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Mapping neuronal network dynamics in developing cerebral organoids

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Motivation

Cerebral organoids represent an attractive, novel model system to study early brain development *in vitro* (Di Lullo and Kriegstein, 2017). Although recent evidence shows that cerebral organoids do recapitulate fundamental milestones of early brain morphogenesis (Lancaster and Knoblich, 2014), the emergence and functionality of brain-organoid neuronal connectivity has not been studied systematically yet. In this study, we apply high-density micro-electrode arrays (MEAs) to record from developing mouse cerebral organoids and characterize their spontaneous neuronal activity. Results provide first evidence on the potential of MEAs as a platform to study the role of spontaneous neuronal activity during brain organoid development and formation of functional microcircuits.

Materials and Methods

Mouse cerebral organoids: The protocol to generate mouse cerebral organoids was adapted from two previous studies (Eiraku et al., 2008; Lancaster et al., 2013). In this study, we use commercially available mouse embryonic stem cells (ESCs) (ES-D3, ATTC, CRL1934). For the generation of mouse cerebral organoids, ESCs were seeded in ultra-low-attachment V-bottom 96 well plates (4000 per well) in medium containing SB431542. After formation of embryoid bodies, primitive neuroepithelium was induced in neural induction medium (Lancaster et al., 2013). Six days after seeding (D6), organoids were embedded in Matrigel droplets to expand neuroepithelial tissue and cultured in maturation medium (Lancaster et al., 2013). For further maturation (D9 onwards), organoids were cultured in maturation medium, supplemented with Vitamin A, and maintained on an orbital shaker within a 37 C / 5% CO2 incubator.

Electrophysiological recordings: Sections of cerebral organoids (300 µm) were obtained from 16-28 day-old cerebral organoids using a vibratome. Spontaneous neuronal activity was recorded with a high-density complementary-metal-oxide-semiconductor (CMOS) based MEA, comprising 26 400 platinum electrodes with 1024 readout channels over an area of 3.85×2.10 mm^2 (Müller et al., 2015). The chip system allows for extra-cellular electrophysiological recordings of large sections of slices at a very high spatial and temporal resolution (17.5 um electrode pitch; 20 kHz sampling rate). MEA recordings were performed in BrainPhys^{TM} medium (Bardy et al., 2015); a small holder was used to assure optimal slice attachment on the MEA. Pharmacological challenges were applied to investigate the mechanisms of observed neuronal dynamics.

Results

Using extracellular high-density MEA recordings, we have acquired spontaneous electrical activity of a large number of neurons in slices of developing mouse cerebral organoids. We found that the percentage of neurons demonstrating spiking activity increased during development, as did their average firing rate. Coherent network-level events could be observed relatively early (D17/18), resembling activity patterns previously reported for hippocampal neurons around birth (Crépel et al., 2008). In more mature organoids, network activity could be modified with the $GABA_A$ receptor antagonist bicuculline and blocked with the voltage-gated sodium channel blocker TTX. Immunohistochemistry confirmed the presence of excitatory and inhibitory neurons, as well as of astrocytes.

Conclusion

The present study combines brain organoid technology with CMOS-based high-density MEAs to investigate the emergence of neuronal spontaneous activity at the cellular- and network-level. MEAs provide a valuable platform for such experiments, since they allow for parallel recordings from a large number of cells at high temporal and spatial precision under controlled conditions. Having established a pipeline for organoids, grown from mouse ESCs, future work will expand on this innovative experimental platform to study cerebral organoids derived from human-induced pluripotent stem cells (hiPSCs).

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