Epilepsy & Behavior 70 (2017) 166–172

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Multisensory temporal function and EEG complexity in patients with epilepsy and psychogenic nonepileptic events

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ARTICLE INFO

Article history:
Received 22 October 2016
Revised 10 February 2017
Accepted 13 February 2017
Available online xxxx

Keywords:
Multisensory
Temporal
Epilepsy
Psychogenic
EEG
Neural complexity

ABSTRACT

Cognitive and perceptual comorbidities frequently accompany epilepsy and psychogenic nonepileptic events (PNEE). However, and despite the fact that perceptual function is built upon a multisensory foundation, little knowledge exists concerning multisensory function in these populations. Here, we characterized facets of multisensory processing abilities in patients with epilepsy and PNEE, and probed the relationship between individual resting-state EEG complexity and these psychophysical measures in each patient. We prospectively studied a cohort of patients with epilepsy (N = 18) and PNEE (N = 20) patients who were admitted to Vanderbilt's Epilepsy Monitoring Unit (EMU) and weaned off of anticonvulsant drugs. Unaffected age-matched persons staying with the patients in the EMU (N = 15) were also recruited as controls. All participants performed two tests of multisensory function: an audio–visual simultaneity judgment and an audio–visual redundant target task. Further, in the cohort of patients with epilepsy and PNEE we quantified resting state EEG gamma power and complexity. Compared with both patients with epilepsy and control subjects, patients with PNEE exhibited significantly poorer acuity in audiovisual temporal function as evidenced in significantly larger temporal binding windows (i.e., they perceived larger stimulus asynchronies as being presented simultaneously). These differences appeared to be specific for temporal function, as there was no difference among the three groups in a non-temporally based measure of multisensory function — the redundant target task. Further, patients with PNEE exhibited more complex resting state EEG patterns as compared to their patients with epilepsy, and EEG complexity correlated with multisensory temporal performance on a subject-by-subject manner. Taken together, findings seem to indicate that patients with PNEE bind information from audition and vision over larger temporal intervals when compared with control subjects as well as patients with epilepsy. This difference in multisensory function appears to be specific to the temporal domain, and may be a contributing factor to the behavioral and perceptual alterations seen in this population.

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1. Introduction

Patients with epilepsy and those with psychogenic non-epileptic events (PNEE) often experience cognitive (e.g., episodic memory) and perceptual (e.g., auditory hallucinations) impairments [1,2]. Although the difficulty these patients have when interacting with their environment may stem from disturbances in higher-order brain networks, they may also be a result of changes in lower-level sensory function (or some combination of these). Indeed, there has been a recent focus on examining changes in sensory processing in patients with epilepsy [3–6], and although a recent account of PNEE reports no systematic study of sensory function in this population [7], several case studies do suggest sensory abnormalities in this understudied population [8,9]. However, this work, in both patients with epilepsy and PNEE, has largely been restricted to examining single sensory systems. Studies of multisensory function (i.e., the ability to synthesize information across the different senses) in the context of epileptic disorders are rare, a surprising gap given the importance of multisensory function in the construction of veridical perceptual and cognitive representations [10,11].

Cases of atypical sensory processing have been linked to an imbalance between neuronal excitation and inhibition, which is a key

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http://dx.doi.org/10.1016/j.yebeh.2017.02.018
1525-5050/Published by Elsevier Inc.

mechanism in the generation of epileptic seizures [12–14]. At a cellular level, recent work has illustrated the importance of synaptic inhibition in gating multisensory integration [15]. This recent observation is well in line with prior work suggesting that inhibition narrows the tuning functions of sensory neurons to their preferred responses and alters the timing and reliability of sensory-driven spike output [16]. Collectively, this work reinforces presumptive links between the changes in inhibitory processes known to accompany epilepsy and fundamental mechanisms of multisensory integration. Lastly, gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the cerebral cortex, in addition to playing a key role in sensory filtering and being deficient in epilepsy [17], has been shown to contribute to the generation of gamma band oscillations [18]. An oscillatory power which spontaneous activity in patients with epilepsy has been suggested to index the onset of an epileptic event [19,20], and a frequency band taken to dictate the degree to which individuals bind information from distinct sensory modalities [21,22]. Indeed, recent work has suggested a tripartite relationship between GABA concentration, gamma power, and multisensory binding [23].

