Bundesamt
für Strahlenschutz

Spotlight on EMF Research

Spotlight on “Radiofrequency regulates the BET-mediated pathways in radial glia differentiation in human cortical development” by Cakir et al. in Cell Reports (2025)

Category [radiofrequency, in vitro study]

Spotlight - Sep/2026 no.1 (Eng)

Competence Centre for Electromagnetic Fields (KEMF)

1 Context

Several systematic reviews and observational studies have investigated whether exposure to radiofrequency electromagnetic fields (RF-EMF), as emitted from wireless devices, may affect the cognition or behaviour of children, or neurodevelopment before birth [2–5]. The certainty of the presence or absence of adverse effects due to RF-EMF exposure was judged very low to low in the systematic reviews [2, 3]. According to the cited studies, the observed effects may be due to residual confounding or reverse causation [2–5]. No mechanism is established that could be responsible for the observed effects. For ethical reasons, detailed investigations into the influence of RF-EMF exposure on the nervous system development and into possible mechanisms are limited to animal studies and *in vitro* experiments on human cells. Current progress in stem cell research enables studying the development of neural tissue from human embryonic stem cells *in vitro* under three-dimensional culture conditions that can mimic *in vivo* settings to some extent [6].

2 Results and conclusions from the perspective of Cakir et al.

The aim of the present paper [1] was to characterise the effects of RF-EMF exposure on developing neural tissue derived from human embryonic stem cells *in vitro*, in particular on the stem cell compartment and its more mature progeny. Cakir et al. generated human cortical organoids from the embryonic stem cells using a specialised protocol. The cortical organoids serve as a model for the nascent human brain cortex. At day 10, tissue patterning in the cortical organoids sets off, and by day 70, they contain relatively mature neurons.

A uniform RF field was delivered using a DSD TECH HC-05 Bluetooth Serial Pass-through Communication module transmitting at a frequency of 2.4 GHz with a transmission output power of 4 dBm (2.4 mW). The exposure device and the cortical organoid culture plates to be exposed were shielded by a copper-based fabric, to minimise any influence from environmental RF-EMF. The RF-EMF source was placed 1 inch (2.54 cm) beneath the organoid culture plates. The power density at 1 inch exposure distance was measured using a "CORNET high-performance Electrosmog meter" with a maximum recorded value of 2.5 mW/m^2. For some experiments, two additional culture plates were placed in the same exposure space but were shielded: one was enclosed in an aluminium foil bag and another in an electromagnetic shield bag. These plates were intended as internal controls: if RF-EMF exposure caused an effect in the unshielded plates, this effect should be reduced or absent in the shielded plates. For all experiments, control cortical organoids were cultured in separate incubators without intentional RF-EMF exposure (incubator controls).

RF-EMF exposure was initiated on day 10 of culture and maintained for 12 or 24 hours per day. When compared to incubator control cultures, cortical organoids exposed for 12 hours per day showed an irregular surface shape from exposure day 8 on, without changes in overall size. Samples exposed for 24 hours per day showed a statistically significant reduction in organoid size at early time points between days 14 and 23 of exposure. After two months of continuous RF-EMF exposure, these differences were no longer observed for both exposure regimens.

Examining the distribution and behaviour of different cell types within the cortical organoids, exposed organoids showed an increased number of immature neural stem/progenitor cells with a higher symmetrical cell division activity, while markers of intermediate progenitors and more mature neurons were decreased at days 35 and days 70 of organoid development. The authors also observed this skewing towards maintaining stem cell identity and a delay in differentiation when they exposed differentiating primary neural stem cell cultures from foetal rhesus macaque cortex to RF-EMF.

At later time points (depending on the experiment, at days 75–120), RF-EMF-exposed cortical organoids showed a higher density of synapses and dendritic spines, more frequent and intense spontaneous calcium transients, and more frequent action potentials in response to depolarising currents, suggesting that RF-EMF exposure increases neuronal activity. Biophysical cell membrane properties were not affected.

