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

Jean-Paul Noel [a,b], LeAnne Kurela [a,b], Sarah H. Baum [b], Hong Yu [c], Joseph S. Neimat [c], Martin J. Gallagher [b,d,1], Mark Wallace [b,e,f,*,1]

[a] Neuroscience Graduate Program, Vanderbilt Brain Institute, Vanderbilt University Medical School, Vanderbilt University, Nashville, TN 37235, USA
[b] Vanderbilt Brain Institute, Vanderbilt University Medical School, Vanderbilt University, Nashville, TN 37235, USA
[c] Department of Neurosurgeory, Vanderbilt University Medical Center, Vanderbilt University, Nashville, TN 37235, USA
[d] Department of Neurology, Vanderbilt University Medical Center, Vanderbilt University, Nashville, TN 37235, USA
[e] Department of Hearing and Speech Sciences, Vanderbilt University Medical Center, Nashville, TN 37235, USA
[f] Department of Psychology, Vanderbilt University, Nashville, TN 37235, USA

ARTICLE INFO

Article history:
Received 22 October 2016
Revised 10 February 2017
Accepted 13 February 2017
Available online 17 April 2017

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.

Published by Elsevier Inc.

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

* Corresponding author at: 7110 MRB III BioSci Bldg, 465, 21st Ave South, Nashville, TN 3721, USA.
E-mail address: mark.wallace@vanderbilt.edu (M. Wallace).
[1] These authors contributed equally to this manuscript.

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