It is under this framework that the study of multisensory temporal binding in a population with epilepsy is interesting beyond its clinical applicability. A key question within the study of neural information processing is the manner by which information is integrated. Influential theoretical views have posited a privileged status regarding information integration for neural oscillations within the gamma range (specifically 40 Hz), in particular as it relates to temporal and/or feature binding [24,25]. Neural complexity, which is aberrant during a seizure [26], is also reflective of neural integration and has been put forward as an important indicator of perceptual awareness [27], a state that is characterized by the unity of our perceptual experiences [28]. Thus, we may expect the unity or integration of the perceptual world to be fundamentally different in patients with epilepsy than in the general population. Hence, a study of this clinical population may provide important neurobiological insights into the general question of information binding.

In the current study, we specifically tested multisensory (i.e., audiovisual) function in the groups with epilepsy and PNEE, taking advantage of psychophysical tasks of both general (redundant target) and temporal (simultaneity judgment) abilities. The focus on a temporal task was grounded in the importance of inhibition (and by extension E/I balance) in mediating temporal processes. In addition, we related multisensory abilities to neural function, particularly resting state gamma power and EEG complexity (measured by Lempel-Ziv complexity, see Methods section).

2. Methods

2.1. Participants

As detailed in Table 1, we prospectively enrolled 53 participants (25 females, mean age = 40.37 years, range = 19–62 years; duration of disease = 13.8 ± 16.2 years). The diagnosis of epilepsy or PNEE was determined by attending epileptologists via video-EEG monitoring and was not known to the investigators at the time of recruitment or psychophysical testing. After completion of the study it was determined that there were 20 patients with PNEE (11 females, mean age = 40.60 years), and 18 patients with epilepsy (7 females, mean age = 38.55 years). In addition, 15 age-matched controls (7 females, mean age = 43.26 years) were recruited. Consistent with a higher incidence of PNEE in women [29], the patient groups did differ in sex (55% females in the group of patients with PNEE vs. 39% females in the group with epilepsy, $p = 0.009$), as well as disease duration (PNEE 3.5 ± 2.6 years, 24 ± 18 years with epilepsy, $p < 0.001$). Control participants were family members or friends of the patients who stayed with the patients in the epilepsy monitoring unit (EMU), and thus had the same EMU environmental exposure as the patients. All anticonvulsant medications were stopped during the course of the stay at the EMU as well as during psychophysical and EEG testing. Patients were gradually weaned off of medication over the course of several days, and psychophysical testing occurred 2–4 days following medication stoppage. All participants had normal or corrected-to-normal visual acuity and self-reported normal auditory acuity. Control participants self-reported to have no psychiatric or neurological history. Vanderbilt University Medical Center's Institutional Review Board approved all experimental protocols, and written informed consent was obtained from all participants.

2.2. Materials and apparatus

2.2.1. Audio–visual simultaneity judgment

Visual and auditory stimuli were controlled via a purpose-made microcontroller (Arduino, refresh rate 10 KHz) and driven by in-house experimental software (ExpyVR, direct serial port communication with microcontroller, [30]). Visual stimuli were presented by means of a red LED (7000 mcd, 640 nm wavelength, 348 radiancy angle), and auditory stimuli were generated by the activation of a piezo speaker (75 dB at 0.3 m, 3.0 kHz). An audiovisual device was built by assembling the auditory and visual stimuli into a 5 cm × 3 cm × 1 cm opaque rectangular box (see Fig. 1A). Both visual and auditory stimuli had a duration of 10 ms and were presented within a range of stimulus onset asynchronies (SOAs) that included 0 ms, ±20 ms, ±50 ms, ±100 ms, ±150 ms, ±200 ms, ±300 ms, and ±500 ms. By convention, positive SOAs indicate conditions in which visual stimuli preceded auditory stimuli. Participant's responses were made via button press. Accurate timing of all components involved in the procedure abovementioned was verified via oscilloscope.

2.2.2. Audio-visual reaction time: multisensory redundant target task

In order to probe auditory, visual, and audio-visual reaction times, we presented participants with sensory stimuli in 9 different conditions in a 3 × 3 factorial design (3 intensities of visual stimuli × 3 intensities of auditory stimuli). Visual and auditory stimuli were presented on a computer monitor and controlled via E-Prime software (Psychology Software Tools). Visual stimuli were either absent (V0) or a white circle presented for 100 ms on a gray background at an intensity of either 0.0036 (V1) or 0.0108 (V2) Michelson Contrast. Auditory stimuli were absent (A0), or a pure tone at 2000 Hz, presented for 100 ms at an intensity of either 15 dB (A1) or 35 dB (A2) SPL. There was no stimulus onset asynchrony between the auditory and visual stimuli in the case of audio–visual presentations.