To more broadly investigate how RF-EMF exposure affects neurodevelopmental processes, Cakir et al. analysed the transcriptome, i.e., the totality of RNA messages that are read from the DNA to guide the produc-

tion of proteins, using single-cell RNA sequencing (scRNA-seq). In addition to incubator controls, this experiment also included exposed cortical organoid cultures enclosed in aluminium foil or an electromagnetic shield. Analysis of the scRNA-seq data further confirmed the shift in the distribution of cell identities towards the stem and progenitor cell compartment. Moreover, RF-EMF-exposed organoids showed differential expression of genes belonging to several neurophysiological and -pathological processes. In particular, exposed cortical organoids showed a higher expression of autism spectrum disorder (ASD) risk genes. This effect was rescued in organoids enclosed by the electromagnetic shield but not by the aluminium foil. The higher expression of ASD risk gene-encoded proteins in RF-EMF-exposed organoids was further demonstrated by immunofluorescence staining.

To further elucidate the mechanism behind exposure-induced effects, Cakir et al. used pharmacological inhibitors of so-called BET proteins, which regulate gene expression epigenetically. Application of the inhibitors rescued several of the aberrant phenotypes observed under RF-EMF exposure, including the decreased organoid size and irregular surface shape, the increased stem cell division activity, the impaired differentiation, the induction of ASD-risk genes and the increased synapse density. These results suggest that RF-EMF exposure acts via epigenetic pathways.

Overall, the authors conclude that RF-EMF-exposed cortical organoids and neurons showed defects in cell fate characterised by delayed differentiation, increases in ASD-associated gene expression, aberrant and enhanced neuron firing, as well as an increase in dendritic spine density, the latter a characteristic of patients on the autism spectrum. They acknowledge that no major neurodevelopmental defect has been linked to RF-EMF exposure, although subtle effects have been observed in animal studies.

3 Comments by the BfS

Based on current knowledge, there is no established evidence that exposure to RF-EMF adversely affects cognition, behaviour, or neurological development in humans or animals [2, 3, 5, 7, 8]. While individual studies, including the one cited by Cakir et al. [9], have reported biological effects, systematic reviews do not support adverse effects overall [2, 3, 7, 8]. However, the potential effects of RF-EMF exposure on early human cerebral cortex development have so far been little studied because of methodological challenges. In their exploratory investigation of this question, Cakir et al. [1] therefore apply state-of-the-art cellular and molecular methods. Based on their findings, they suggest that exposure to RF-EMF may dysregulate neurological development and lead to changes similar to those observed in autism spectrum disorders. However, the reliability of these conclusions is limited by several issues.

In the present study [1], no sham-exposed control cultures were used. Sham-exposed controls would have been subjected to the exact same environmental conditions as the RF-EMF-exposed cultures, with the only difference that the exposure device would have been kept turned off. Instead, incubator controls and, in some experiments, cultures with intended shielding from RF-EMF exposure by enclosure in aluminium foil or an electromagnetic shield served as the reference. Since exposed and control cultures were placed in two different incubators, while only the exposure setup was enclosed in an RF shield, changes in the microenvironment, such as in temperature, gas exchange, pH or evaporation rate, may have influenced the investigated endpoints. Several of these microenvironmental factors are known to affect embryonic stem cell culture and neural differentiation [10–12]. Additionally, enclosure of culture plates by aluminium foil or an electromagnetic shield – the characteristics of which were not specified in the paper – may also have affected these microenvironmental factors. It was not reported whether any of them (e.g., medium temperature, pH, osmolarity, O_2/CO_2 partial pressure) were verified to be equal between RF-EMF-exposed conditions and incubator controls. Therefore, it is uncertain whether the experimental results were unaffected by the lack of rigorous control of environmental conditions.

The confidence one can have in the exposure contrast is limited. Although the authors describe the experimental setup as enclosed by an RF shield, they state that both the incubator controls and RF-EMF-exposed conditions may have been exposed to ambient RF-EMF levels, yet no measurements to quantify or exclude this ambient exposure were reported.

