Concentration-Response Evaluation of ToxCast Compounds for Multivariate Activity Patterns of Neural Network Function

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Summary

Microelectrode arrays (MEAs) have been used to assess neuroactivity of ToxCast compounds.

•Screened 384 compounds in concentration response across 43 network activity parameters using MEAs.

•Identified 15 parameters crucial in characterizing neuroactivity of 237 compounds.

•For known neurotoxic compounds, these chemical-parameter potencies were more sensitive than for most ToxCast assays.

•Identified three clusters of chemical-parameter activity with varied bioactivity patterns and chemical structural features.

Introduction

•ToxCast evaluates activity of chemicals using high-throughput screening (HTS).[1]
- -Over 1,000 assays.
- -Cannot assess breadth of neurotoxicity targets.

•Microelectrode Arrays (MEAs) can record activity in plated neural networks.

•Previous analysis: 1056 ToxCast chemicals screened at single concentration on MEAs.[2]
- -326 altered mean firing rate (MFR).

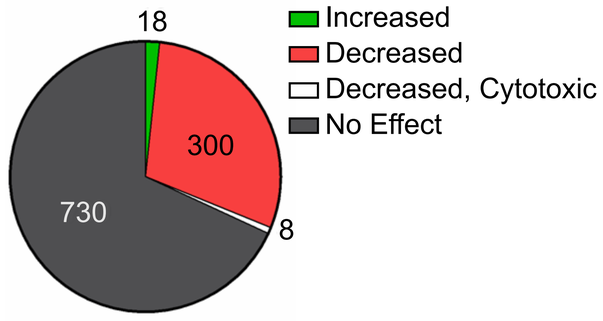

Figure 1. MFR activity in ToxCast compounds.[2]

Methods

Compound-parameter activity determined with Axion Maestro 1st generation MEA system and classic MEA M768-KAP-48 plates.

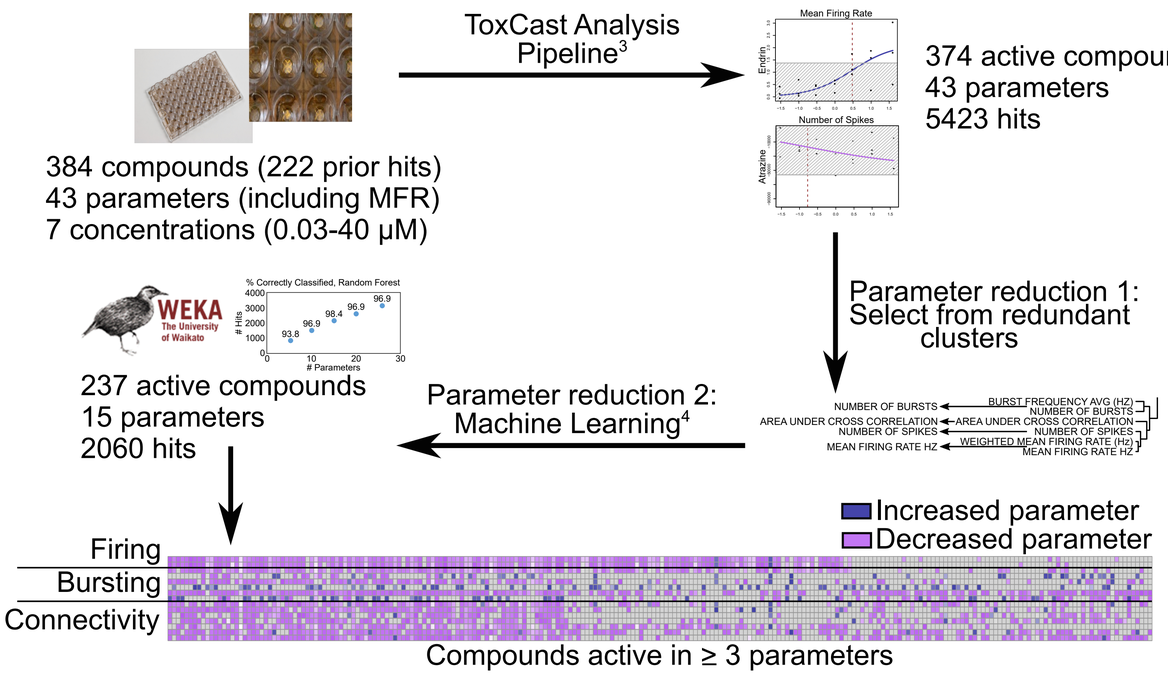

Figure 2. Methods to characterize active compound-parameter associations (heatmap). Darker colors = more potent.

