Q J Med 2010; **103**:545–554
doi:10.1093/qjmed/hcq079 Advance Access Publication 16 June 2010

Review

QJM

Bioelectromagnetics, *complex behaviour* and psychotherapeutic potential

D.T. POOLEY

From the Institute of Medical Engineering and Medical Physics, Cardiff School of Engineering, Cardiff University, Queen's Buildings, The Parade, CARDIFF CF24 3AA, Wales, UK

Address correspondence to D. T. Pooley, Institute of Medical Engineering and Medical Physics, Cardiff School of Engineering, Cardiff University, Queen's Buildings, The Parade, CARDIFF CF24 3AA, Wales, UK. email: pooleyd1@cf.ac.uk

Summary

The brain is a complex non-linear dynamical system that is associated with a wide repertoire of behaviours. There is an ongoing debate as to whether low-intensity radio frequency (RF) bioelectromagnetic interactions induce a biological response. If they do, it is reasonable to expect that the interaction is non-linear. Contradictory reports are found in the literature and attempts to reproduce the subtle effects have often proved difficult. Researchers have already speculated that low-intensity RF radiation may offer therapeutic potential and millimetre-wave therapy is established in the countries of the former Soviet Union. A recent study using transgenic mice that exhibit Alzheimer's-like cognitive impairment shows that microwave radiation may possibly have therapeutic application. By using a highly dynamic stimulus and feedback it may be possible to augment the small effects that have been reported using static parameters. If a firm connection between low-intensity RF radiation and biological effects is established then the possibility arises for its psychotherapeutic application. Low intensity millimetre-wave and peripheral nervous system interactions also merit further investigation. Controlled RF exposure could be associated with quite novel characteristics and dynamics when compared to those associated with pharmacotherapy.

Introduction

The purpose of this communication is to provide a brief non-technical insight into developments from normally disparate fields of endeavour that may in the future have relevance to psychiatric phenomena, such as schizophrenia, affective disorders and other conditions. These are commonly highly disabling and include disorders of thought and perception, and have associated with them significant social and economic consequences.

Currently, pharmacotherapy is the first-line treatment and although the side-effect profile of modern psychiatric drugs has improved, in terms of efficacy there has been little development in recent years. Other therapeutic modalities are available such as electroconvulsive therapy and, more recently, trans-cranial magnetic stimulation.[1] These techniques involve the induction of currents using contact electrodes or through strong alternating magnetic fields. Presumably, the mode of action relates to current and its interaction with excitable tissues in the brain and these approaches will no doubt find increasing utility in clinical practice. Although many details still need to be resolved in terms of our theoretical understanding, these regimes do not present conceptual problems when one considers the magnitude of the current in relation to electrophysiological parameters.

These technologies need to be differentiated from the low-intensity bioelectromagnetic interactions discussed in this communication, which involve high-frequency electromagnetic fields, possessing properties that are not shared by direct electrical currents. Specifically, experimental and theoretical evidence for low-intensity bioelectromagnetic interactions, with wavelength between 0.1 mm and 10 cm, is considered. These regions are also referred to as 'microwave', 'millimetre-wave' and 'sub-millimetre' and span a frequency range between 300 MHz and 3 THz, which in this article we refer to as 'radio frequency' or 'RF'.

There is a long-standing debate and division of consensus among scientists involved in research into the biological effects of RF radiation.[2–5] In particular, there are contradictory claims as to whether all RF energy deposited in biological systems simply manifests thermally, or whether or not other non-thermal interactions can occur. Biological effects outside the thermal regime have been a source of controversy since the 1960s.[6,7] More recently there have been important developments in terms of the understanding of biological systems, including non-linear behaviour. Neuropsychiatric disorders are often associated with non-linear trajectories.[8,9] Moreover, collectively the experimental evidence relating to RF bioelectromagnetic phenomena suggests that in some cases interactions could have non-linear characteristics, which may militate against the successful use of methods normally applied in the investigation of psychopharmacological interactions.

