Epilepsy & Behavior 60 (2016) 7–10

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Brief Communication

"God has sent me to you": Right temporal epilepsy, left prefrontal psychosis

Shahar Arzy [a,b,*], Roey Schurr [a]

[a] Neuropsychiatry Lab, Department of Neurology, Hadassah Hebrew University Medical Center, Jerusalem 9112001, Israel
[b] Department of Medical Neuroscience, Faculty of Medicine, The Hebrew University, Jerusalem 9112001, Israel

ARTICLE INFO

Article history:
Received 19 January 2016
Revised 8 April 2016
Accepted 8 April 2016
Available online xxxx

Keywords:
Postictal psychosis
Delusion
Religious
EEG

ABSTRACT

Religious experiences have long been documented in patients with epilepsy, though their exact underlying neural mechanisms are still unclear. Here, we had the rare opportunity to record a delusional religious conversion in real time in a patient with right temporal lobe epilepsy undergoing continuous video-EEG. In this patient, a messianic revelation experience occurred several hours after a complex partial seizure of temporal origin, compatible with postictal psychosis (PIP). We analyzed the recorded resting-state EEG epochs separately for each of the conventional frequency bands. Topographical analysis of the bandpass filtered EEG epochs revealed increased activity in the low-gamma range (30–40 Hz) during religious conversion compared with activity during the patient's habitual state. The brain generator underlying this activity was localized to the left prefrontal cortex. This suggests that religious conversion in PIP is related to control mechanisms in the prefrontal lobe-related processes rather than medial temporal lobe-related processes.

1. Introduction

As a brain-based cognitive phenomenon, our understanding of religion may profit much from neuroscientific investigation of people with religious and spiritual conversions as well as practicing mystics [1–4]. A special case of religious conversion may occur in psychosis related to various neuropsychiatric disorders, such as epilepsy (especially temporal lobe epilepsy, TLE) and schizophrenia [5]. In epilepsy, clinical observations suggest an association of religious experiences not only with epileptic ictus (seizures), but also with the interictal (between seizures) and postictal (after seizures) phases [5,6]. Notably, the majority of prominent religious experiences in patients with epilepsy occur during postictal phases [7]. Therefore, most of them are diagnosed as "postictal psychosis" (PIP) [8–11]. Postictal psychosis refers to brief psychotic episodes that follow a cluster of seizures or seizure exacerbation and has been reported in the setting of presurgical evaluation, in which antiepileptic drugs are tapered to provoke seizures [9,12–14]. The psychotic symptoms may resemble positive symptoms of schizophrenia, including grandiose delusions, delusions of reference, hallucinations and religious delusions, as well as affective symptoms (such as mania and depression) [9,12,13].

The association between religion and psychosis is also widely acknowledged. Delusions and hallucinations with religious contents are common in psychotic disorders including bipolar disorder, schizophrenia, and hallucinogen-induced psychosis, and their prevalence ranges from 38% to 91% in different cultures and studies [15,16]. Phenomenologically, religious content is common in the acute phase of schizophrenia (religious delusions and hallucinations with religious content) and in habits of patients in the chronic phase. Religious content also influences treatment adherence in individuals diagnosed with schizophrenia [17]. Religious contents are abundant in auditory hallucinations of God, the devil, prophets, or saints; paranoid delusions of possession; and grandiose delusions of one being a heroic savior. Though the presence of religious content in psychoses is not restricted to a specific type of religion, the content itself was found to be associated with patients' religious upbringing and culture [15].

In neuropsychiatry, understanding of the underlying mechanism of clinical disorders may be valuable for comprehension of not only the disorder itself but also the disturbed function. Analysis of neuroscientific data of religious conversion may shed light on both the cognitive mechanisms of religious belief as well as the neurological basis of delusional psychosis. Here we were able to record the very moments of religious conversion under video-EEG. This enabled us to compare brain activity before religious conversion with that during conversion.

