, left frontal eye field; LIPL, left inferior parietal lobe; LITG, left inferior temporal gyrus; LMFG, left middle frontal gyrus; LMT, left middle temporal gyrus; LPIG, left posterior insular gyrus; LSTG, left superior temporal gyrus; MEG, magnetoencephalography; MMPI-2, Minnesota Multiphasic Personality Inventory 2; PCC, posterior cingulum cortex; PGAD, persistent genital arausal disorder; RFEF, right frontal eye field; RIPL, right inferior parietal lobe; RITG, right inferior temporal gyrus; RMFG, right middle frontal gyrus; RMT, right middle temporal gyrus; RSTG, right superior temporal gyrus; SFG, superior frontal gyrus.

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poral lobes of dominant or non-dominant hemispheres were equally described (Janszky et al., 2002, 2004).

We describe a case of epileptic focal activity and cortical hyperconnectivity in a woman presenting with persistent vaginal sensations of sexual excitation and unpleasant and distressing orgasmic feelings who was diagnosed for long time as affected by PGAD due to psychic mechanism, with no consciousness involvement during persistent and orgasmic feelings. Symptoms were constantly present during day and night time; automatisms were never observed.

By means of resting state functional magnetic resonance imaging (fMRI) we could investigate the cortical functional connectivity (FC) between specific brain areas in the presence of the disorder and then evaluate possible changes in FC after the administration of the antiepileptic drug topiramate 300 mg/day. Resting state FC represents an index of the functional connections of brain cortices. It identifies anatomically distinct cortical areas that have strong temporally-correlated low frequency ($<$0.1 Hz) blood oxygen level-dependent (BOLD) signal. These temporal correlations are presumed to reflect intrinsic functional connectivity and might therefore identify distinct networks (De Luca et al., 2006). We performed in the same day 2 EEG/MEG and fMRI acquisitions; at the time of symptoms occurrence and after resolution of symptoms obtained with pharmacological treatment (topiramate 300 mg/day). Our findings can offer an unusual insight on brain activity during sexual arousal, and might explain a possible mechanism of PGAD.

EXPERIMENTAL PROCEDURES

Case report

A 40-year-old, right-handed woman referred to our neurology clinics after 18 months of inconclusive medical examinations leading to the diagnosis of PGAD of psychic origin and unsuccessfully treated with antidepressants. Her medical history was significant only for unspecified abnormal febrile behaviours until the age of 13 and for a head trauma with short duration commotion and no need for therapy when she was 2 years old. At the age of 39 she began to experience recurrent episodes, approximately every day, increasing during the night, in which she suddenly became aware of an internal, ascending feeling indistinguishable from an orgasm, preceded by an abrupt exciting but unpleasant sensation that rose from the genitals, associated with clitoral warmth and tachycardia, often accompanied by genital pain and a sensation of fear. This feeling lasted several minutes, was present in clusters during day and night and was unrelieved by masturbation or coitus, which the patient therefore avoided, fearing of an increment of the unpleasant sensations. Symptoms were reported as distressing and accompanied by a variety of negative feelings including frustration, guilt and anxiety, which lasted several minutes. In the last 18 months she reported a persistent feeling of sexual arousal through the day and multiple daily episodes of orgasm-like sensations, not accompanied by alteration of consciousness. She reported only post-event asthenia. She did not report the presence of any triggers for her orgasmic episodes. Therefore two different symptoms were reported: an ictal acute sensation and a background persistent feeling. The ictal excitation consisted of sudden increase of sensation of genital arousal, accompanied by the feeling of pulsating vaginal spasms, lasting approximately 1–5 min, interpretable as epileptic orgasm. These feelings were always felt as intrusive and unpleasant, were never accompanied by the sensation of sexual gratification nor by alterations of arousal. The background feeling consisted of a persistent sensation of vaginal congestion and hypersensitivity or tingling accompanied by frustration, guilt, anxiety and distress. The two different sensations will be indicated, through the paper, as ictal excitation and as PGAD symptoms. In gynaecological assessments vaginal lubrification was not considered evidently abnormal and clitoral priapism was excluded.

General and neurological examinations were normal. Previous EEG recordings and brain MRI were normal. In particular, no signs of hyppocampal sclerosis or atrophy were detected. She was therefore diagnosed in other psychiatric institutions as affected by PGAD of psychic origin and treated for almost 1 year with antidepressants (paroxetina, venlafaxine) and low dose benzodiazepines (lorazepam, diazepam, clonazepam) with no effect beyond diurnal somnolence. When she was first observed in our Institution, no personality abnormality was evidenced by the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) (Butcher et al., 1989; Pancheri et al., 1996).

At first examination, an Holter-EEG was recorded to detect frequent orgasm-like episodes reported by the patient to occur at night time. Following Holter EEG, a MEG recording and an fMRI study were performed during spontaneous activity. Antiepileptic treatment with topiramate was introduced: topiramate dose was gradually increased up to 300 mg/day until complete resolution of symptoms. After 3 months, MEG and fMRI recordings were repeated. Spontaneous orgasms and related sensations like ascending feelings and abrupt genital engorgement were not reported. Patient reported that anxiety and other negative perceptions, that had accompanied her orgasmic experiences before treatment, had disappeared. On a 6-month follow-up visit no seizures were reported.