'Linearity' essentially means that the effects in a system are proportional to their causes, and linear systems can be easily analysed mathematically.[10] A 'chaotic' system is defined as one that exhibits unforeseen behaviour even though in principle no randomness is involved in determining a future state.[11] Non-linear systems can give stable states, periodic behaviour or chaotic behaviour, depending on the equations and the initial state.[11] It has become increasingly common for researchers to attempt to describe the temporal evolution of biological systems in terms of non-linear dynamics.[12]

On some levels, biological systems exhibit a high degree of spatial and temporal order as demonstrated by homeostatic-feedback mechanisms, such as that used to control blood pressure.[11] By necessity these parameters are controlled within tight limits. However, recent research shows that in other physiological systems, such as the brain, non-linearity is used to confer benefit and represents a strategy to achieve rapid and highly adaptive behaviour.[13] Non-linearity appears to be involved in the response to ambiguous, new and unlearned situations.[11] The brain is therefore a highly dynamic and adaptive non-linear system where homeostatic mechanisms are sometimes destabilized in order to allow entirely new patterns of behaviour to emerge.[14] It is evident that some psychiatric phenomena are likely to be connected with this inherent instability. The term 'controlled chaos' has been used to describe something essential to the functioning of biological systems and is operative on many levels ranging from self preservation[11] through to complex psychosocial interaction,[11] and is ultimately important on an evolutionary level.[11]

One of the ideas presented in this article is to explore whether or not RF bioelectromagnetic interactions, under certain conditions, may contribute to the highly complex and multiple interactions associated with brain physiology that underlies its non-linear behaviour.[15] This may be associated with therapeutic benefit and have a completely different mode of action to conventional pharmacotherapy, which may be an effective intervention, but not a dynamical one. This could involve the synchronisation of dynamical systems, which is a key non-linear phenomenon.[16]

A feature of chaotic systems is their unpredictability, due to the influence of small unobservable fluctuations that change the trajectory of the system.[17] This can be observed in other non-linear systems, such as the stock market, which are difficult to predict. Also, it is not possible to measure these fluctuations with sufficient precision to make predictions even though, on a microscopic level, the system may involve no randomness in the development of its future state.[11] This is referred to as 'deterministic chaos'.[18] In a non-linear system small perturbations may be associated with large effects and it is suggested here that the idea of 'critical perturbation' is an important concept in low-intensity bioelectromagnetic interactions within the brain. In clinical practice approximations and phenomenological approaches are used whereby the most important factors are considered initially and others treated as perturbations, which in reality can often be reliable.

Brain physiology is associated with a wide repertoire of dynamics.[19] Biological systems are dissipative, (they are non-equilibrium systems where energy is exchanged with the environment) and tend to adopt typical patterns of behaviour.[20] In this way non-linearity is not usually represented in all possible states of a system, but there is a bias towards certain states and these are referred to as 'attractors'.[20] Different quantitative measures are used in the description of attractors reflecting such things as the 'complexity' of the dynamics.[19] System behaviour can also be explored in terms of Lyapunov exponents, which measure how quickly two almost identical initial states change with respect to each other in time. The maximal Lyapunov exponent is a measure of the predictability of a dynamical system[21] and can be derived from electroencephalographic (EEG) data.[21]

Changes in control parameters can result in, what are termed 'phase transitions' or 'bifurcations'.[17] Control parameters are those properties that can influence the dynamics of the system and, as a dynamical system may have more than one attractor, the system can exhibit a phenomenon called 'multistability'.[19,21] A system may be 'pushed' from one attractor to another by external perturbations.[19] Bifurcations occur when control parameters are changed, reaching a critical point, which results in a rapid and radical change to the attractor landscape.[19] A possible manifestation could be the almost instantaneous reduction of the excitatory thresholds of nerve-cell populations.[11] Bifurcations are characteristic of networks that are sensitive to very weak initial conditions and this can lead to widespread changes throughout the whole system.[11]

Macroscopic electrophysiological phenomena (EEG/MEG)

With the introduction of new anatomical and functional imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), it was thought that older techniques such as the EEG would be superseded.[19] In fact, there has been renewed interest in the EEG as it has been realized that it contains important information that cannot be derived using the newer imaging modalities.[19] In particular, the EEG offers a much higher temporal resolution than fMRI, in the order of 1 ms, but with poor spatial resolution.[22] The EEG provides a highly dynamic macroscopic view of the electrical activity of the brain.[22] Neurons produce electrical activity in the form of discrete action potentials. Neuronal networks are associated with synchronous behaviour and oscillations over characteristic frequency ranges.[22] Therefore brain function involves a complex network of coupled dynamical systems but the synchronisation of even simple oscillators is still not completely understood.[18] Out of complex neuronal networks emerge the large-scale synchronous behaviour observed in both EEG and magnetoencephalography (MEG).[22]

In the early development of EEG technology all interpretation work was empirical, partly because the signal is noisy, and so reliably deriving quantitative information from the EEG continues to remain a challenge. However, during the 1980s[23] researchers began to apply a non-linear approach to modelling and the understanding of the bioelectric potentials of the brain.