2. Patient

The patient was a 45-year-old single man, a factory worker with low-level education. He was an orthodox religious Jew of Sephardic origin, practicing rituals regularly, as is common in his surrounding society, without any special religious involvement, deep religious feelings, or scholarly interest. The patient suffered from generalized tonic–clonic

* Corresponding author at: Neuropsychiatry Lab, Department of Neurology, Hadassah Hebrew University Medical Center, Jerusalem, Israel. Tel.: +972 2 6776 940.
E-mail address: shahar.arzy@ekmd.huji.ac.il (S. Arzy).

http://dx.doi.org/10.1016/j.yebeh.2016.04.022
1525-5050/

seizures (GTCSs) since the age of seven. He was treated with phenytoin for nine years. The patient was subsequently free of seizures until he reached the age of 23, when GTCSs relapsed. The patient was administered phenytoin again and was later switched to carbamazepine, with no GTCS relapse ever since. In the recent years, he suffered from attacks during which he first reported "lip tremor" accompanied by anxiety. These were followed by a "change in speech", especially with respect to prosody, followed by a "general slowing in thought processes" for several minutes. There was no loss of consciousness, and there were no lateralized focal signs or other motor manifestations. The duration of these events was 30–60 s, sometimes up to 20 times a day, though the patient would sometimes be free of attacks for several weeks. When events occurred in a cluster, the patient suffered from a general anxiety state. Treatment with valproic acid was added with no clinical effect, and the patient was referred to our epilepsy center.

The patient's neurological status was unremarkable. Neuropsychological evaluation showed a low yet normal level of general intelligence with impairment in memory functions. Electroencephalogram showed intermittent right temporal slowing in the theta range. The patient was further evaluated by prolonged video-EEG recording. While medications were tapered down, several stereotypic attacks were observed in which the patient first reported a vague "feeling" that an attack approaches; then, he laid in bed, started masticating, looked to the left, and then moved slowly his left hand (which was in a dystonic position). This was followed by similar movements also in the right hand, as well as extensive anxiety. The patient was amnesic to the attack and confused for several minutes later yet did not exhibit loss of consciousness. Electroencephalogram during the attack showed right temporal rhythmic activity (Fig. 1A), followed by a generalized spike-and-wave activity. Interictal epileptiform activity was found in both temporal lobes, most prominently in the left. Magnetic resonance imaging showed an extensive right mesial temporal sclerosis (MTS; Fig. 1B). The patient was subsequently treated with a combination of carbamazepine and phenobarbital.

Eight hours following the last seizure, while lying in bed, the patient abruptly "froze" and stared at the ceiling for several minutes, stating later that he felt that God was approaching him. He then started chanting prayers quietly, looked for his Kippa and put it on his head, chanting the prayers more excessively. Then, abruptly, he yelled "And you are Adonai (name of the Hebrew God) the Lord!", stating later that god had revealed to him, ordering him to bring redemption to the people of Israel. The patient then stood up, detached the EEG electrodes from his skin, and went around the department trying to convince people to follow him, stating that "God has sent me to you". When further questioned, he said that he does not have a concrete plan, but he is sure that God is going to instruct him what he and his followers should do on their way to redemption. In an in-depth psychiatric evaluation, the patient was diagnosed as suffering from postictal psychosis (PIP), with no other psychiatric illness. The patient was treated with olanzapine. The psychotic state resolved within several hours.