Holter-EEG recording

The patient was monitored for a whole night with nine scalp electrodes. The electrode configuration applied according to the international 10–20 system was as follow: Fp2-C4, C4-O2, Fp2-T4, T4-O2, Fp1-C3, C3-O1, Fp1-T3, T3-O1, T4-C4, C4-Cz, Cz-C3 and C3-T3. Ocular and cardiac channels were also applied. Electrodes were attached with collodion and gauze. Impedances were kept below 5 kΩ. A test recording was performed and patient was sent home with the electrodes applied to the scalp wrapped with a clinging bandage. Electrodes were connected to a portable battery-powered EEG device, which can record and store data for off line analysis displaying EEG waveforms and providing conventional EEG measures. To temporally correlate the EEG changes with sensory phenomena we asked the patient's husband to write a detailed log of the night. The day after, EEG data were downloaded to a computer for off-line analysis. Automated artefact detection system and visual inspection of traces ensured that EEG measures were derived from clean EEG signals.

Simultaneous EEG/MEG recordings

Magnetic field recordings were performed using the neuromagnetic system operating at the University of Chieti (Della Penna et al., 2000). The system is equipped with 165 SQUID magnetometers, 153 of which are placed over an helmet-shaped support providing a whole scalp coverage, and 12 are used for subtraction of the magnetic field noise. Thirteen EEG channels were also simultaneously recorded including mini-zygomatic electrodes (Silverman, 1960; Sperling and Engel, 1985). In addition, cardiac and ocular activities were also monitored to filter out possible heart and eyes contaminations of the MEG signals. Using the ECG signal, the QRS complex was detected and the heart rate in beats per second was evaluated as the inverse of the temporal distance between two consecutive R-wave spikes.

The correct position of the head with respect to the sensor was determined by placing five coils on the subject scalp; the location of the coils and the anatomical landmarks on the subject head were

digitised by means of a 3D–Digitizer (Polhemus, 3Space Fastrak). Spontaneous activity recordings were performed with open and closed eyes (10–15 min each) and data were stored on computer for off-line analysis (1025 Hz sampling rate, bandwidth 0.16–300 Hz). An experienced neurophysiologist identified and marked the abnormal electrical activity on EEG channels. Then the corresponding magnetic activity was localized by means of the equivalent current dipole (ECD) model using BESA software (Megis, Germany). To superimpose the ECD to the detailed anatomical structure of the patient's brain, a high-resolution whole head structural image MRI was performed via a 3D MPRAGE sequence.

FMRI session

FMRI acquisition was performed on the same day of EEG/MEG recordings. Functional images were acquired with a Philips scanner at 1.5 T by means of T2*-weighted echo planar imaging with the following parameters: echo time (TE), 50 ms; field of view (FOV), 240 mm; in-plane voxel size, 3.75×3.75 mm^2; slice thickness, 8 mm; and no gap. Functional volumes consisted of 16 bicommissural slices, acquired with a volume repeat time (TR) of 1409 ms. A total of five runs were acquired during resting state with closed eyes, 200 volumes were acquired for each run. Subsequently, a high-resolution structural volume was acquired via a 3D MPRAGE sequence to provide the anatomical reference for the functional scan.

Data analyses were conducted using Brain Voyager Qx software (Brain Innovation, The Netherlands). Pre-processing included slice timing correction, slice realignment for head motion correction and spatial smoothing with an 8 mm Gaussian core full width half maximum, FWHM. FMRI data were coregistered with their own 3D anatomical images that were transformed into stereotaxic coordinates of the space of Talairach. Spatial independent component analysis (ICA) processing was applied to functional data to extract maximally independent patterns of brain activity. For each of the five runs, 30 independent components (ICs) were extracted. Each IC consists of a temporal waveform and an associated spatial map expressed in terms of z scores that reflect the degree to which a given voxel time-course correlates with the corresponding IC waveform. Fingerprints were used to characterize and select the ICs (De Martino et al., 2007). IC-fingerprint is a polar plot that represents the spatial (degree of clustering, kurtosis, skewness, spatial entropy), temporal (one-lag autocorrelation, temporal entropy) and spectral (power contribution in the following frequency band: 0–0.008 Hz, 0.008–0.02 Hz, 0.02–0.05 Hz, 0.05–0.1 Hz) properties of each IC.

The final spatial map resulted from the group analysis on the five runs.

For each run the bold signal time course converted to z-score was extracted. The different values obtained from each run were concatenated to obtain the time courses of the selected regions over all the runs and correlation analysis was computed for all brain regions. Only those pairs with FC greater than 0.4 were retained for subsequent analysis. FC values of the selected pairs were then computed for each run and pre and post treatment values were compared using a repeated-measures ANOVA including pre-post treatment factor (two levels) and brain region functional connectivity factor (46 levels). Duncan's post hoc test was applied to the significant main effects and interactions.

RESULTS

Holter-EEG pre treatment

In awakening conditions the ictal EEG (Fig. 1) showed discharges of bilateral fronto-centro-temporal spikes complexes of 200–250 μV amplitude (about 40–50 ms duration for each spike) followed by bilateral slow activity (5–6 Hz frequency, 180–200 μV amplitude). The maximum spike amplitude (250 μV) was seen in the left fronto-centro-temporal derivations. EEG recording showed a cluster of seven ictal discharges occurring every 3–5 min. The first and the second ones lasted about 12–15 s. The following three epileptic paroxysms lasted 3–5 s and the last two only 1–2 s. The ictal EEG did not reveal a specific epileptogenic zone, but spike amplitude was higher in the left than in the right side supporting the hypothesis of an epileptic focus in the left hemisphere confirmed by the MEG study. The patient reported spontaneous exciting but unpleasant sensation of fullness and tingling in clitoris and vagina. Sensory phenomena was accompanied by sweating and tachycardia.