In normal cognition, most studies show that the EEG reflects a weak but significant non-linear structure.[24] Sensory stimuli, such as music and performing cognitive tasks with their associated changes in emotion and affect are reflected in non-linear measures such as dimension and Lyapunov exponents.[25] The sleep EEG has also been the subject of research.[26] Moreover, genetic variations can be correlated with changes in EEG measures[27] and this could be important in the wider research picture. Contradictory reports in the literature relating to a correlation between non-linear EEG measures and IQ have been reported.[16,19]

Non-linear techniques have been used to investigate the effects of psychopharmocology and abnormal brain bioelectric potentials associated with epileptic seizures. In the case of epileptiform activity, non-linear parameters are markedly changed and this is being developed as a seizure prediction/detection methodology.[28]

Non-linearity in psychiatric illnesses

Non-linearity in psychiatric illness can manifest itself on multiple levels, from neural substrate through to symptoms and social behaviour.[10] For example, if psychoticity dynamics associated with schizophrenia are analysed over a long time series, a large proportion of psychoses will show a non-linear evolution of the symptom's course.[29] Non-linear analysis has also been applied to Freudian psychodynamics.[30]

Non-linear analysis is frequently applied to EEG data and the majority of studies that have employed such analysis have sought to establish whether or not schizophrenia is associated with a loss of dynamical complexity or to an increase in complexity.[19] Comparative analysis of data, using non-linear techniques in control subjects and those exhibiting a psychiatric disease such as schizophrenia or affective disorders, have been made.[31] Most investigators have found lower measures of complexity.[8,21,32,33]

Sleep architecture has also been investigated in schizophrenic patients using non-linear methods.[34] In this study diminished complexity of EEG time series, during awake and REM sleep, may underlie the impaired ability to process information in psychotic disorders such as schizophrenia.[34] Effects have been observed in terms of non-linear complexity recorded using sleep EEGs. In major depression, increased predictability in waking EEG has been reported.[31] Manic episodes associated with affective disorders are associated with an increase in EEG complexity.[35] The confounding effects of different medication regimes have been identified as one possible source of error in some studies.

Theoretical considerations relating to RF-bioelectromagnetic interactions

This communication considers the effects of low-intensity, high-frequency, non-ionising radiation. The way that power is absorbed in biological systems differs significantly at different frequencies within the RF range. RF bioelectromagnetics research is typically health effects orientated. Particularly controversial is the concept of non-thermal interactions, and the various experimental and theoretical arguments are hereby briefly discussed. The biological effects of terahertz radiation have only just started to be explored due to advances in technology required to generate such frequencies.[36–38]

RF interactions with biological systems cause dielectric heating.[39] Polar molecules with an electric dipole moment, such as water, generate heat by friction.[39] It is the action of these molecules continually re-orientating themselves in an alternating RF field that generates heat. Local heating is dissipated by conduction and physiological mechanisms.[40] In the millimetre-wave, a region characterized by the rapid attenuation of power,[41] there is evidence for micro-thermal effects associated with the rate of change of temperature rather than hyperthermia.[42,43]

A common argument invoked against the possibility of non-thermal interactions is based on the energy required to disrupt chemical bonds, and the way in which this is much larger than the energy associated with RF photons.[44] It is argued that any non-thermal contribution would be 'masked' by random thermal motion.[44] A number of theoretical models overcome this objection, such as that postulated by Fröhlich in 1968.[45] He showed that a driven system that might be present in biological systems can be rendered sensitive to certain weak electromagnetic stimuli,[46,47] an example of 'macroscopic quantum coherence'.[48] Although there is some experimental evidence in terms of biological effects in the millimetre-wave region, definitive evidence has not yet been forthcoming.[4,7]

The latest theoretical work does not support the possibility of, what has been termed, 'strong' coherent condensates but instead suggests the possibility of a 'weak' condensate which may still have profound, but greatly varying, effects in biological systems.[7] Using this paradigm, energy may be supplied by metabolic activity or by the exogenous application of RF or terahertz fields.