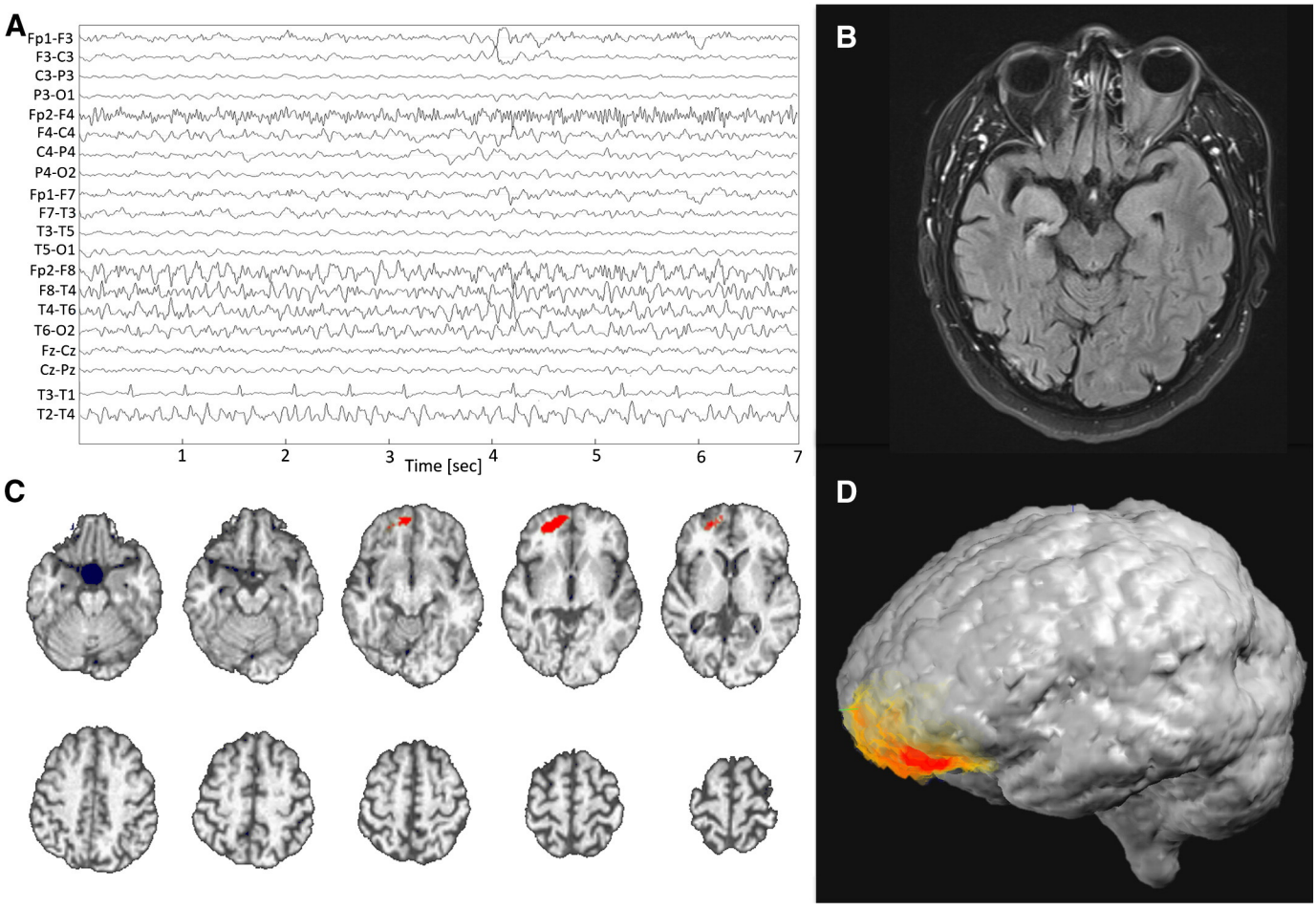

Fig. 1. (A). Ictal EEG activity during the seizure that preceded religious conversion was localized to the right temporal lobe. (B) MRI (T2, axial slice) of the patient's brain shows prominent right mesial temporal sclerosis. (C). Comparison of resting-state EEG periods recorded during postictal psychosis of delusional religious conversion and those recorded during interictal epochs using topographical electrophysiological analysis in the frequency domain revealed a significant hyperactivation in low-gamma power (30–40 Hz) in left PFC during the psychotic event. EEG generators are projected on the patient's MRI in axial slices. (D) The same EEG generators projected on the patient's MRI in 3D reconstruction.