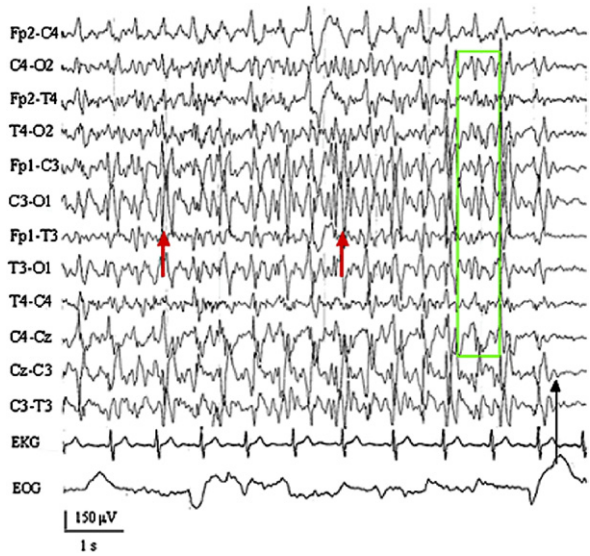

Fig. 1. ictal EEG in awakening conditions. Figure shows the first recorded discharge, ending abruptly after 15 s (black arrow): bilateral fronto-centro-temporal complexes of spikes of 200–250 μV amplitude and 40–50 ms duration were followed by bilateral slow activity 5–6 Hz, 180–200 μV (green rectangle). Note that maximum amplitude (250 μV) was seen in left fronto-centro-temporal derivations (red arrow). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

EEG/MEG: pre and post-treatment

In both EEG/MEG sessions the patient was in quiet rest, as monitored by EEG, showing a normal awake background activity with continuous 9 Hz posterior alpha rhythm. No drops in vigilance were noted, as assessed by vigilance/sleep criteria (alpha amplitude variation, slowing of background activity, eye movements, sleep EEG elements). During the pre-treatment EEG/MEG session, an EEG ictal pattern of slow activity of about 5 Hz in the left zygomatic (LZ) – T3 channel and an activity at 7 Hz in T5–T3 channel were observed when patient reported unpleasant sensation of fullness and tingling in clitoris and vagina which lasted for few seconds. During the ictal pattern heart rate values increased of about 10%. Fig. 2a shows the EEG signal and the corresponding power spectrum for the left and right temporal derivations, evidencing the bilateral slow activity. The power spectrum showed a prominent

Fig. 2. Epileptic focus localization (EEG/MEG session). (a): EEG signal and the corresponding power spectrum for the left and right temporal lobe, evidencing the slow activity in the left and right hemisphere. The power spectrum showed a prominent slow activity in the left temporal derivations. Note that the ictal pattern of slow activity was about 5 Hz in the left zygomatic (LZ) − T3 channel and 7 Hz in T5–T3 channel. (b): the magnetic flux map during the abnormal slow activity. (c): dipole was localized in the left posterior insular cortex. The coordinates of the dipole were x=−42, y=−18, z=15 in Talairach space.

slow activity on the left temporal derivations than on the right. The recorded magnetic field corresponding to the ictal pattern marked in the figure was used to localize the epileptic focus. Fig. 2b shows the magnetic flux map during the abnormal slow activity. Dipole was localized in the left posterior insular gyrus (Fig. 2c). The coordinates of the dipole were x=−42, y=−18, z=15 in Talairach space.

The second EEG/MEG recording session was performed after 3 months of treatment with topiramate 300 mg/day (minimum effective dose to eliminate symptoms). During this session normal activity was found in both left and right temporal hemispheres. No exciting sensations were reported by the patient.

fMRI: pre and post-treatment

During pre-treatment fMRI acquisition the patient reported genital sensations similar to the ones experienced during coitus followed by painful and frightening feeling of orgasm. These symptoms lasted for few seconds. The post-treatment acquisition was performed after 3 months from the beginning of treatment with topiramate 300 mg/day. During this acquisition the patient reported no symptoms.

The ICA process showed similar spatial map for pre and post-treatment acquisition. The centres of clusters involved in the two sessions were not significantly different.

