



RESEARCH ARTICLE

Spontaneous Neuronal Signaling is Inherently Musical and Mathematical: Insight into the Universal Human Affinity for Music

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Abstract:

Objective:

Audio files of spontaneous signal streams generated by *ex vivo* neuronal networks cultured on multi-electrode arrays generated an oscillating sine wave with an inherent musical quality. This was not anticipated considering that synaptic signals are “all - or - none”, and therefore digital, events.

Methods:

These findings may provide insight into why music can be perceived as pleasurable and invoke a calm mood despite that music is ultimately perceived and stored as a series of digital signals; it is speculated that music may reinforce and/or enhance this spontaneous digital stream.

Results and Conclusion:

These findings also support the relationship between music and mathematics.

Keywords: Multi-electrode array, Neurons, Music, Signaling, Binary, Inhibitory.

1. INTRODUCTION

Music is often referred to as a universal language [1]. While distinct differences are observed among cultures, music is prevalent in all cultures [2], which may derive from the ability of some forms of music to provoke an emotional response and to instill a calming mood [3, 4]. Music has been utilized as therapy even in preliterate cultures and currently for both children and adults affected a variety of conditions that are accompanied by depression or agitation [5 - 10].

The sound is initially perceived as sonic vibrations that induce vibration of eardrum, which is sequentially transmitted to auditory neurons. Information regarding pitch and volume is delivered by differential stimulation of auditory sensory neurons. However, continued transmission to the central nervous system is *via* all - or - none synaptic signaling. Importantly, all sound, including music, is therefore ultimately perceived and stored in memory, as a series of digital signals. Pleasing sensations arising from hearing music are of necessity therefore derived from a corresponding sequence of synaptic pulses that has been stripped of the original analog nature. It remains unclear as to how the digital translation of music can retain what is perceived as pleasurable. To address this, we examined synaptic signal streams generated by neuronal networks established on multi-electrode arrays (MEAs) that interfaced with computer software.

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2. METHODS

Primary murine embryonic cortical neurons harvested at day 17 of gestation from C57B/6 mice were plated and maintained in commercial Multi-Electrode Array (MEA) culture chambers (Multichannel Systems; Fig. 1A). Sacrifice of the pregnant female mice and generation of cultures were according to a protocol approved by this institution's Institutional Animal Care and Use Committee. Neuronal signaling was monitored and recorded by interfacing MEAs with MatLab software as described in detail previously [11].

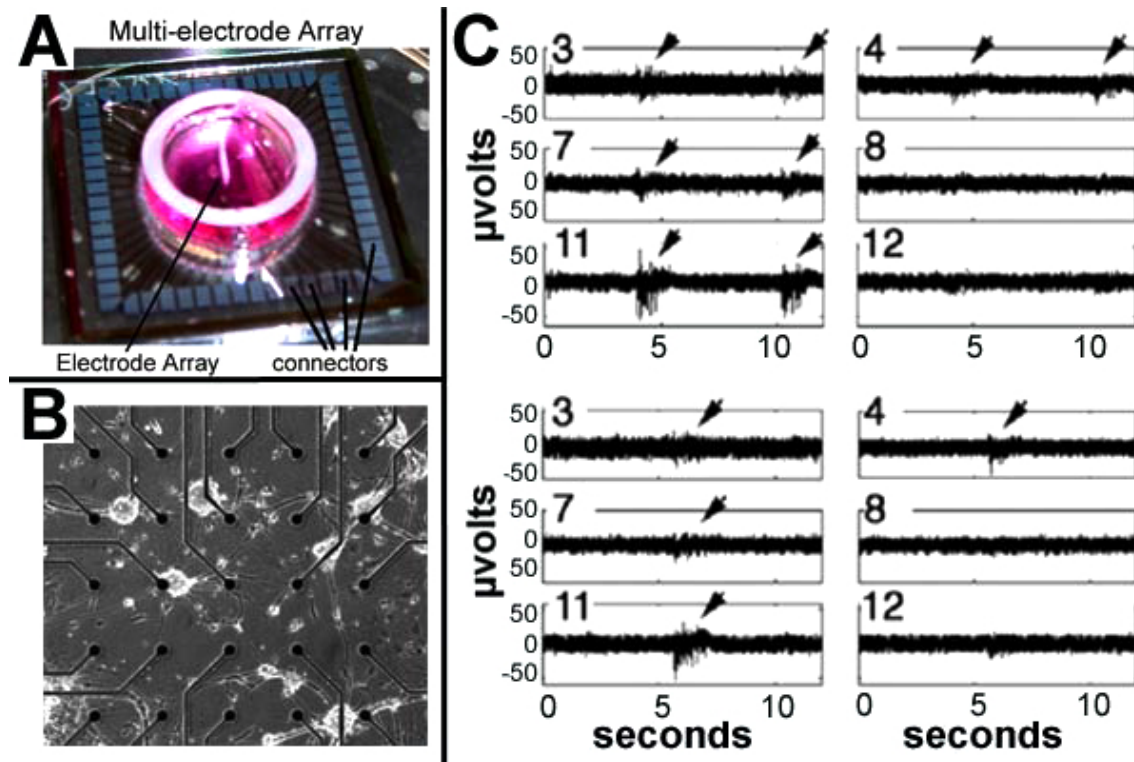


Fig. (1). Multi-electrode arrays.