Results

For known neuroactive compounds, MEA parameter potencies are more sensitive than ToxCast assays for most compounds

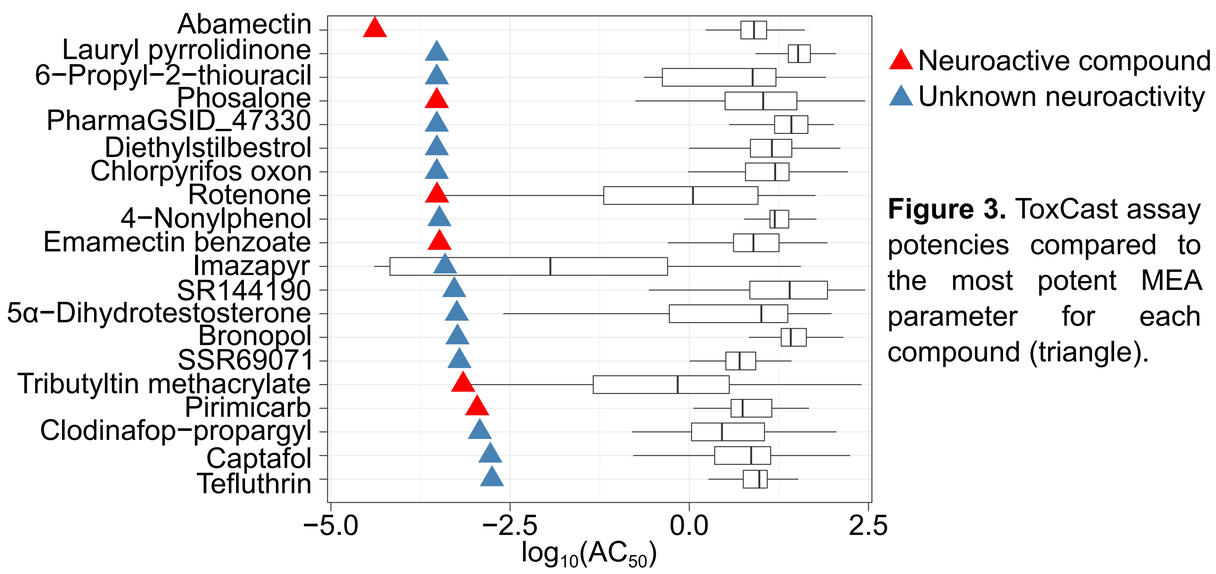

Figure 3. ToxCast assay potencies compared to the most potent MEA parameter for each compound (triangle).

Results

MEA parameters distinguish three clusters of compounds with distinct bioactivity patterns

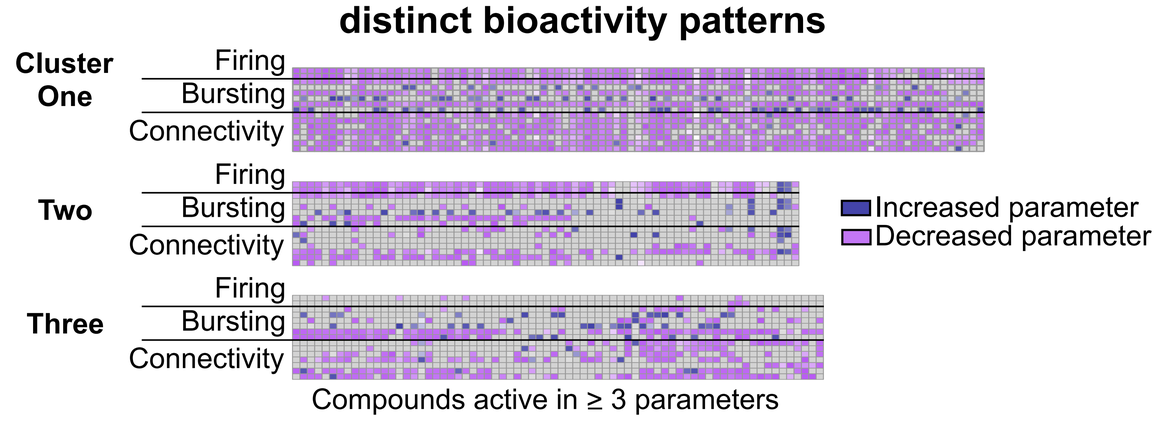

Figure 4. Bioactivity patterns of three MEA clusters determined through k-means clustering of compound-parameter potencies. Darker colors = more potent.