Fig. 3. provides an example of IC spatial map involving the bilateral inferior parietal lobe (IPL), the posterior cingulum (PCC), the bilateral superior frontal gyrus (SFG) and the medial frontal gyrus (MFG) representing the so-called default mode network (Greicius et al., 2009). Together with IC map, time course, power spectrum and eleven-dimensional fingerprint of IC were included in the figure to show the peak in the frequency domain at 0.03 Hz and the typical fingerprint associated to the component (De Martino et al., 2007). For each IC component frequency peak and fingerprint were evaluated to exclude IC resulted from

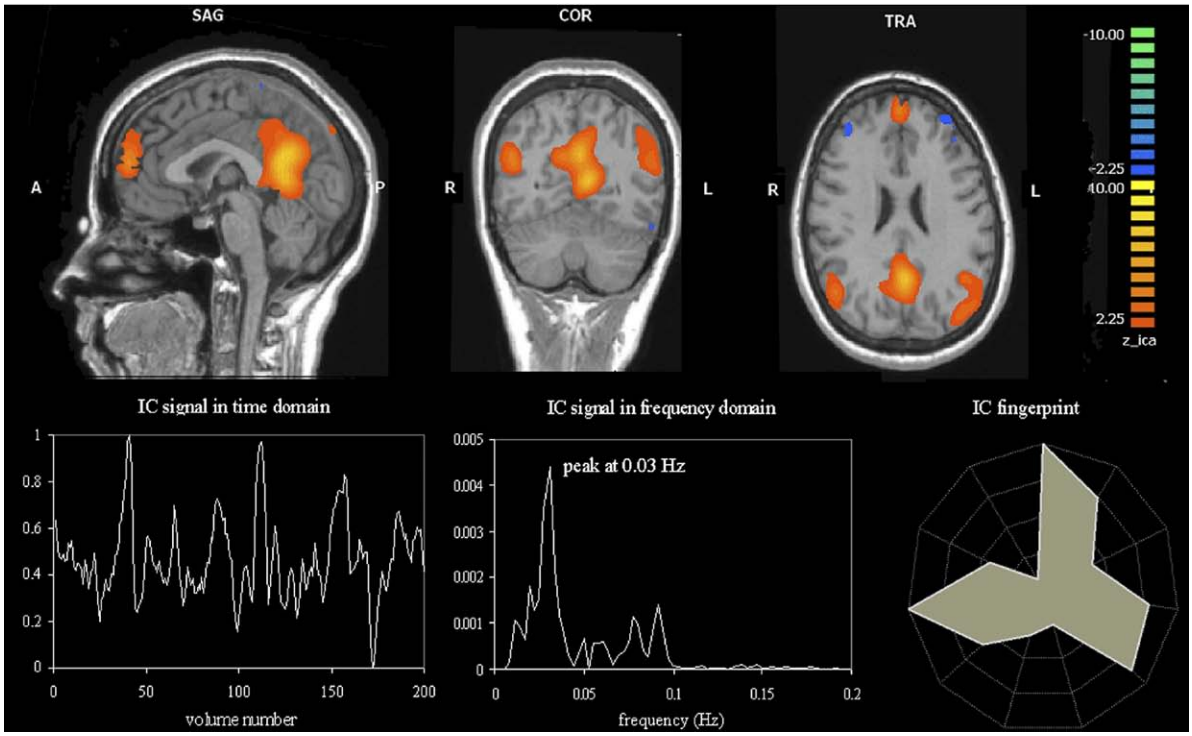

Fig. 3. Example of IC separated by ICA from one run of fMRI data set. Sagittal, coronal and axial functional maps, are shown, along with the related IC waveform in time and frequency domains and IC fingerprint. Brain areas are respectively in yellow–red or in green–blue in case of positive and negative correlation between area and IC waveform.

artefact contributions. For pre and post-treatment fMRI sessions, ICA decomposition evidenced also the following bilateral brain areas: frontal eye field (FEF), MFG, middle temporal gyrus (MTG), inferior (ITG) and superior temporal gyrus (STG). Moreover ICA analysis on the pre-treatment session evidenced also an area (MEG-focus) placed in the proximity of the epileptic focus localized by means of MEG.

Functional connectivity values were calculated for all brain areas mentioned before. Table 1 lists all brain areas with FC values greater than 0.4. The comparison of the FC values between the two sessions evidenced reduction of functional connectivity after therapy for the majority of the connections involved. The maximum reduction in percentage of the FC after therapy was found in the left hemisphere. The brain area named MEG-focus was found to be functionally connected with MFG, IPL, ITG and STG during the pre-treatment fMRI session. The pharmacological therapy disrupted the functional connection between the MEG-focus area and the frontal, parietal and temporal regions ($P<0.001$).

Statistical comparison on five runs acquired before and after therapy showed significant main effect of the pre-post treatment factor ($F(1,4)=13$, $P<0.03$) as well as of the functional connectivity factor ($F(45,180)=13.8$, $P<0.000\,01$). These results indicated that the FC decreased after the treatment in all the involved brain connections. The interaction of the two factors was also significant ($F(45,180)=5$, $P<0.000\,001$). Duncan post-hoc analysis was then performed on the interaction. Significant P-values were reported in Table 1.

Fig. 4 shows the cortical representation of the middle frontal gyrus, inferior parietal lobe, superior and inferior temporal gyrus and the connections which have the largest and significant change in FC in the comparison between pre and post treatment. The figure also shows the bold signal in the time domain of left middle frontal gyrus (LMFG), left inferior temporal gyrus (LITG) and left inferior parietal lobe (LIPL) before and after treatment evidencing higher inter-regional correlation before than after therapy.