For the dosimetric characterisation of the exposure, power density was measured at a distance of 1 inch (2.54 cm) from the RF-EMF source using a hand-held, so-called “Electrosmog” meter. Such meters can give reasonable readings in the far field region of an RF-EMF source, but they cannot reliably measure the power density at a distance to the source that amounts only to a fraction of the free space wavelength, as in this case. Since the exact model number of the meter is unknown and, for example, no information is provided on whether internal or external sensors were used, it is not possible to adequately assess uncertainties regarding the measurement distance and other factors. Furthermore, the lateral dimensions of the culture plates exceed the distance of 1 inch, and the effective exposure of the organoids is likely to be influenced by the different positions of the plates relative to the source, plate geometry, culture medium and organoid position. The reported power density represents an incident field at a certain point in space, but it does not reflect the spatial radiation characteristic of the source, or the actual rate of RF-EMF energy absorbed by the biological samples, which for *in vitro* experiments is usually characterised by the specific absorption rate (SAR) [13]. No numerical modelling or dosimetry was carried out to consider the complex interplay between plate geometry, suspension culture conditions, and the changing size and dielectric properties of organoids as they grow over time. As a consequence, not only the actual magnitude, but also the claimed uniformity of the RF-EMF field applied to the experimental setup and thus the uniformity of the RF-EMF exposure is questionable.

The conclusion by Cakir et al. that RF-EMF exposure induces ASD-associated gene expression changes in human cortical organoids has an important caveat concerning directionality. Most of the ASD risk genes the authors highlight as upregulated in RF-EMF-exposed organoids are implicated in autism primarily through loss-of-function mutations or haploinsufficiency, as can be verified in the SFARI database [14] on which their analysis relies [1]. If the transcriptional effects observed in this study were directly mimicking the pathogenic mechanism in humans, one would instead expect a reduction in effective gene function, not a generalised upregulation of mRNA levels. Thus, although the observed changes may indicate a disturbance of core neurodevelopmental programmes, a direct, mechanistically coherent link to ASD cannot be inferred from these data, given the opposing directionality between the *in vitro* expression changes and the predominant genetic evidence in patients.

In summary, the present study provides an interesting and sophisticated experimental mode to interrogate the biological effects of RF-EMF exposure. Due to the discussed shortcomings, in particular in the electromagnetic dosimetry and performance bias domain (no sham-exposed control), its implications for radiation protection are limited.

References

[1] Cakir, B, Tanaka, Y, Choe, MS, Kiral, FR, Kim, J, Micali, N, Kang, YJ, Dharmadhikari, B, Patterson, B, Yang, WS, Cho, Y, Xiang, Y, Zhong, M, Lee, SH, Patra, P, Rakic, P, Park, IH. Radiofrequency regulates the BET-mediated pathways in radial glia differentiation in human cortical development. *Cell Reports*. 2025; 44(10):116238.
DOI: https://doi.org/10.1016/j.celrep.2025.116238.

[2] Benke, G, Abramson, MJ, Brzozek, C, McDonald, S, Kelsall, H, Sanagou, M, Zeleke, BM, Kaufman, J, Brennan, S, Verbeek, J, Karipidis, K. The effects of radiofrequency exposure on cognition: A systematic review and meta-analysis of human observational studies. *Environment International*. 2024; 188:108779.
DOI: https://doi.org/10.1016/j.envint.2024.108779.

[3] Bodewein, L, Dechent, D, Graefrath, D, Kraus, T, Krause, T, Driessen, S. Systematic review of the physiological and health-related effects of radiofrequency electromagnetic field exposure from wireless communication devices on children and adolescents in experimental and epidemiological human studies. *PloS One*. 2022; 17(6):e0268641.
DOI: https://doi.org/10.1371/journal.pone.0268641.

[4] Birks, L, Guxens, M, Papadopoulou, E, Alexander, J, Ballester, F, Estarlich, M, Gallastegi, M, Ha, M, Haugen, M, Huss, A, Kheifets, L, Lim, H, Olsen, J, Santa-Marina, L, Sudan, M, Vermeulen, R, Vrijkotte, T, Cardis, E, Vrijheid, M. Maternal cell phone use during pregnancy and child behavioral problems in five birth cohorts. *Environment International*. 2017; 104:122–131.
DOI: https://doi.org/10.1016/j.envint.2017.03.024.

[5] Sudan, M, Birks, LE, Aurrekoetxea, JJ, Ferrero, A, Gallastegi, M, Guxens, M, Ha, M, Lim, H, Olsen, J, Gonzalez-Safont, L, Vrijheid, M, Kheifets, L. Maternal cell phone use during pregnancy and child cognition at age 5 years in 3 birth cohorts. *Environment International*. 2018; 120:155–162.
DOI: https://doi.org/10.1016/j.envint.2018.07.043.