2.2.3. EEG resting state

Patients, but not control subjects, underwent continuous video-EEG monitoring in order to ascertain the focus of their seizures. As part of their clinical assessment, a resting-state eyes-closed epoch for at least 5 min was collected. By “resting-state”, we refer to the fact that participants were not actively completing an experimental task and were simply instructed to relax and keep their eyes closed. Spontaneous cortical electrical activity was recorded with a 19-channel EEG system (EEG-1000/EEG-1200, Nihon Kohden, Inc., Tokyo, Japan), filtered through a 0.53–120 Hz band-pass filter, and sampled at 200 Hz. The EEG was recorded with the electrodes positioned according to the international 10–20 system (i.e., Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz) using a linked-ears reference. For some patients, additional electrodes were added if clinically necessary. Electrode impedances were kept below 5 kΩ. For each patient, a 300-s artifact-free, resting–awake segment was manually selected by visual inspection using Neuroworkbench software (Nihon Kohden, Inc., Tokyo, Japan).

2.3. Procedure

Patients (both with PNEE and epilepsy) and control participants performed both a simultaneity judgment task (SJT) and a multisensory

Table 1
Participants' demographics. Gender, age, years since diagnosis (PNEE 3.5 ± 2.6 years; epilepsy 24 ± 18 years), diagnosis, and seizure focus and medication (if applicable) for all participants recruited.

Gender	Age	Disease duration	Diagnosis	Seizure focus	Medications
F	49	5	Epilepsy	R fontal focus	Levetiracetam, lamotrigine
F	30	16	Epilepsy	Idiopathic generalized epilepsy	Zonisamide, levetiracetam
M	40	32	Epilepsy	Idiopathic generalized epilepsy	
F	25	12	Epilepsy	Primary generalized epilepsy	Lacosamide, lamotrigine
F	34	15	Epilepsy	Generalized epilepsy	Oxcarbazepine
M	20	7	Epilepsy	R Hemisphere epilepsy	Zonisamide
M	40	39	Epilepsy	Complex partial LT	Divalproex, Lacosamide
M	29	13	Epilepsy	RT epilepsy	Lacosamide, levetiracetam
M	62	60	Epilepsy	Focal epilepsy RH	Oxcarbazepine, levetiracetam
M	30	16	Epilepsy	Partial epilepsy L&RH	Lamotrigine, topiramate
M	37	11	Epilepsy	RT epilepsy	Levetiracetam, lamotrigine
F	40	28	Epilepsy	Idiopathic generalized epilepsy	Levetiracetam, topiramate
M	48	10	Epilepsy	Idiopathic generalized epilepsy	Levetiracetam
M	24	16	Epilepsy	Cryptogenic partial epilepsy	Oxcarbazepine
F	21	7	Epilepsy	Idiopathic generalized epilepsy	Lamotrigine, lacosamide
M	51	41	Epilepsy	LT epilepsy	Zonisamide, clonazepam
F	62	60	Epilepsy	Partial epilepsy L&RH	Topiramate, levetiracetam, lamotrigine
M	52	44	Epilepsy	Idiopathic generalized epilepsy	Zonisamide
M	22	3	PNEE		Levetiracetam, oxcarbazepine
F	56	5	PNEE		Gabapentin, topiramate
F	51	1	PNEE		Levothyroxine
M	49	Since childhood	PNEE		
F	22	2	PNEE		Lacosamide
M	47	6	PNEE		
F	41	3	PNEE		Levetiracetam, Gabapentin
F	53	2	PNEE		Divalproex, gabapentin
F	49	7	PNEE		
M	19	2	PNEE		Oxcarbazepine
F	25	9	PNEE		Levetiracetam, lamotrigine
M	36	8	PNEE		Lacosamide
M	56	3	PNEE		Lamotrigine
F	21	3	PNEE		Levetiracetam
M	48	1	PNEE		Clonazepam
F	22	3	PNEE		Levetiracetam, topiramate
F	60	1	PNEE		Levetiracetam
M	40	1	PNEE		Lacosamide, gabapentin
F	58	6	PNEE		Topiramate, gabapentin
F	35		Control		
M	41		Control		
F	40		Control		
M	37		Control		
M	41		Control		
M	34		Control		
M	47		Control		
F	54		Control		
M	37		Control		
F	48		Control		
M	37		Control		
M	43		Control		
F	51		Control		
F	42		Control		
F	47		Control		