DISCUSSION

The patient described in our study had typical PGAD symptoms with vaginal congestion, hypersensitivity and tingling, experienced as intrusive and unpleasant. The persistent disorder was so typical that she had been treated as affected by PGAD for more than 18 months by an expert center. Yet an atypical element emerged when she was addressed to our observation: rarely during the day and almost every night she experienced sudden increments of vaginal sensations with pulsating spasms that were tentatively interpreted as ictal orgasms. With dynamic EEG, a bilateral fronto-centro-temporal epileptic activity was found associated with symptoms. Before the administration of the pharmacological therapy MEG recordings localized the epileptic focus in the left posterior insular gyrus (LPIG) and fMRI showed high values of functional connectivity in different areas of the left hemisphere. Antiepileptic treatment

Table 1. FC values before and after the therapy, the reduction in percentage and the statistical comparison

Brain areas	Pre-treatment	Post treatment	Reduction %	*P*-level
LFEF				
RFEF	0.79	0.74	6	n.s.
LMT	0.73	0.68	7	n.s.
RMT	0.69	0.79	−14	n.s.
MFG	0.72	0.68	6	n.s.
PCC	0.71	0.75	−6	n.s.
RFEF				
LMT	0.61	0.51	16	n.s.
RMT	0.76	0.67	12	n.s.
MFG	0.64	0.52	19	n.s.
PCC	0.63	0.58	8	n.s.
LMFG				
RMFG	0.50	0.31	38	0.04
LIPL	0.69	0.22	68	0.000001
RIPL	0.59	0.19	68	0.000002
LITG	0.56	0.13	77	0.000001
RITG	0.43	0.37	14	n.s.
LSTG	0.42	0.19	55	0.0004
MEG-focus	0.41	0.05	83	0.0001
RMFG				
RIPL	0.60	0.53	12	n.s.
LITG	0.45	0.26	42	n.s.
RITG	0.61	0.42	31	n.s.
LSTG	0.43	0.46	−7	n.s.
RSTG	0.67	0.62	7	n.s.
MEG-focus	0.40	0.10	75	0.001
LIPL				
RIPL	0.75	0.57	24	n.s.
LITG	0.70	0.47	33	0.05
RITG	0.50	0.42	16	n.s.
LSTG	0.41	0.38	7	n.s.
MEG-focus	0.49	0.02	96	0.000001
RIPL				
LITG	0.56	0.50	11	n.s.
RITG	0.68	0.45	34	0.03
RSTG	0.51	0.36	29	n.s.
MEG-focus	0.52	0.00	100	0.000001
LMT				
RMT	0.78	0.66	15	n.s.
MFG	0.70	0.60	14	n.s.
PCC	0.79	0.71	10	n.s.
RMT				
MFG	0.69	0.65	6	n.s.
PCC	0.80	0.71	11	n.s.
MFG				
PCC	0.79	0.79	0	n.s.
LITG				
RITG	0.61	0.53	13	n.s.
LSTG	0.56	0.63	−13	n.s.
RSTG	0.41	0.28	32	n.s.
MEG-focus	0.55	0.02	96	0.000001
RITG				
LSTG	0.55	0.50	9	n.s.
RSTG	0.73	0.64	12	n.s.
MEG-focus	0.61	0.06	90	0.0000001
LSTG				
MEG-focus	0.64	0.08	88	0.000001
RSTG				
MEG-focus	0.59	0.15	75	0.000001

LFEF and RFEF, left and right frontal eye field; LMFG and RMFG, left and right middle frontal gyrus; MEG-focus, brain area placed near the epilectic focus localized with MEG; LIPL and RIPL, left and right inferior parietal lobe; LMT and RMT, left and right middle temporal gyrus; LITG and RITG, left and right inferior temporal gyrus; LSTG and RSTG, left and right superior temporal gyrus; PCC, posterior cingulum cortex.

suppressed both disorders: orgasmic seizures and PGAD like symptoms, abolished the MEG-evidenced epileptic focus and reduced the fMRI evidenced cortical hyperconnectivity. Our conclusion was that in this patient orgasmic seizures and PGAD symptoms were linked with each other and therefore that this case supports the hypothesis, previously suggested mostly on theoretical basis (Goldstein et al., 2006), that PGAD might be dependent on neural-epileptic dysfunction. The hypothesis of a psychiatric disease as the main cause of PGAD should be supplanted by our evidence of a neurologic cause of symptoms. Yet our study provided further information: MEG recordings localized the epileptic focus, probably linked to orgasmic seizures, in the left posterior insular gyrus. This finding confirms that MEG is superior to EEG in localization of interictal epileptiform activity, as MEG can localize epileptic activity in areas of cortex which are commonly inaccessible to EEG recording unless intraoperative electrocorticography is performed (Santisute et al., 2008; Dalal et al., 2009). Insular Gyri can poorly be explored by scalp EEG while MEG could locate the epileptic focus in this area: Posterior Insular Gyri are probably involved in the generation of orgasmic sensation but also are involved in a wide range of conditions and behaviours, including bowel movements, orgasm, craving, emotional feelings and maternal love (Craig, 2002; Kikyo et al., 2002; Ostrowsky et al., 2002; Kaido et al., 2006; Heimer and van Hoesen, 2006; Ryvlin, 2006) and, according to recent hypothesis, in decision making, insight (Craig, 2009) and awareness. The insula has wide connections with neocortex, basal ganglia, thalamus, limbic structures and olfactory cortex. Yet the identification of the epileptic activity in the insula might explain only partly the complex pattern of symptoms emerging in our patient, as the persistent quality of symptoms, that had led to specific diagnosis of PGAD, need further explanations. Our study could evidence also functional states of altered connectivity during the experience of PGAD symptoms.