Panel A: Representative image of cortical neurons after 7 days of culturing in a MEA chamber. The dark circles are electrodes and the corresponding black lines interface with the amplifier. **Panel B:** Two sets of spontaneous recordings from the indicated electrodes; recordings in each set were captured simultaneously. Arrows denote clear spontaneous signals. Note synchronous signaling at multiple electrodes.

Signal profiles (15 sec in duration) recorded between two electrodes that were demonstrably synaptically-connected by neuronal clusters (e.g., Fig. 1C) were processed *via* the voltage-controlled oscillator (VCO) with a continuous tuning range [12] as detailed in the Signal Processing Toolbox of MathWorks (<https://www.mathworks.com/help/signal/ref/vco.html>). Baseline tone and range for VCO were arbitrarily selected.

3. RESULTS

Within approximately one month in culture, these neurons form a functional network that elaborates regular spontaneous signals among interconnected neurons (Fig. 1) [11]. Spontaneous signals exhibited a regular amplitude ($40.0 \pm 5.0 \mu\text{V}$), duration ($0.8 \pm 0.2 \text{ sec}$, mean \pm SD, $n=20$) and periodicity (intervals of $4.2 \pm 0.3 \text{ sec}$ between events ($n=7$)).

Audio files of spontaneous signal streams generated by a VCO generated an oscillating sine wave with an inherent musical quality (Supplemental files 1 and 2). As with graphical displays of signaling streams (Fig. 1C), audio streams contained signals of apparently identical amplitude, range and periodicity, that remained in relative synchrony with occasional drifts out of phase among signaling neurons.

4. DISCUSSION

Despite the random synaptogenesis inherent in dissociated cultures, *ex vivo* neuronal networks neurons retain the ability to transmit information in an organized manner [13]. Notably, synaptic signals are comprised of multiple all - or - none signals and therefore are inherently digital. While graphical representation of these signal streams revealed regular oscillations that were shared among synaptically-connected neurons, displaying them as audio files nevertheless revealed an unanticipated musical nature. While the perception of music is complex and involves multiple cortical regions [14, 15], our findings lead us to speculate that the digital input from music may also encompass an underlying reinforcement and/or augmentation of spontaneous signaling patterns. Herein, the consistent stream of spontaneous signals varied in pitch but not volume. Spontaneous signals may, therefore, represent a “background” continuous pulse. Music can modulate activity in brain structures involved in emotion [3]. While music may simply invoke a calm mood by masking background noise [16], music may also influence brain activity in the same sense as biofeedback can positively influence mood [17]. In this regard, the intrinsic oscillatory properties of neurons have been suggested to underlie brainwaves [18]. With particular regard to music, auditory feedback can be as effective as more conventional visual feedback approaches [15, 19] and auditory biofeedback can also enhance musical performance [20].

Digital and musical aspects of spontaneous signal streams provide additional potential insight with regard to the relationship between music and mathematics. Mathematics has long been regarded as a universal language since it relies on numbers and consistent operations, although this terminology has been met with a degree of a practical challenge since comprehension is dependent upon literacy [21 - 23]. Connections have been recognized between music and mathematics in terms of logic and organization [4, 24, 25]. Basic mathematical ideas can be recognized within music and, conversely, mathematical consideration of patterns can expose organizing principles of music [26]. Mathematics has been studied in the context of artificial neural networks [27]. In this regard, we have demonstrated key processing similarities between artificial neural networks (which consist of software-defined nodes that are designed to approximate neurons) and our *ex vivo* neuronal networks (which consist of bona-fide neurons) [28, 29]. Music consists of pitch, tone, volume and rhythm. The rhythm component is well-recognized as mathematical in that, it consists of a sequence of pulses at regular intervals [30]. The findings herein underscore that the additional components - pitch, tone and volume – are also mathematical. A corollary of these findings is that music can be considered as an analog expression of mathematics. As such, music and mathematics can be considered as two dialects of a single language.

Herein, we have only examined simple signaling generated by dissociated *ex vivo* neuronal networks. Since the MEA system allows external stimulation, neuronal network signaling is altered in response to external stimulation [11], this system would accommodate the analysis of synaptic signaling patterns arising from the various digitized musical input. Since these networks can display complex signaling patterns [13], this system would also allow examination of whether VCO processing of all synaptic signaling reveals an inherent musical nature or whether such is confined to only spontaneous, oscillatory patterns as observed herein. Further examination of synaptic signaling streams may provide additional insight into the human affinity for music.

CONCLUSION

The inherent musical quality of spontaneous signal streams, despite that they are digital in nature, prompts the speculation that music may provide a calming influence by reinforcement of this spontaneous digital stream. These findings also support the relationship between music and mathematics.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol is approved by The University of Massachusetts Lowell’s Institutional Animal Care.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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