[6] Chiaradia, I, Lancaster, MA. Brain organoids for the study of human neurobiology at the interface of in vitro and in vivo. *Nature Neuroscience*. 2020; 23(12):1496–1508.
DOI: https://doi.org/10.1038/s41593-020-00730-3.

[7] Pophof, B, Kuhne, J, Schmid, G, Weiser, E, Dorn, H, Henschenmacher, B, Burns, J, Danker-Hopfe, H, Sauter, C. The effect of exposure to radiofrequency electromagnetic fields on cognitive performance in human experimental studies: Systematic review and meta-analyses. *Environment International*. 2024; 191:108899.
DOI: https://doi.org/10.1016/j.envint.2024.108899.

[8] Cordelli, E, Ardoino, L, Benassi, B, Consales, C, Eleuteri, P, Marino, C, Sciortino, M, Villani, P, Brinkworth, MH, Chen, G, McNamee, JP, Wood, AW, Belackova, L, Verbeek, J, Pacchierotti, F. Effects of radiofrequency electromagnetic field (RF-EMF) exposure on pregnancy and birth outcomes: A systematic review of experimental studies on non-human mammals. *Environment International*. 2023; 180:108178.
DOI: https://doi.org/10.1016/j.envint.2023.108178.

[9] Aldad, TS, Gan, G, Gao, X-B, Taylor, HS. Fetal radiofrequency radiation exposure from 800–1900 MHz-rated cellular telephones affects neurodevelopment and behavior in mice. *Scientific Reports*. 2012; 2:312.
DOI: https://doi.org/10.1038/srep00312.

[10] Okada, R, Onodera, K, Ito, T, Doyu, M, Okano, HJ, Okada, Y. Modulation of oxygen tension, acidosis, and cell density is crucial for neural differentiation of human induced pluripotent stem cells. *Neuroscience Research*. 2021; 163:34–42.
DOI: https://doi.org/10.1016/j.neures.2020.01.015.

[11] Chui, JS, Izuel-Idoype, T, Qualizza, A, de Almeida, RP, Piessens, L, van der Veer, BK, Vanmarcke, G, Malesa, A, Athanasouli, P, Boon, R, Vriens, J, van Grunsven, L, Koh, KP, Verfaillie, CM, Lluis, F. Osmolar modulation drives reversible cell cycle exit and human pluripotent cell differentiation via NF-kappacapital VE, Cyrillic and WNT signaling. *Advanced Science*. 2024; 11(7):e2307554. DOI: https://doi.org/10.1002/advs.202307554.

[12] Wang, S, Cheng, F, Ji, Q, Song, M, Wu, Z, Zhang, Y, Ji, Z, Feng, H, Belmonte, JCI, Zhou, Q, Qu, J, Li, W, Liu, GH, Zhang, W. Hyperthermia differentially affects specific human stem cells and their differentiated derivatives. *Protein & Cell*. 2022; 13(8):615–622. DOI: https://doi.org/10.1007/s13238-021-00887-y.

[13] Schuderer, J, Samaras, T, Oesch, W, Spät, D, Kuster, N. High peak SAR exposure unit with tight exposure and environmental control for in vitro experiments at 1800 MHz. *IEEE Transactions on Microwave Theory and Techniques*. 2004; 52(8):2057–2066. DOI: https://doi.org/10.1109/Tmtt.2004.832009.

[14] Abrahams, BS, Arking, DE, Campbell, DB, Mefford, HC, Morrow, EM, Weiss, LA, Menashe, I, Wadkins, T, Banerjee-Basu, S, Packer, A. SFARI Gene 2.0: a community-driven knowledgebase for the autism spectrum disorders (ASDs). *Molecular Autism*. 2013; 4(1):36. DOI: https://doi.org/10.1186/2040-2392-4-36.

Impressum
Bundesamt für Strahlenschutz
Postfach 10 01 49
38201 Salzgitter

www.bfs.de

Tel.: +49 30 18333-0
Fax: +49 30 18333-1885
E-Mail: spotlight@bfs.de

Please always use the following URN when citing this document:
urn:nbn:de:0221-2026090962484

Spotlight - Sep/2026 no.1 (Eng)