“God has sent me to you”: right temporal epilepsy, left prefrontal psychosis

Shahar Arzy^{1,2} and Roey Schurr¹

¹ Neuropsychiatry Lab, Department of Neurology, Hadassah Hebrew University Medical Center, Jerusalem 9112001, Israel

*²Department of Medical Neuroscience, Faculty of Medicine, The Hebrew University,
Jerusalem 9112001, Israel*

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Correspondence should be addressed to:

Shahar Arzy, MD PhD
Neuropsychiatry Lab,
Department of Neurology
Hadassah Hebrew University Medical Center
Jerusalem, Israel
Tel: +972-2-6776-940
e-mail: shahar.arzy@ekmd.huji.ac.il

Neuropsychiatry Lab,

Department of Neurology

Hadassah Hebrew University Medical Center

Jerusalem, Israel

Tel: +972-2-6776-940

e-mail: shahar.arzy@ekmd.huji.ac.il

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33 **Abstract**

34 Religious experiences have long been documented in epileptic patients, though their
35 exact underlying neural mechanism is still unclear. Here we had the rare opportunity
36 to record a delusional religious conversion in real time in a patient with right temporal
37 lobe epilepsy undergoing continuous video-EEG. In this patient, a messianic
38 revelation experience occurred several hours after a complex partial seizure of
39 temporal origin, compatible with postictal psychosis (PIP). We analyzed the recorded
40 resting-state EEG epochs separately for each of the conventional frequency bands.
41 Topographical analysis of the bandpass filtered EEG epochs revealed increased
42 activity in the low gamma range (30-40 Hz) during religious conversion, as compared
43 to activity during the patient's habitual state. The brain generator underlying this
44 activity was localized to the left prefrontal cortex. This suggests that religious
45 conversion in PIP is related to control mechanisms in the prefrontal lobe rather than to
46 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 to epileptic ictus (seizures), but also to the interictal (between seizures) and post-ictal (after seizures) phases [5,6]. Notably, the majority of prominent religious experiences in patients with epilepsy occur during post-ictal phases [7]. Therefore, most of them are diagnosed as “post-ictal psychosis” (PIP) [8–11]. PIP are brief psychotic episodes that follow a cluster of seizures or seizure exacerbation, and have been reported in the setting of presurgical evaluation, in which anti-epileptic 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 (mania, 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 hallucinogens 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 not only for comprehension of the disorder itself, but also to that of 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. Recently, we were able to record the very moments of religious conversion under video-EEG. This enabled us to compare brain activity before and during conversion.

2. Patient

The patient was a 45-year-old single man of Sephardic origin, factory-worker with low-level education. He was an orthodox religious Jew, 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 seizures (GTCS) since the age of seven years old. He was treated with phenytoin for nine years. The patient was subsequently free of seizures till the age of 23, when GTCS has relapsed. Phenytoin was administered again, and 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,

97 followed by a “general slowing in thought processes” for several minutes. There was
98 no rupture of contact, no lateralized focal signs or other motor manifestations. The
99 duration of these events was 30-60 seconds, sometimes up to 20 times a day, though
100 the patient would sometimes be free of attacks for several weeks. When events
101 occurred in cluster, the patient suffered from a general anxiety state. Treatment with
102 valproic acid was added with no clinical effect and the patient was referred to our
103 epilepsy center.

104
105 The patient’s neurological status was unremarkable. Neuropsychological evaluation
106 showed a low yet normal level of general intelligence with impairment in memory
107 functions. EEG showed intermittent right temporal slowing in the theta range. The
108 patient was further evaluated by prolonged video-EEG recording. While medications
109 were tapered down, several stereotypic attacks were observed in which the patient
110 first reported a vague “feeling” that an attack approaches; then he laid in [bed](#), started
111 masticating, looked to the left, then moved slowly his left hand (which was in a
112 dystonic position). This was followed by similar movements also in the right hand, as
113 well as extensive anxiety. The patient was amnesic to the attack and confused for
114 several minutes later, yet did not exhibit loss of consciousness. EEG during the attack
115 showed right temporal rhythmic activity (Figure 1A), followed by a generalized
116 spike-and-wave activity. Interictal [epileptiform](#) activity was found in both temporal
117 lobes, most prominently in the left. MRI showed an extensive right mesial temporal
118 sclerosis (MTS; Figure 1B). The patient was subsequently treated with a combination
119 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 post-ictal psychosis (PIP), with no other psychiatric illness. The patient was treated with olanzapine. The psychotic state has been resolved within several hours.

3. Methods

We compared EEG recorded during the first moments of the event to resting-state inter-ictal EEG as recorded several hours before. EEG 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. EEG recordings from two different time periods were also compared in 12 healthy subjects (28 ± 8 years old, mean $\pm$ 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). EEG 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 1s 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]. EEG 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 family-wise 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 $6 \times 6 \times 6$ 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 during the non-psychotic 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 $\pm$ std of 180 ± 160 ms in the PIP phase compared to 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, has shown such a significant increased activity during religious conversion. The neural EEG generators underlying this map were localized to the left prefrontal cortex (Fig. 1C, 1D). 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

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

204

205 The pathophysiological mechanisms of PIP are poorly understood. As PIP occurs
206 frequently in the framework of presurgical video-EEG monitoring, data is
207 nevertheless available in the form of both continuous EEG recording as well as
208 neuroimaging. With respect to EEG, several studies have reported frequent interictal
209 discharges in patients with PIP, suggesting that ictal activity in the temporal lobe is
210 directly related to this kind of psychosis [9,12,13,24]. To the best of our knowledge,
211 analyses of the ictal non-epileptic activity as analyzed here have never been reported.
212 Many presurgical monitoring units are also equipped with hexamethyl-
213 propylenamine-oxime tracer to be injected during seizures and scanned later using
214 single photon emission computerized tomography (SPECT). Several studies have
215 used SPECT during the acute phase of PIP, and further compared findings to a second
216 scan post recovery. Leutmezer and colleagues [13] studied five patients with PIP and
217 found hyperperfusion in the temporal and medial prefrontal lobes bilaterally, as well
218 as in the left lateral prefrontal cortex (PFC). Fong and colleagues [25] studied two
219 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 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.

PIP 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 a 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, similarly 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 either 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 to 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. Second, 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 [framework 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.

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Conflict of interest statement

The authors report no conflicts of interest.

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394

395 **Legends.**

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

405