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Antiepileptic properties of music in refractory epilepsy

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What are interictal spikes?

- Brief electrographic transients (<70ms; <250ms), consisting of a short sharp wave, followed by a lasting slow wave (Maharati et al., 2019)
 - Occur both near the SOZ and in cortical regions far from the SOZ
 - Biomarker for epileptic brain regions
- 3 IEA subtypes: (Kleen et al, 2013)
 - 1. Repetitive, high amplitude interictal spike wave complexes
 - 2. High amplitude isolated spikes
 - 3. Atypical epileptiform activity without classical spike morphology
- Higher spike rates are associated with:
 - Cognitive impairments (especially during memory encoding/retrieval) (Horak et al., 2017; Chapman et al., 2015)
 - Delayed RT/STM (Holmes & Lench-Santini, 2006)





Objective: To investigate the potential anti-epileptic effects of 40Hz auditory tones and Mozart's Sonata for Two Pianos in D Major (K448)



"Entrainment posits that the brain aligns temporal high/low excitability phases to predictable periods of relevant/irrelevant sensory input." (Weisz & Lithari, 2017)

- <u>40-Hz entrainment</u> was previously utilized for reducing brain pathology, anticipating cognitive impairments, and predicting the prognosis for a variety of neurological disorders
 - Alzheimer's disease:
 - Transgenic mouse study showed 50% decline in insoluble amyloid-Beta load in the cortex of AD mouse after 1-hour exposure to 40Hz light stimulation for 7 days (laccarino et al., 2016)
 - Schizophrenia:
 - Deficient 40Hz ASSR; SZ is associated with deficient phase resetting and diminished magnitude of gamma oscillations in response to 40 auditory stimuli (Roach et al., 2013)
 - Epilepsy:
 - Symmetrical hemispheric contralaterality was revealed in HCs, but predominant reductions in contralateral responses targeting the hemisphere with mTLE were revealed (Matsubara et al., 2019)

SCIENTIFIC CORRESPONDENCE



H1: Exposure to the 40Hz tone and K448 would result in reductions in spike rates compared to a control period.

H2: Altering the carrier frequency of the 40Hz tone (i.e. 440Hz amplitude modulated to 40Hz) and the envelope of K448 (i.e. K448 with an envelope amplitude modulated to 40Hz) would elicit similar anti-epileptic responses.

H3: Specific brain regions would be significantly associated with alterations in spike rates during exposure to the auditory stimuli.

The Experiment

- Eight subjects with refractory epilepsy participated in this study while undergoing intracranial EEG monitoring (4 Male, 4 Female)
 - Electrode coverage in both hemispheres with between 50 to 92 artifact free channels (mean = 69.75)
 - 20-minute experiment session. Each experiment session consisted of 40 auditory stimuli and 40 control periods, and these sessions were repeated twice per subject.
- Stimuli:
 - 40Hz tone produced by a pure sine wave
 - 440Hz tone that was amplitude modulated to 40Hz
 - Mozart's Sonata for Two Pianos in D Major (K448)
 - Mozart's Sonata for Two Pianos in D Major amplitude modulated to 40Hz (modK448)





Subject	Gender	Age	Handedness	SOZ	Baseline	Left	Right
					(spikes/15s)	Channels	Channels
High Spi	ike Rate:						
Α	Female	65	Left	Right	7.23	46	46
В	Female	38	Right	Right	5.33	38	42
С	Female	28	Left	Left	10.58	57	18
D	Male	24	Right	Bilateral	5.05	17	56
Low Spil	ke Rate:						
E	Male	39	Right	Right	2.71	32	29
F	Female	68	Right	Right	0.42	17	47
G	Male	35	Right	Right	1.97	20	30
Н	Male	53	Right	Bilateral	0.096	33	30

Table1. Subject demographic and clinical information.

The Spike Detector

- Template-matching: (Horak et al. 2015)
 - 1. Preprocess sEEG recording and a template
 - 2. Cross-correlate the template with the recording
 - 3. Normalize the cross-correlation by the median SD from 1s sliding windows
 - 4. Label local peaks above an empirical threshold as IEDs
- <u>Template-matching detector</u> performed comparably with experts (trained neurologists) and with a supervised learning algorithm (learn defining characteristics of IEDs)
- Template-matching detector showed improvements in its agreement with experts if tuned to return similar numbers of detections





Percent change in interictal spike rates

- % change in spike rates for each auditory stimulus relative to the control period for all subjects combined.
 - Accounted for differences in baseline spike rates and electrode coverage between subjects
- * Significant alterations in interictal spike rates with a false discovery rate controlled at a level of 0.05.



Within subject odds of altering interictal spike rates with auditory stimuli

- Likelihood of altering interictal spike rates for each subject during exposure to the different auditory stimuli relative to the control
- Odds less than one indicate a reduced probability of interictal spikes during exposure to the auditory stimuli



Electrodes associated with reductions in global interictal spike rates



Stimuli • 40Hz (13) • 440Hz (3) • K448 (6) • mod-K448 (4)

(A) Electrodes with an <u>increased odd of spiking</u> that are correlated with overall reductions in spike rates at other brain regions

(B) Electrodes with a <u>decreased odd of spiking</u> that are correlated with overall reductions in spike rates at other brain regions

Parcellated analysis of the percentage of activated electrodes exhibiting significant interictal spike rate reductions during exposure to 40Hz



(A) %age of channels with a significant reduction in interictal spike rates FC Frontal Cortex, AMY Amygdala, HIP Hippocampus, STC Superior Temporal Cortex, MTC Middle Temporal Cortex

Conclusions

- 40Hz auditory stimuli <u>reduced interictal spike rates in 75%</u> (3/4) of the subjects with high baseline spike rates
- Subject-level decreases in spike rates were associated with increased interictal spiking in certain regions of the right hemisphere, predominantly music processing centers of the brain
- These findings may be useful for:
 - Guiding work on understanding auditory stimuli and their interaction with the pathology of epilepsy
 - Development of noninvasive musical interventions for the management of refractory epilepsy and its related comorbidities

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