MEA clusters of compounds are enriched for different chemical structural features

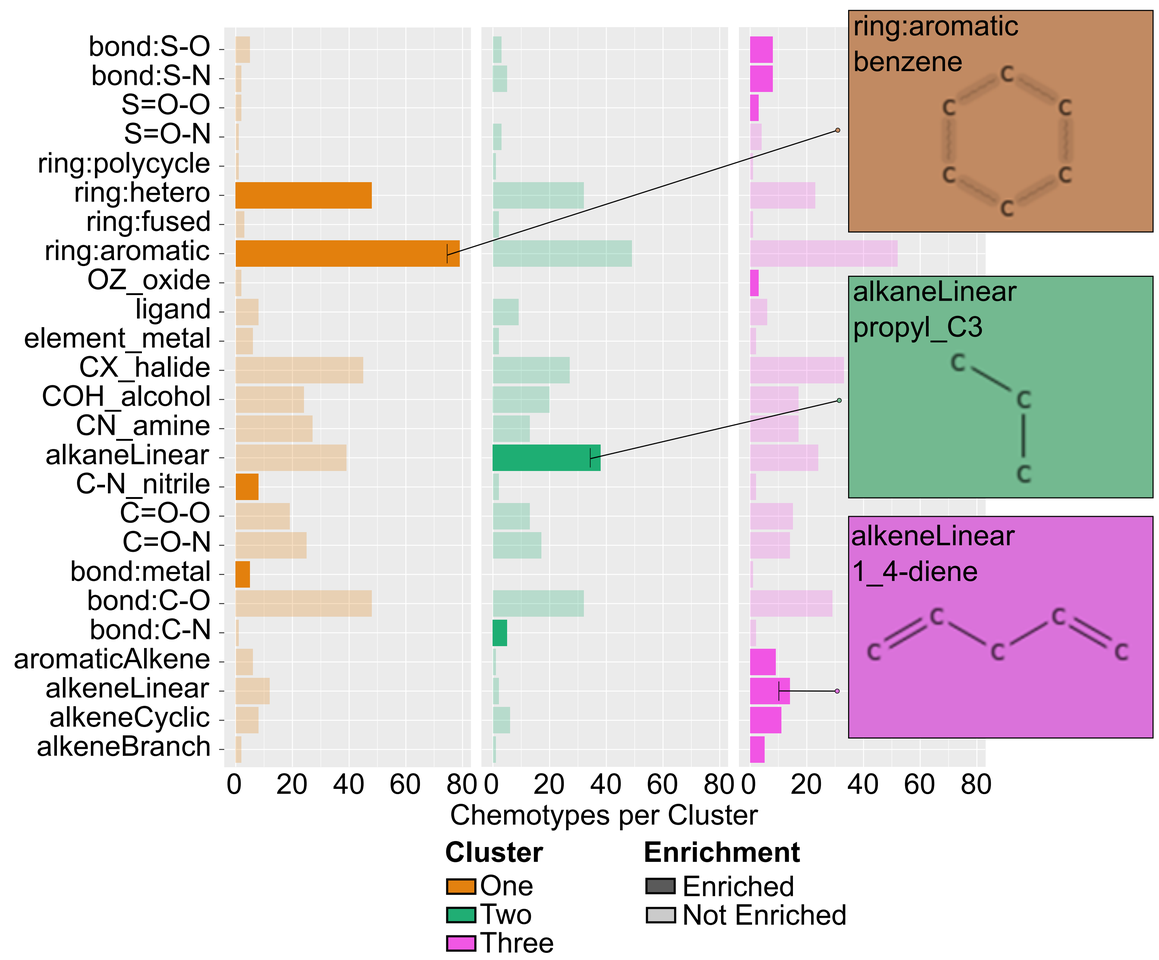

Figure 5. Chemical features (identified as chemotypes[5]) enriched within each cluster using hypergeometric test. Inset images depict example structures within respective chemotype.

Conclusions

•We developed a robust assessment for neuroactivity across 15 network parameters (Figure 2).

•For known neuroactive compounds, MEA parameters were more sensitive overall than other ToxCast assays (Figure 3).

•MEA chemical-parameter potencies can be used to group compounds based on bioactivity (Figure 4).

•Biological activity groups were consistent with the underlying structure of the compounds (Figure 5).

•Multivariate MEA activity patterns can efficiently screen for diverse chemical neuroactivities.

•MEA activity patterns may have predictive value related to chemical structural features.

References & Funding

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