redundant target (MRT) task. All participants, including controls, were comfortably seated within their clinical rooms in the EMU. In the case of the SJT, participants were asked to judge whether an audiovisual event happened synchronously or asynchronously and to indicate their response via button press. Accuracy was emphasized over speed. They completed two separate experimental blocks, each consisting of 120 trials (8 repetitions × 15 SOAs), for a total of 240 trials (16 repetitions per condition). Trial order within each block was fully randomized, with an inter-trial interval between 1 and 2 s (uniform distribution).

In the MRT, participants were asked to respond via button-press as fast as possible when they first detected any stimuli presentation (unisensory audio or visual, or multisensory audiovisual). A total of 240 experimental trials were presented equally divided between the 8 experimental conditions (i.e., A0V1, A0V2, A1V0, A1V1, A1V2, A2V0, A2V1, A2V2), which were each repeated 30 times. In addition, 60 catch trials (i.e., A0V0) were also presented. The inter-trial interval was 2000 ms ± 700 ms. Trial order was fully randomized, and task order (SJT vs. MRT) was counter-balanced between participants. Total experimental duration was approximately 45 min.

2.4. Analysis

2.4.1. Behavioral

For the SJT, distributions of perceived simultaneity (i.e., report of synchrony) as a function of SOA were compiled and averaged for each participant. All trials were included in the analysis and there was no response time restriction. Individual participant's average report of synchrony as a function of SOA was fitted with a two-term Gaussian (Eq. (1), Fig. 2A) whose amplitude (amp, fraction of perceived simultaneity), mean, and standard deviation were free to vary. A two-term Gaussian was utilized in order to assure an accurate description of the underlying shape of the distribution detailing reports of synchrony as a function of SOA both in the control and patient populations. The shape of the normal distribution proved to accurately describe the

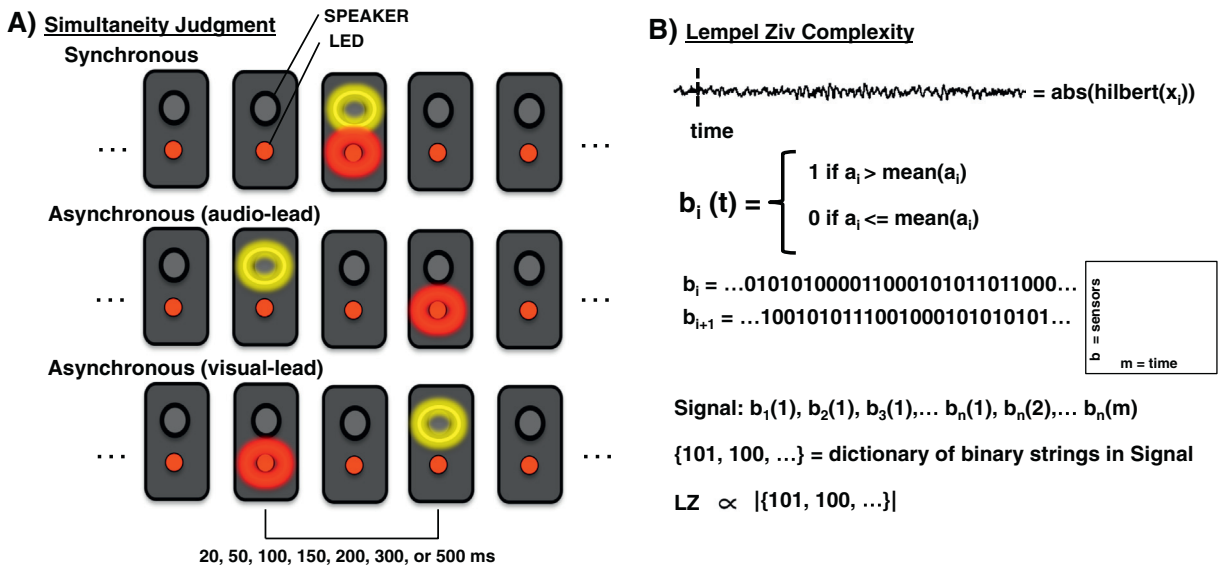

Fig. 1. Experimental protocol and analysis. A) An LED and Piezo Speaker were mounted onto a single audiovisual device, and their onset was manipulated in order to be synchronous (top row), or asynchronous (bottom two rows). Participants were to judge the simultaneity (or lack thereof) of the stimuli presented. B) The Lempel-Ziv algorithm analysis was undertaken in order to measure resting state neural complexity (detail provided in text).