RF exposures and induced changes in the EEG

The EEG is a dynamic and complex physiological signal and integrative reporter of brain function. Some common findings in the experimental literature include the heterogeneous nature of responses within a sample population[49] and the possibly non-linear nature of the interaction.[50] These factors may go some way to explain why it is inherently difficult to reproduce experimental results and account for contradictory reports in the literature. In much simpler unicellular systems investigators have reported that induction of effects is multfactorial and dependent on genetic, physical and physiological variables.[2] There are particular technical challenges associated with RF exposure, for example dosimetry, and the possibility for experimental artefact has not been unambiguously eliminated in all cases.

The first reports of low-level microwave-induced effects observed in the EEG date back to the 1970s.[51] The frequencies employed in these studies are able to couple trans-cranially with reasonable efficiency, and therefore the potential exists, although it has not been fully proven, that interaction and modulation of endogenous processes within the brain could occur.

Reiser *et al.*[52] used common measures of EEG parameters in a controlled comparative study with sham/ irradiated systems, using two sources of RF radiation, and found statistically significant effects.

Huber *et al.*, in a series of communications, used two complementary modalities: PET and EEG.[53–55] Studies involving the EEG and a double blind crossover methodology revealed changes in the analysed spectra,[53] in particular change was observed in terms of power in the alpha band when the exposure was modulated.[54] The dynamics and architecture of the sleep EEG have also been the subject of experimental work and changes with pulse-modulated fields were reported in oscillatory EEG events in stage 2 sleep which have a characteristic spindle shape.[54] Later work using PET imaging techniques to measure regional cerebral blood flow showed that brain physiology is altered by modulated RF exposures.[54] Mann *et al.*[56] failed to replicate an earlier finding from exploratory work on microwave-induced alterations associated with the sleep EEG.[57,58] Bachmann *et al.* applied a non-linear analysis which revealed statistically-significant effects which would not be apparent using a linear analysis.[59,60]

Microwaves and their effects on Alzheimer's disease mice

Arendash *et al.*[61] investigate the effects of 980 MHz microwave radiation on transgenic mice that progress to exhibit an Alzheimer's-like disease. Both cognitive-protective and cognitive enhancing effects of microwave exposure in normal and transgenic mice were reported in the study. Brain amyloid-β deposition was changed in the microwave exposed group compared with the control group. Mechanisms are suggested on a physiological level and include increased neuronal activity, temperature and amyloid-β clearance.

Biological effects of millimetre-waves (30–300 GHz)

Millimetre-wave effects are not so well known outside the former Soviet Bloc countries, where an extensive research program was undertaken.[5] The first anomalous biological effects of low-intensity millimetre-waves date back to the 1960s when developments in military technology made exposures possible.[62] RF radiation, with frequencies higher than 20 GHz, are very rapidly absorbed in biological systems and have associated with them high specific absorption rates in superficial tissues of the skin.[63,64] However, from a theoretical perspective, it is predicted, and more likely, that bioelectromagnetic interactions in this spectral region may confer unusual properties.[45]

Initial studies were limited to lower organisms where frequency specificity and non-linear dependence on power were observed.[2,65,66] Some attempts to replicate this early work have failed,[3,4] but again, this may be because of multiple parameters that must be controlled to induce effects. It could alternatively be defects in experimental design, which inadvertently generate quasi-frequency and power-dependent effects, which in turn generate artefacts that are not related to genuine non-thermal phenomena.[67]

Belyaev *et al.*,[2] in a long series of experimental work, identifies some important physical parameters such as modulation, frequency and polarisation. The careful evaluation of these, in higher organisms, is certainly warranted. Moreover, Belyaev *et al.*[2] demonstrates strong evidence for the non-thermal nature of the effect on genome conformational state by changing parameters such as polarisation, haploid length and the use of ultra-low intensities, although no attempts to independently replicate this work have been forthcoming.

A spin-out technology from the early Soviet work involved the application of low-intensity millimetre-waves therapeutically. The reader may find the following English-language reviews provide further information.[5,43,68] The authors emphasize that the methodologies and protocols associated with the development of medical technologies in the West were not always followed, and so many studies have to be considered conjectural. However, Ziskin *et al.*, in the United States, has independently replicated some results using controlled trials,[69–74] and it is claimed that the biological effects associated with millimetre-wave exposure could be used to offer therapeutic potential for a wide range of conditions.