FMRI results showed higher values of functional connectivity (hyperconnectivity) in the pre-treatment than post-treatment acquisition for the majority of the investigated brain regions and in particular for the connections involving the localized epileptic focus (MEG-focus). Resolution of symptoms by topiramate administration was accompanied by significant reduction of functional connectivity between

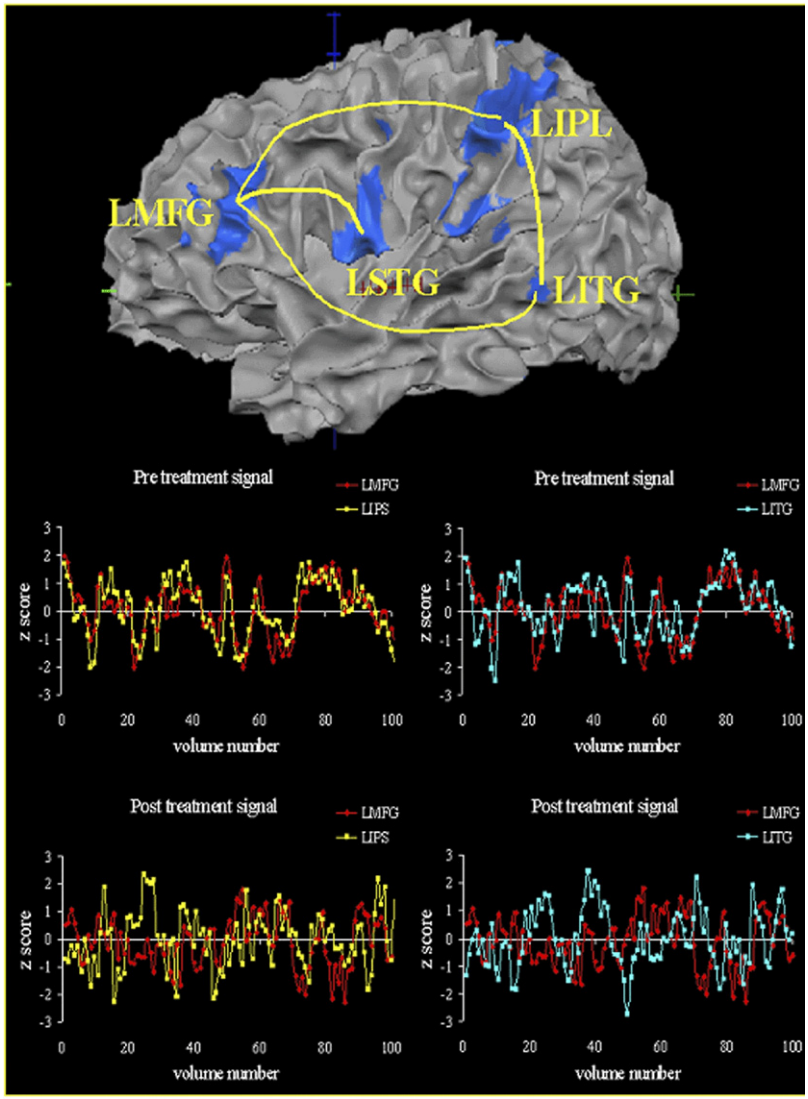

Fig. 4. Cortical representation of the LMFG, LIPL, LSTG and LITG. The yellow lines indices the connections in the left hemisphere which showed statistical difference in FC values for the comparison between pre and post treatment acquisition. Bold signals in the time domain of LMFG, LITG and LIPL are also shown before and after the treatment.

LMFG and IPL, ITG, STG in the left hemisphere, between IPL and ITG in the right hemisphere and between LMFG and right middle frontal gyrus (RMFG) and right inferior parietal lobe (RIPL).

We suggest that the intra-hemispheric hyperconnectivity found during pre-treatment acquisition between inferior parietal lobe and inferior temporal gyrus in the left and the right side could explain the persistent quality of sensations reported by the patient. We hypothesize that genital sensations and negative feelings reported by our patient resulted from functional hyperconnectivity in a neuronal network including the epileptic focus and the connected brain regions located in parietal, temporal and frontal lobes. Several clinical and SPECT studies described sensory disturbance in parietal and temporal lobe epilepsy (Cascino et al., 1993; Ho et al., 1994; Akimura et al., 2003; Erickson et al., 2006); negative feelings were reported by patients with temporal, frontal and insular cortex epilepsy (Kim et al., 2004; Ryvlin, 2006; Swinkels et al., 2006; Nguyen et al., 2009; Pizzi et al., 2009). Recent evidences indicated that frontal regions could interact with specific posterior regions such as parietal lobe and superior temporal lobe in order to produce awareness in different sensory modalities (Eriksson et al., 2007; Kirchner et al., 2009). Therefore multilobar connections are needed in order to explain feelings and awareness of feelings accompanying sensations in a single modality. Functional hyperconnectivity might similarly explain cases of multilobar epilepsy in which symptoms from different brain areas are simultaneously present.

The antiepileptic drug administered to our patient, able to abolish symptoms, could probably reduce both excitability and functional connectivity in the epileptogenic network, localized in the left hemisphere.

We hypothesize that the hyperconnectivity was the prevalent background of the PGAD symptoms presented by our patient.

Finally we suggest that feelings of sexual excitation and occurrence of orgasm might be dependent on the attainment of similar state of hyperconnectivity.