reports of synchrony (mean $R^2 = 0.95$; One-Way ANOVA, $p = 0.88$). The mean of the first term was taken as the point of subjective simultaneity (PSS; the stimuli asynchrony at which participants are most likely to report synchrony), and the distribution's standard deviation (first term) as a measure of the temporal binding window (TBW; the temporal extent over which participants are highly likely to report stimuli as being synchronous, [31]). In this manner, although a two-term Gaussian was utilized in order to restrict parameters and most faithfully describe the underlying function we were fitting, the analysis was performed solely on the first terms, as in all previous accounts of normal distributions describing the shape of reports of synchrony as a function of SOA. For the MRT, reaction time and detection data were compiled for each participant as a function of audiovisual stimuli intensity, and then averaged across subjects.

$$P(response|SOA) = amp \times exp^{-\left(\frac{(SOA-PSS)^2}{2SD^2}\right)} + amp_2 \times exp^{-\left(\frac{(SOA-PSS_2)^2}{2SD_2{}^2}\right)} \quad (1)$$

2.4.2. EEG — Lempel-Ziv complexity

The Lempel-Ziv (LZ) complexity algorithm calculates the approximate amount of non-redundant information contained within a string by estimating the minimal size of the 'vocabulary' necessary to describe the entirety of the information contained within the string in a lossless

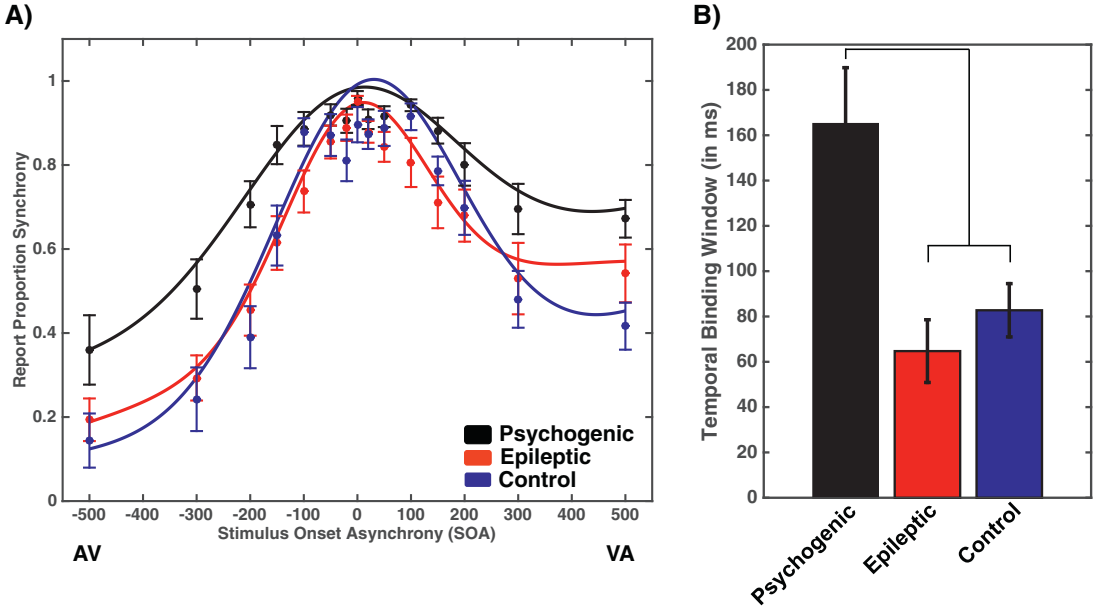

Fig. 2. Reports of synchrony and temporal binding window. A) Reports of synchrony as a function of stimulus onset asynchrony (SOA; x-axis) and participant group. Patients with PNEE (black) show a greater tendency, as compared to patients with epilepsy (red) and controls (blue), to perceive audiovisual stimuli presented at large asynchronies (audio-leading on the left and visual-leading on the right). B) Temporal binding windows (standard deviation of the distribution of reports of synchrony) are significantly larger for patients with PNEE than for patients with epilepsy and control subjects.