The obvious and reasonable objection to millimetre-wave therapy relates to the transmission of power into the body and to the site of disease.[63,64] Unless the possibility of an ultra-low intensity interaction[75] is considered, the effects of millimetre-waves on neuro-psychiatric conditions must be mediated indirectly through interactions with the skin.[76] There is ongoing debate as to whether these effects are mediated by micro-thermal effects associated with high rates of temperature change or possibly require a different interpretation.[45] Either mode of action could potentially be useful psychotherapeutically. The release of endogenous opiates,[77] associated concomitant with millimetre-wave exposure, is one frequently replicated effect that could be used therapeutically. The number of publications of millimetre-wave effects has dramatically fallen, but this reflects a reduction in overall output in countries from the former Soviet Union and does not necessarily relate to poor clinical efficacy. Millimetre-wave therapy has been reported to have a much lower incidence of side effects than pharmaceuticals.[43]

Very little is known about the possible biological effects of terahertz radiation. Recently, terahertz radiation has been used in imaging biological systems[38] and other applications are likely to be forthcoming.

Molecular level effects of RF radiation

Over the last couple of decades there has been a concerted effort to link the expression profiles of certain genes with psychopathology,[78] although the application of non-linear analysis has not been reported. One approach is to use global expression reporters such as DNA microarrays, to identify differential gene expression in disorders such as schizophrenia (genomics).[79] The science of 'proteomics' refers to the large scale study of proteins. A common limitation is the requirement for post-mortem brain tissue in many studies,[80] although this approach may be appropriate in the investigation of RF fields in animal models. The potential benefits associated with 'pharmacogenomics', the prescription of psychotropic agents, based on genetics, has only recently started to be translated into something useful clinically. Peripheral biomarkers for central nervous system (CNS) disorders are also being developed and these may be useful in understanding bioelectromagnetic interactions.

Millimetre-wave exposure has been associated with epigenetic effects[2] (changes in the expression of genes that do not relate to changes in underlying sequence) but mutagenic effects are not reported. The conformation state of the bacterial chromosome has also been reported to change with exposure to low-intensity millimetre-waves.[2] Conformational change has also been linked to modulations in gene expression[81] and found to be dependent on a wide range of factors such as physical parameters, which include polarisation, frequency, power and modulation.[2] Extrapolating from unicellular organisms to complex multicellular activity might be inappropriate but it does hint, as does the whole body of millimetre-wave evidence, that small differences in parameters, such as frequency, power and polarisation, could be important in inducing biological effects. Pooley *et al.*[82] describes, for the first time, apparatus that is capable of searching parameter space, rapidly using a high-throughput methodology of the type used to find candidate compounds that could be developed into drugs. However, the extrapolation of results from lower organisms to complex multi-cellular systems may not be valid.

Thermodynamic modelling

Thermodynamic modelling of DNA may reveal tracts of DNA with a high propensity to form non-canonical conformational states.[83] However, there are many factors that contribute to DNA conformation, such as electrostatics, methylation, topoisomerase activity and active gene transcription. As yet no unified model is available.[84] Potentially, molecular biology offers powerful techniques, such as conformation-mapping using restriction endonucleases.[85]

Ultradian biology

Ultradian rhythms refer to oscillations in biological systems with a period of less than 24 h.[76] Ultradian clocks are temperature-compensated timekeeping systems that are important for coherent and coordinated biological activity,[86] examples include the periodic oscillations that occur in lower organisms, such as the yeast *Saccharomyces cerevisiae*[86] and cardiomyocytes.[87] There is evidence that millimetre-waves could represent an input to biological timekeeping systems which are necessary for coordinated and synchronous activity.[88]

Discussion

It remains an open question as to whether the exogenous application of low-intensity RF fields could have a psychotherapeutic role. They may be associated with quite novel characteristics when applied clinically, which do not resemble a cognitive-behavioural approach or the kinetics of a pharmaceutical. Recent progress in terms of the therapeutic efficacy of psychiatric drugs has been modest, and this might reflect fundamental limitations in this approach in relation to their application to dynamical systems. Bioelectromagnetics could potentially represent a highly adaptive and agile interaction, in contrast to pharmacotherapy which is potentially more limited in the context of dynamic non-linear systems. Phenomena such as chaos may be important in normal architecture and function of the brain and potentially could facilitate adaptive behaviour.[13]