3. Methods

We compared EEG recorded during the first moments of the event with resting-state interictal EEG as recorded several hours before. Electroencephalogram recordings were extracted from the beginning of the psychotic phase in which the patient was lying still in bed staring at the ceiling as well as from shortly after admission. Electroencephalogram recordings from two different time periods were also compared in 12 healthy subjects (28 ± 8 years old, mean ± SD, 5 females). Video-EEG was recorded with a Micromed® system (impedances < 10 kW; vertex referenced; 256 Hz digitization; bandpass filtered: 0.1–1500 Hz). Electroencephalogram electrodes were applied at the international 10/20 positions. Subsequent analyses were performed using Cartool software [18] as follows. From the first artifact-free epochs of each recording, 35 EEG epochs of 1 s were extracted for each phase, with no applied reference. These epochs were subjected to topographic analysis in the frequency domain using fast Fourier transform (FFT) applied on conventional frequency bands of delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), low beta (13–18 Hz), medium beta (18–24 Hz), high beta (24–30 Hz), low gamma (30–40 Hz), mid gamma (40–55 Hz), and high gamma (55–70 Hz). After applying the bandpass filter to the different frequency bands, the analyzed multichannel data were transformed into topographic maps, also termed "microstates" [19,20]. For each frequency band, 10 different microstates were found across the two phases using a k-means clustering approach [21]. Electroencephalogram in each time frame was then fitted to the most similar map. Several parameters of each topographic map in each frequency band were then compared between the two phases in terms of mean values over all epochs: the map's total duration (the number of time frames per epoch fitted to this map), the mean correlation per epoch between the map values and the voltage recorded over all electrodes and all time frames, the highest correlation per epoch between the map values and the voltage recorded over all electrodes and all time frames, and the global explained variance (the mean variance in voltage values over all electrodes per time frame in each epoch, that is explained by the map, weighted by the standard deviation over all electrodes) [18]. All parameters were subjected to a two-tailed unpaired t-test ($p < 0.01$, Bonferroni corrected) between the two phases (before and during conversion), showing a topographic change between them without accounting for intensity. To control for the familywise error rate, Bonferroni correction for multiple comparisons was used to adjust the p value in each frequency band.

The neural generators underlying the topographic maps of the aforementioned procedure that showed significant differences between conditions were estimated by a distributed linear inverse solution based on a low-resolution electromagnetic tomography (LORETA) [20,22,23]. LORETA uses spatial regularization to select the source configuration that resembles the biophysical behavior of electric vector fields (i.e., activity at one point depends on the activity at neighboring points). The solution space was calculated on a realistic head model that included 3005 nodes, selected from a 6 × 6 × 6-mm grid equally distributed within the gray matter of the patient's MRI.

4. Results

Comparison of EEG signals recorded in resting state during delusional religious conversion and with those during the nonpsychotic phase using power frequency analysis, and topographical statistical comparison tests revealed a significantly increased duration of a specific topographic FFT map in the low-gamma band (30–40 Hz; mean ± std of 180 ± 160 ms in the PIP phase compared with 3 ± 9 ms in the non-PIP phase; $p < 0.01$ after Bonferroni correction). Notably, only the map's duration, restricted to this frequency band, showed such a significant increased activity during religious conversion. The neural EEG generators underlying this map were localized to the left prefrontal cortex (Fig. 1C, D). No such differences were found in any other frequency band, nor in 12 control subjects in which the same analysis was conducted on two periods with the same time interval.

5. Discussion

Delusional religious thoughts are important in psychosis, of which religious conversion is an extreme expression. Postictal psychosis is a relatively rare phenomenon, which has a special importance for the comprehension of the mysterious nature of psychosis, as it hints at the brain origin of the disorder. In the above, we have described a patient with epilepsy and right MTS who during video-EEG monitoring presented grandiose religious delusion of revelation and missionary zeal in the context of PIP. Electroencephalogram analysis in the frequency domain identified hyperactivity in the left prefrontal region in the low-gamma (30–40 Hz) frequency band during religious conversion. This is discussed with respect to both PIP and the role of religious delusions in psychosis.

The pathophysiological mechanisms of PIP are poorly understood. As PIP occurs frequently in the framework of presurgical video-EEG monitoring, data are, nevertheless, available in the form of both continuous EEG recording as well as neuroimaging. With respect to EEG, several studies have reported frequent interictal discharges in patients with PIP, suggesting that ictal activity in the temporal lobe is directly related to this kind of psychosis [9,12,13,24]. To the best of our knowledge, analyses of the ictal nonepileptic activity as analyzed here have never been reported. Many presurgical monitoring units are also equipped with hexamethyl propylenamine oxime tracer to be injected during seizures and scanned later using single-photon emission computerized tomography (SPECT). Several studies have used SPECT during the acute phase of PIP and further compared findings with a second scan postrecovery. Leutmezer and colleagues [13] studied five patients with PIP and found hyperperfusion in the temporal and medial prefrontal lobes bilaterally, as well as in the left lateral prefrontal cortex (PFC). Fong and colleagues [25] studied two patients with right TLE who had developed PIP in whom SPECT showed right temporal and left basal ganglia hyperperfusion. Taken together, these studies demonstrated both temporal hyperperfusion and extratemporal (mostly prefrontal) hyperperfusion in PIP.