manner [32]. The LZ complexity algorithm is used to quantify distinct patterns in symbolic sequences, especially binary signals and has recently been employed to analyze resting state EEG patterns in a number of neuropsychiatric diseases [33,34]. To apply the LZ algorithm, we first converted the signals in all electrodes to a binary sequence by thresholding our voltage data based on the instantaneous amplitude of the Hilbert transform for each particular channel. Data points of a particular channel above the mean of that channel were assigned '1', while those under the mean were assigned a value of '0'. Next, binary strings were constructed by column-wise concatenating the values at each of the 19 electrodes [33] (Fig. 1B). Finally, the LZ complexity algorithm determined the size of the dictionary needed to account for the pattern of binary strings observed. No normalization was undertaken, as all epochs compared were of equal length.

2.4.3. EEG — gamma band power

We applied a fast Fourier transform (FFT) to the resting state EEG data described above to obtain the absolute spectral power for each channel in the low-gamma band, defined as frequencies between 30 and 50 Hz, at a 4-Hz resolution.

3. Results

Because seizures are linked with imbalances in excitatory/inhibitory signaling, we expected that patients with epilepsy would exhibit alterations in multisensory function, in particular on the temporal task. In the more general measure of audiovisual integration, the redundant target task, we found no significant performance differences across the three groups (control, epilepsy, and PNEE). A two-way mixed-model ANOVA [Stimulus Intensity (Within-subject variable) × Group (Between-subject variable)] demonstrated that reaction times were generally faster ($F(7, 287) = 27.73$, $p < 0.001$) for more intense stimuli (e.g., A2V2: M = 304.34 ms, SD = 80.62 ms) when compared with less intense stimuli (e.g., A1V1; M = 494.35 ms, SD = 180.25 ms). Importantly, however, there was no main effect of group ($F(2, 41) = 2.56$, $p = 0.089$), nor a Stimulus Intensity × Group interaction ($F(14, 287) < 1$, $p = 0.94$). The accuracy results for this task revealed an equivalent pattern, demonstrating a main effect of Stimulus Intensity ($F(7, 287) = 168.45$, $p < 0.001$), but no main effect of Group ($F(2, 41) = 1.66$, $p = 0.20$), nor an interaction between these factors ($F(14, 287) = 1.58$, $p = 0.22$).

In contrast, significant differences were found for the audiovisual temporal task. Surprisingly, the key finding here was that patients with PNEE had poorer audiovisual temporal acuity, as evidenced by larger multisensory binding windows, when compared with controls or patients with epilepsy (Fig. 2). A one-way ANOVA ($F(2, 53) = 10.87$, $p < 0.001$) demonstrated that patients with PNEE exhibited significantly larger temporal binding windows (M = 165.96 ms, SD = 95.57 ms) as compared to their counterparts with epilepsy (M = 64.72 ms, SD = 53.60 ms; unpaired t-test vs. patients with PNEE, $t(37) = 3.87$, $p < 0.001$), as well as controls (M = 82.75 ms, SD = 47.00 ms; $t(38) = 3.25$, $p = 0.002$). A second measure of multisensory temporal function (but not acuity), the PSS, revealed no differences between the three groups. For this measure, a one-way ANOVA ($F(2, 53) = 1.44$, $p = 0.24$) revealed that patients with PNEE (M = 4.43 ms, SD = 59.43 ms), patients with epilepsy (M = 14.34 ms, SD = 48.32 ms), and control participants (M = 32.18 ms, SD = 33.76 ms) all displayed moderately positive PSS values. A positive PSS is consistent with the sensory statistics of natural audiovisual stimuli in the environment and in which the arrival of visual energy at the sensory apparatus invariably precedes the arrival of auditory energy [35]. Lastly, there was no difference with regard to the maximum amplitude of the distributions which best described the reports of synchrony as a function of group ($F(2, 53) < 1$, $p = 0.99$; PNEE, M = 0.98, SD = 3.06; epilepsy, M = 0.95, SD = 2.59; control, M = 1.00, SD = 4.05), which argues against the differences in TBW size being a consequence of a response bias. That is, it is unlikely that the difference in audiovisual temporal performance across groups was simply due to the fact that one group was simply more (or less) likely to report synchrony across all SOAs.