We cannot exclude the possibility that seizure-like orgasms have a different underlying cerebral mechanism than physiologic orgasms, it is however reasonable to assume that orgasmic seizures are caused by epileptic activation of the same brain regions which produce the physiologic orgasm.

REFERENCES

Akimura T, Fujii M, Ideguchi M, Yoshikawa K, Suzuki M (2003) Ictal onset and spreading of seizures of parietal lobe origin. Neurol Med Chir 43(11):534–540.

Amsterdam A, Abu-Rustum N, Carter J, Krychman M (2005) Persistent sexual arousal associated with increased soy intake. J Sex Med 2(3):338–340.

Aull-Watschinger S, Pataraia E, Baumgartner C (2008) Sexual auras: predominance of epileptic activity within the mesial temporal lobe. Epilepsy Behav 12(1):124–127.

Bancaud J, Favel P, Bonis A, Bordas-Ferrer M, Miravet J, Talairach J (1971) Paroxysmal sexual manifestation and temporal epilepsy. Electroencephalogr Clin Neurophysiol 30(4):371.

Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Kugl-Meyer K, Graziottin A, Heiman JR, Laan E, Meston C, Schover L, van Lankveld J, Weijmar Schultz W (2003) Definitions of women's sexual dysfunction reconsidered: advocating expansion and revision. J Psychosom Obstet Gynaecol 24:221–229.

Betts T, Crawford P (1998) Women and epilepsy. (Dunitz M, ed), p 33. London.

Butcher JN, Dahlstrom WG, Graham JR, Tellegen A, Kaemmer B (1989) Minnesota multiphasic personality inventory-2 (MMPI-2): manual for administration and scoring. Minneapolis, DC: University of Minnesota Press.

Cascino GD, Hulihan JF, Sharbrough FW, Kelly PJ (1993) Parietal lobe lesional epilepsy: electroclinical correlation and operative outcome. Epilepsia 34(3):522–527.

Craig AD (2002) How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3:655–666.

Craig AD (2009) How do you feel-now? The anterior insula and human awareness. Nat Rev Neurosci 10(1):59–70.

Currier RD, Little SC, Suess JF, Andy OJ (1971) Sexual seizures. Arch Neurol 25(3):260–264.

Dalal SS, Baillet S, Adam C, Ducorps A, Schwartz D, Jerbi K, Bertrand O, Garnero L, Martinerie J, Lachaux JP (2009) Simultaneous MEG and intracranial EEG recordings during attentive reading. Neuroimage 45(4):1289–1304.

Della Penna S, Del Gratta C, Granata C, Pasquarelli A, Pizzella V, Rossi R, Russo M, Torquati K, Ernè SN (2000) Biomagnetic systems for clinical use. Philos Mag B 80:937–948.

De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM (2006) fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29(4):1359–1367.

De Martino F, Gentile F, Esposito F, Balsi M, Di Salle F, Goebel R, Formisano E (2007) Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. Neuroimage 34(1):177–194.

Dobesberger J, Walser G, Unterberger I, Embacher N, Luef G, Bauer G, Benke T, Bartha L, Ulmer H, Ortler M, Trinka E (2004) Genital automatisms: a video-EEG study in patients with medically refractory seizures. Epilepsia 45(7):777–780.

Erickson JC, Clapp LE, Ford G, Jabbari B (2006) Somatosensory auras in refractory temporal lobe epilepsy. Epilepsia 47(1):202–206.

Eriksson J, Larsson A, Ahlström KR, Nyberg L (2007) Similar frontal and distinct posterior cortical regions mediate visual and auditory perceptual awareness. Cereb Cortex 17(4):760–765.

Freeman R, Schachter SC (1995) Autonomic epilepsy. Semin Neurol 15(2):158–166.

Goldmeier D, Bell C, Richardson D (2006) Withdrawal of selective serotonin reuptake inhibitors (SSRIs) may cause increased atrial natriuretic peptide (ANP) and persistent sexual arousal in women? J Sex Med 3(2):376.

Goldstein I, De EJB, Johnson J (2006) Persistent sexual arousal syndrome and clitoral priapism. In: Women's sexual function and dysfunction: study, diagnosis, and treatment, (Goldstein I, Meston C, Davis S, Traish A, eds), pp 674–685. London: taylor and Francis.

Greicius MD, Supekar K, Menon V, Dougherty RF (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 19(1):72–78.

Heimer L, van Hoesen, GW (2006) The limbic lobe and its output channels: implications for emotional functions and adaptative behaviour. Neurosci Biobehav Rev 30:126–147.

Ho SS, Berkovic SF, Newton MR, Austin MC, McKay WJ, Bladin PF (1994) Parietal lobe epilepsy: clinical features and seizures localization by ictal SPECT. Neurology 44(12):2277–2284.

Janszky J, Szücs A, Halàsz P, Borbèly C, Hollò A, Barsi P, Mirnics Z (2002) Orgasmic aura originates from the right hemisphere. Neurology 58(2):302–304.

Janszky J, Ebner A, Szupera Z, Schulz R, Hollo A, Szücs A, Clemens B (2004) Orgasmic aura: a report of seven cases. Seizure 13(6):441–444.