Implication of the PFC in psychosis is well established (for review, see [26]). For instance, patients with new-onset psychosis show prominent gray matter reduction in the PFC. Behavioral studies as well as task-related fMRI showed deficits in source monitoring in these patients during encoding and retrieval of memories [26–29]. While the latter are processed in the MTL, the first is governed by mechanisms at the PFC [30]. Accordingly, Cannon [26] hypothesized that delusions "may emerge as a consequence of a progressive loss of connectivity of regions involved in source monitoring during memory encoding and retrieval" as based on aberrant PFC activity. Our results agree with this hypothesis as religious delusions were found to be associated with increased activity in the left PFC in accordance with both the above SPECT studies as well as studies in patients with psychosis. While previous SPECT studies highlighted both the documented temporal as well as the prefrontal activity, our EEG results, which reflect a unique part of the recorded brain activity, may specify the PIP-related prefrontal activity exclusively. Modification of gamma power reflects changes within local cortical regions, unlike changes in lower frequency bands which reflect interregional communication [31,32]. Changes in gamma-power might, therefore, reflect changes in the electrical property of the PFC specifically, rather than general changes in a whole-brain network.

Postictal psychosis appears almost exclusively in patients with temporal lobe epilepsy, predominantly with MTS [10,33]. Most of the reported patients suffered from bilateral MTS/aberrant temporal activity, though unilateral MTS was also described [9,13,34]. Our patient suffered from prominent right MTS with bilateral independent interictal discharges. The similarity between temporal lobe phenomena and psychotic symptoms does not necessarily imply common underlying

mechanisms for the two sets [12]. Moreover, the delusion of messianic conversion, as occurred in our patient, may be classified as beliefs of grandeur, reference, and religious significance, similar to schizophrenic delusions, which involve influence, persecution, and self-significance, rather than classical semiology of TLE. Taken together, the recurrent findings over studies of PIP revealing mesial temporal epilepsy and PFC aberrant activity during PIP point to a disturbance of a large-scale network, which encompasses both the PFC and the MTL. Such a network may be the default mode network (DMN), which manages self-referenced activity [35] and mental orientation to the surrounding environment [36,37], and is known to be disturbed in psychosis [38].

Previous studies have speculated that PIP may be derived from repeated electrical discharges or that the epilepsy and psychosis share a common neuropathology that may be localized (with emphasis on temporal or frontal lobe) [12]. Our study suggests an alternative explanation of a large-scale network disturbance underlying PIP.

Generalization is difficult as based on one patient. Our study, however, is in line with findings in other studies of PIP, both with respect to PIP's relation to temporal origin and PFC activity during PIP. In addition, both epilepsy and psychosis are heterogeneous phenomena, and their categorization should be systematically studied before any association is described [12]. In the current study, we, nevertheless, focused on a certain type of epilepsy (TLE) and psychosis (delusional religious conversion). Finally, hyperactivity, as defined here, is based on prolonged duration of the corresponding topographical EEG map. Map duration was found previously to characterize pathological neuropsychiatric states [19].

In conclusion, EEG analysis in this patient showed that delusional religious conversion in the context of PIP is related to hyperactivity in the left PFC in the low-gamma range, following a precedent aberrant temporal lobe epileptic activity. This suggests that psychosis is related to disturbed dynamic activity in the PFC. Further research of this network and its dynamics may shed new light not only on PIP but also on acute psychosis and, specifically, on delusional religious conversion.

Acknowledgments

The authors would like to thank Mor Nitzan (Hebrew University) for helpful comments on the manuscript; Dr Dana Ekstein and Dr Renana Eitan for continuous clinical and scientific collaboration, and Mrs Orit Gerbi and the EEG team. This study was supported by the Israeli National Science Foundation and the Ministry of Science and Technology of Israel (3-10789).