Prior studies suggested a strong relationship between gamma band power and temporal function and abilities, and thus we sought to quantify gamma power in patients with PNEE and epilepsy. Although on average, as demonstrated via the FFT, patients with PNEE exhibited numerically higher power within the gamma range ($M = 26.07 \times 10^{-3}$ μV²/Hz, $SD = 36.56 \times 10^{-3}$ μV²/Hz) as compared to patients with epilepsy ($M = 14.63 \times 10^{-3}$ μV²/Hz, $SD = 11.27 \times 10^{-3}$ μV²/Hz), this difference failed to reach statistical significance ($t(21) = 1.032$, $p = 0.33$) within our dataset. Nonetheless, because of the difficulty in recording reliable gamma band activity via scalp EEG and the possibility that participants' transition between wakefulness and drowsiness states during the resting-state recording period, these results must be interpreted cautiously.

On the other hand, LZ complexity analysis of the resting state EEG demonstrated that patients with PNEE (M = 1136, SD = 246) had more complex resting state EEGs than patients with epilepsy (M = 977, SD = 282). Interestingly, both within the PNEE ($R = 0.64$, $P = 0.02$) and the epilepsy ($R = 0.41$, $P = 0.05$) groups, there were significant correlations between measures of complexity and audiovisual temporal acuity. In this analysis, the relationship was such that the more complex a particular individual's EEG resting state, the greater the size of their temporal binding windows (i.e., the poorer their audiovisual temporal acuity, see Fig. 3). Such a correlation did not hold between the complexity of an individual's resting state EEG and either unisensory or multisensory reaction times (as measured in the redundant target task), thus highlighting the specificity of the association between the neural complexity measure and audiovisual temporal acuity.

4. Discussion

The major finding of the current study is that patients with PNEE, but not patients with epilepsy, exhibit changes in multisensory function when compared with healthy controls, contrary to our original hypothesis. Furthermore, this difference was unique to the multisensory

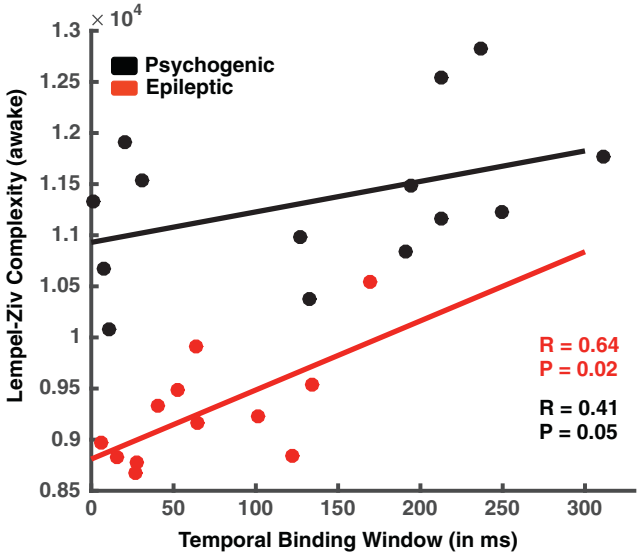

Fig. 3. Correlation between Lempel-Ziv complexity and temporal binding window. Patients with PNEE (black) did not only exhibit on average a higher degree of neural resting state complexity than did patients with epilepsy (red), but also within groups, the degree to which an individual's resting state neural response was complex (y-axis) correlated with the size of the individual's temporal binding window (x-axis).

temporal task, with no significant difference between groups found in a more generalized measure of multisensory function — the redundant target task. To the best of our knowledge, this study represents the first attempt to characterize the multisensory processing abilities of these two patient groups. Because multisensory binding is a core component in the creation of veridical perceptual representations [10,30], the observed changes in multisensory processing may play an important contributing role in the etiology and cognitive comorbidity seen in patients with epilepsy [36].