Kaido T, Otsuki T, Nakama H, Kaneko Y, Kubota Y, Sugai K, Saito O (2006) Complex behavioural automatism arising from insular cortex. Epilepsy Behav 8(1):315–319.

Kikyo H, Ohki K, Miyashita Y (2002) Neural correlates for feeling-of-knowing: an fMRI parametric analysis. Neuron 36:177–186.

Kim DW, Lee SK, Yun CH, Kim KK, Lee DS, Chung CK, Chung KH (2004) Parietal lobe epilepsy: the semeiology, yield of diagnostic workup and surgical outcome. Epilepsia 45(6):641–649.

Kirchner H, Barbeau EJ, Thorpe SJ, Regis J, Liégeois-Chauvel C (2009) Ultra-rapid sensory responses in the human frontal eye field region. J Neurosci 29(23):7599–7606.

Krychman ML, Amsterdam A, Carter J, Castiel M, DeAngelis L (2004) Brain cancer and sexual health: a case report. Palliat Support Care 2(3):315–318.

Leiblum SR, Nathan SG (2001) Persistent sexual arousal syndrome: a newly discovered pattern of female sexuality. J Sex Marital Ther 27(4):365–380.

Leiblum SR, Chivers ML (2007) Normal and persistent genital arousal in women: new prospectives. J Sex Marital Ther 33(4):357–373.

Mahoney S, Zarate C (2007) Persistent sexual arousal syndrome: a case report and review of the literature. J Sex Marital Ther 33 (1):65–71.

Mascia A, Di Gennaro G, Esposito V, Grammaldo LG, Meldolesi GN, Giampà T, Sebastiano F, Falco C, Onorati P, Manfredi M, Cantore G, Quarato PP (2005) Genital and sexual manifestations in drug-resistant partial epilepsy. Seizure 14(2):133–138.

Medina CA (2002) Clitoral priapism; a rare condition presenting as vulvar pain. Obstet Gynecol 100(5 Pt 2):1089–1091.

Nappi R, Salonia A, Traish AM, van Lunsen RH, Vardi Y, Kodiglu A, Goldstein I (2005) Clinical biologic pathophysiologies of women's sexual dysfunction. J Sex Med 2(1):4–25.

Nguyen DK, Nguyen DB, Malak R, Bouthillier A (2009) Insular cortex epilepsy: an overview. Can J Neurol Sci 36(Suppl 2):S58–S62.

Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guénot M, Mauguière F (2002) Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb cortex 12(4):376–385.

Ozkara C, Ozdemir S, Yilmaz A, Uzan M, Yeni N, Ozmen M (2006) Orgasm-induced seizures: a study of six patients. Epilepsia 47 (12):2193–2197.

Pancheri P, Sirigatti S, Biondi M (1996) Adaptation of the MMPI-2 in Italy. In: International adaptation of the MMPI-2: research and clinical applications (Butcher JN, ed), pp 416–441. Minneapolis: University of Minnesota Press.

Pizzi AM, Chapin JS, Tesar GE, Busch RM (2009) Comparison of personality traits in patients with frontal and temporal lobe epilepsies. Epilepsy Behav 15(2):225–229.

Reading PJ, Will RG (1997) Unwelcome orgasms. Lancet 350:1746.

Rémillard GM, Andermann F, Testa GF, Gloor P, Aubé M, Martin JB, Feindel W, Guberman A, Simpson C (1983) Sexual ictal manifestation predominate in women with temporal lobe epilepsy: a finding suggesting sexual dimorphism in the human brain. Neurology 33(3):323–330.

Ryvlin P (2006) Avoid falling into the depths of the insular trap. Epileptic Disord 8(Suppl 2):S37–S56.

Ruff RL (1980) Orgasmic epilepsy. Neurology 30(11):1252.

Santisute M, Nowak R, Russi A, Taracon T, Oliver B, Ayats E, Scheler G, Graetz G (2008) Simultaneous magnetoencephalography and intracranial EEG registration: technical and clinical aspects. J Clin Neurophysiol 25(6):331–339.

Schenck CH, Arnulf I, Mahowald MW (2007) Sleep and sex: what can go wrong? A review of the literature on sleep related disorders and abnormal sexual behaviours and experiences. Sleep 30(6):683–702.

Silverman D (1960) The anterior temporal electrode and the ten-twenty system. Electroencephalogr Clin Neurophysiol 12:735–737.

Sperling MR, Engel J (1985) Electroencephalographic recording from temporal lobes: a comparison of ear, anterior temporal and nasopharyngeal electrodes. Ann Neurol 17(5):510–513.

Stoffels C, Munari C, Bonis A, Bancaud J, Talairach J (1980) Genital and sexual manifestations occurring in the course of partial seizures in man (author's transl). Rev Electroencephalogr Neurophysiol Clin 10(4):386–392.

Swinkels WA, van Emde Boas W, Kuyk J, van Dyck R, Spinhoven P (2006) Interictal depression, anxiety, personality traits, and psychological dissociation in patients with temporal lobe epilepsy (TLE) and extra-TLE. Epilepsia 47(12):2092–2103.

Toone B (1991) Sex, sexual seizures and the female with epilepsy. In: Woman and epilepsy (Trimble MR, ed), pp 201–206. London: John Wiley & Sons.

Van den Hout M, Barlowd D (2000) Attention, arousal and expectancies in anxiety and sexual disorders. J Affect Disord 61(3):241–256.

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