Conflict of interest statement

The authors report no conflicts of interest.

References

[1] McNamara P. The neuroscience of religious experience. Cambridge University Press; 2009.
[2] Arzy S, Idel M. Kabbalah: a neurocognitive approach to mystical experiences. Yale University Press; 2015.
[3] Leuba JH. The psychology of religious mysticism. New York: Harcourt, Brace & Co.; 1925.
[4] Graziano MSA. God soul mind brain: a neuroscientist's reflections on the spirit world. Teaticket, MA: Leapfrog Press; 2010.
[5] Devinsky O, Lai G. Spirituality and religion in epilepsy. Epilepsy Behav 2008;12:636–43. http://dx.doi.org/10.1016/j.yebeh.2007.11.011.
[6] Dewhurst K, Beard AW. Sudden religious conversions in temporal lobe epilepsy. Br J Psychiatry 1970;117:497–507.
[7] Devinsky O. Postictal psychosis: common, dangerous, and treatable. Epilepsy Curr 2008;8:31–4. http://dx.doi.org/10.1111/j.1535-7511.2008.00227.x.
[8] Trimble MR. The psychoses of epilepsy. Raven Press, Publishers; 1991.
[9] Kanner AM, Stagno S, Kotagal P, Morris HH. Postictal psychiatric events during prolonged video-electroencephalographic monitoring studies. Arch Neurol 1996;53:258–63. http://dx.doi.org/10.1001/archneur.1996.00550030070024.
[10] Trimble MR, Kanner AM, Schmitz B. Postictal psychosis. Epilepsy Behav 2010;19:159–61. http://dx.doi.org/10.1016/j.yebeh.2010.06.027.
[11] Kuba R, Brázdil M, Rektor I. Postictal psychosis and its electrophysiological correlates in invasive EEG: a case report study and literature review. Epilepsy Behav 2012;23:426–30. http://dx.doi.org/10.1016/j.yebeh.2012.02.004.
[12] Sachdev P. Schizophrenia-like psychosis and epilepsy: the status of the association. Am J Psychiatry 1998;155:325–36. http://dx.doi.org/10.1176/ajp.155.3.325.
[13] Leutmezer F, Podreka I, Asenbaum S, Pietrzyk U, Lucht H, Back C, et al. Postictal psychosis in temporal lobe epilepsy. Epilepsia 2003;44:582–90.
[14] Logsdail SJ, Toone BK. Post-ictal psychoses. A clinical and phenomenological description. Br J Psychiatry 1988;152:246–52.
[15] Brewerton TD. Hyperreligiosity in psychotic disorders. J Nerv Ment Dis 1994;182:302–4.
[16] Grover S, Davuluri T, Chakrabarti S. Religion, spirituality, and schizophrenia: a review. Indian J Psychol Med 2014;36:119–24. http://dx.doi.org/10.4103/0253-7176.130962.
[17] Mohr S, Brandt P-Y, Borras L, Gilliéron C, Huguelet P. Toward an integration of spirituality and religiousness into the psychosocial dimension of schizophrenia. Am J Psychiatry 2006;163:1952–9. http://dx.doi.org/10.1176/ajp.2006.163.11.1952.
[18] Brunet D, Murray MM, Michel CM. Spatiotemporal analysis of multichannel EEG: CARTOOL. Comput Intell Neurosci 2011;2011. http://dx.doi.org/10.1155/2011/813870.
[19] Arzy S, Mohr C, Molnar-Szakacs I, Blanke O. Schizotypal perceptual aberrations of time: correlation between score, behavior and brain activity. PLoS One 2011;6,e16154. http://dx.doi.org/10.1371/journal.pone.0016154.
[20] Arzy S, Allali G, Brunet D, Michel CM, Kaplan PW, Seeck M. Antiepileptic drugs modify power of high EEG frequencies and their neural generators. Eur J Neurol 2010;17:1308–12. http://dx.doi.org/10.1111/j.1468-1331.2010.03018.x.
[21] Pascual-Marqui RD, Michel CM, Lehmann D. Segmentation of brain electrical activity into microstates: model estimation and validation. IEEE Trans Biomed Eng 1995;42:658–65. http://dx.doi.org/10.1109/10.391164.