Patients with epilepsy did not differ from control subjects in the performance of either of these psychophysical tasks. Given the evidence for changes in excitatory/inhibitory balance in epilepsy and the importance of excitatory/inhibitory signaling in the creation and maintenance of sensory and multisensory filters, this negative result was unexpected. One possibility is that disruptions in excitatory/inhibitory balance in the patients with epilepsy in this study did not substantially affect the network responsible for either of the multisensory tasks. Prior work has suggested that performance on the multisensory temporal task used in the current study is mediated by a network centered on the posterior superior temporal sulcus and involving reciprocal connectivity with visual and auditory cortices [37]. Although six of the patients enrolled in the current study were diagnosed with focal temporal lobe epilepsy (Table 1), the majority of patients did not have seizures originating from this area, and even for the six with focal temporal lobe epilepsy it is possible that the epileptiform focus was far from the temporal lobe areas implicated in multisensory temporal function. Future studies of patients with lateral temporal lobe seizures may identify differences in audiovisual multisensory processing in these patients.

The pathophysiological causes of PNEE remain unknown [36], but it is clear that it is not associated with gross structural or physiological abnormalities. Therefore, we were surprised that patients with PNEE exhibited significant differences in audiovisual temporal function when compared with patients with epilepsy and healthy controls. This finding suggests that the brain networks involved in audiovisual temporal integration, including regions of the superior temporal sulcus, may be affected in PNEE. Interestingly, a recent diffusion tensor imaging study demonstrated that patients with PNEE had significantly higher fractional anisotropy values in the left superior temporal lobe relative to control subjects [38]. An alternative possibility in these patients is that the changes in higher-order (i.e., cognitive) networks responsible for their psychogenic seizures also give rise to multisensory temporal changes. More specifically, it could be that the effort associated within segregating sensory stimuli in time or the willingness to report a closely spaced audiovisual stimulus as simultaneous differs in these patients, thus giving rise to a larger binding window in the PNEE patients. Although such a change in attention or effort in patients with PNEE in comparison to controls and patients with epilepsy is seemingly unlikely here due to the specificity of the psychophysical anomaly described (no difference in reaction time and only at select temporal disparities under the simultaneity judgment task), future work could begin to tease out the respective contributions of stimulus statistics and cognitive biases to this task, and to the differences observed between controls and patients with PNEE and epilepsy.

Multisensory processing differences, most notably in the temporal dimension, are being increasingly recognized in diseases such as autism [39,40] and schizophrenia [41,42]. Studies in autism have associated the observed reduced multisensory temporal acuity to higher-order domains, such as language and social communication [39,41]. Such work is suggestive that the changes in audiovisual temporal binding in patients with PNEE may contribute to some of the clinical and cognitive deficits seen in these individuals.

Because patients with epilepsy, but not those with PNEE, have hypersynchronous discharges, we expected that patients with PNEE would exhibit greater complexity within their EEG resting state traces than their non-psychogenic counterparts as measured using the LZ algorithm. Indeed, our results confirmed this hypothesis, and perhaps even more interesting in this analysis was the fact that for individuals within both the groups with PNEE and epilepsy, measures of EEG resting state complexity directly correlated with multisensory temporal acuity. That is, the greater the "dictionary" needed to fully explain the spatio-temporal patterns of voltages across the scalp of a particular individual during a resting state EEG, the larger the participant's binding window. In this sense, our results are the counterpart of Gazzaniga's seminal observation that split-brain patients have i) less complex brain dynamics — as they effectively possess two-half brains as opposed to an integrated whole, and ii) an uncanny ability to segregate information in a rapid serial visual presentation paradigm [43]. Here, our results suggest that the more complex an individual's resting state EEG, the more this individual integrates sensory information. A limitation of the current study, however, was that we were not able to measure the resting state EEG data from control participants, and thus, do not know whether patients with PNEE exhibit a different EEG complexity during resting state than controls. Namely, it is entirely possible that patients with PNEE do not show abnormally complex resting state EEGs, but rather that patients with epilepsy show abnormally simple EGG resting states. Further, it will be interesting in future work to extend these analyses to healthy individuals in an effort to determine if there is a positive correlation between resting state EEG complexity and TBW size in the general population.

In conclusion, we demonstrated that patients with PNEE, but not patients with epilepsy, exhibited enlarged temporal windows within which they bind together audiovisual information relative to control subjects. This reduced audiovisual acuity may be associated with the cognitive deficits in these individuals, and may be a result of changes in networks responsible for the computation of audiovisual temporal relations, networks responsible for cognitive biases, or a combination of these networks.

Disclosure of conflict of interest

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments

Support for this work was provided by NIH DC010927, CA183492, HD83211, Autism Speaks #9717, and by the Wallace Foundation.

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