[22] Grave de Peralta Menendez R, Murray MM, Michel CM, Martuzzi R, Gonzalez Andino SL. Electrical neuroimaging based on biophysical constraints. Neuroimage 2004;21:527–39. http://dx.doi.org/10.1016/j.neuroimage.2003.09.051.
[23] Arzy S, Collette S, Wissmeyer M, Lazeyras F, Kaplan PW, Blanke O. Psychogenic amnesia and self-identity: a multimodal functional investigation. Eur J Neurol 2011;18:1422–5. http://dx.doi.org/10.1111/j.1468-1331.2011.03423.x.
[24] Elliott B, Joyce E, Shorvon S. Delusions, illusions and hallucinations in epilepsy: 2. Complex phenomena and psychosis. Epilepsy Res 2009;85:172–86. http://dx.doi.org/10.1016/j.eplepsyres.2009.03.017.
[25] Fong GCY, Fong KY, Mak W, Tsang KL, Chan KH, Cheung RTF, et al. Postictal psychosis related regional cerebral hyperperfusion. J Neurol Neurosurg Psychiatry 2000;68:100–1. http://dx.doi.org/10.1136/jnnp.68.1.100.
[26] Cannon TD. How schizophrenia develops: cognitive and brain mechanisms underlying onset of psychosis. Trends Cogn Sci 2015;19:744–56. http://dx.doi.org/10.1016/j.tics.2015.09.009.
[27] Buda M, Fornito A, Bergström ZM, Simons JS. A specific brain structural basis for individual differences in reality monitoring. J Neurosci 2011;31:14308–13. http://dx.doi.org/10.1523/JNEUROSCI.3595-11.2011.
[28] Simons JS, Henson RNA, Gilbert SJ, Fletcher PC. Separable forms of reality monitoring supported by anterior prefrontal cortex. J Cogn Neurosci 2008;20:447–57. http://dx.doi.org/10.1162/jocn.2008.20036.
[29] Sugimori E, Mitchell KJ, Raye CL, Greene EJ, Johnson MK. Brain mechanisms underlying reality monitoring for heard and imagined words. Psychol Sci 2014;25:403–13. http://dx.doi.org/10.1177/0956797613505776.
[30] Mitchell KJ, Johnson MK, Raye CL, Greene EJ. Prefrontal cortex activity associated with source monitoring in a working memory task. J Cogn Neurosci 2009;16:921–34. http://dx.doi.org/10.1162/0898929041502724.
[31] von Stein A, Sarnthein J. Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. Int J Psychophysiol 2000;38:301–13. http://dx.doi.org/10.1016/S0167-8760(00)00172-0.
[32] Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. Brain 2006;129:1593–608. http://dx.doi.org/10.1093/brain/awl085.
[33] Briellmann RS, Kalnins RM, Hopwood MJ, Ward C, Berkovic SF, Jackson GD. TLE patients with postictal psychosis: mesial dysplasia and anterior hippocampal preservation. Neurology 2000;55:1027–30.
[34] Devinsky O, Abramson H, Alper K, FitzGerald LS, Perrine K, Calderon J, et al. Postictal psychosis: a case control series of 20 patients and 150 controls. Epilepsy Res 1995;20:247–53. http://dx.doi.org/10.1016/0920-1211(94)00085-B.
[35] Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A 2001;98:4259–64. http://dx.doi.org/10.1073/pnas.071043098.
[36] Peer M, Lyon R, Arzy S. Orientation and disorientation: lessons from patients with epilepsy. Epilepsy Behav 2014;41:149–57. http://dx.doi.org/10.1016/j.yebeh.2014.09.055.
[37] Peer M, Salomon R, Goldberg I, Blanke O, Arzy S. Brain system for mental orientation in space, time, and person. Proc Natl Acad Sci 2015;112:11072–7. http://dx.doi.org/10.1073/pnas.1504242112.
[38] Zhang D, Raichle ME. Disease and the brain's dark energy. Nat Rev Neurol 2010;6:15–28. http://dx.doi.org/10.1038/nrneurol.2009.198.