The RF bioeffects literature contains many conflicting claims. What is certain is that there are serious difficulties in reproducing phenomena, and those that are reported are often extremely subtle. It is argued here that to fully evaluate the possibility of low-intensity RF interactions with the brain, a shift in thinking is required from experiments employing fixed RF parameters to a more dynamic stimulus. This situation is quite different from that of Huber *et al.*[54] where parameters, such as frequency, power and modulation, all remain stationary.

Physiological signals (such as the EEG) can be used in feedback systems to 'tune' multiple stimulus parameters, potentially augmenting subtle effects.

It should also be noted that this is different from conventional biofeedback in the sense it is entirely passive, with the RF radiation directly coupling with brain function. There is no requirement for the CNS to process information through normal sensory channels.

Aggregate measures, such as the Lyapunov exponent, may reflect underlying abnormalities in brain function.[19] These analyses may also have a role in therapy, although the current simplistic models used to explain brain dynamics appear to be too simple.[19] The assumption that simple linear and non-linear measure can be correlated with a pathological state might not be valid. Moreover, ideas traditionally associated with biofeedback, such as operant conditioning where clinical efficacy is coupled to the induction or augmentation of a trait in a particular physiological measure, may also not be correct. The hypothesis presented here is that a weak, carefully controlled, stimulus may perturb a system. Speculatively, further work may indicate the necessary application of 'synthetic' RF signals that may induce a more synchronous mode of behaviour, or perhaps using other parameters a more chaotic one. This does not necessarily imply a kind of 'entrainment', in fact the opposite could be valid, and one of the biological functions of chaos may be to prevent entrainment.

Furthermore, from the existing experimental evidence it is possible that subject response could be highly heterogeneous, so reflecting genetic, physiological and physical parameters. Because of these characteristics, biofeedback certainly has a role in investigative bioelectromagnetics. Methodologies that employ active, as opposed to passive, strategies for identifying interaction are required. New measures, and in particular non-linear measures, are constantly evolving and being developed and may prove useful in brain/bioelectromagnetics research.

It is difficult to envisage a modality, such as transcranial magnetic stimulation outside the clinical environment, whereas RF devices could easily be deployed in community settings although the ethics of such an intervention needs careful consideration. There are some practical problems and obvious disadvantages associated with RF radiation. In non-linear systems, the idea of 'dose' doesn't really exist in the same way that it does with a pharmaceutical. Therapeutically, the formulation of the algorithm is probably going to be more important than dose. The administration of RF may be associated with effects that are difficult to predict. Some reports indicate that non-linear response within a window might extend over many orders of magnitude. Non therapeutic exposure could certainly occur in the microwave region whereas millimetre-waves will be largely contained within most rooms.

There have been a number of developments in inexpensive EEG systems which can be ambulatory and/or employ telemetry, in order that it is acceptable to the patient. One embodiment might involve monitoring sleep EEG and attempting to improve sleep architecture. This hypothesis is possibly supported by Mann *et al*.[56] RF sources are potentially inexpensive to fabricate and deploy.

RF fields do not need to be used as a monotherapy and may represent a useful adjunct to conventional methods.[43] After extensive use in research and therapy, Soviet experiences suggest that low-intensity millimetre-waves are associated with minimal adverse side-effects, although studies were not conducted with the rigour of biomedical research in the West.[43]

It is possible that, as is the case of the reports in the RF experimental literature in general, reproducibility and predictability of effects may be poor, so precluding its use clinically. Furthermore, reports of non-thermal interactions may turn out to be experimental artefacts, in which case there would be little dependence on parameters such as frequency.

However, there is a significant body of published data where dependence of MW effects is found on frequency, polarization, modulation and biological parameters, such as genome length which collectively provide strong evidence for the non-thermal nature of the interaction. This may in turn have therapeutic application.[89,90]

Another idea specific to millimetre-wave radiation interactions, which could both be useful psychotherapeutically and also be a confounding factor in understanding mode of action, relates to very rapid changes in the skin temperature and not bulk temperature rise. Millimetre-waves can drive rapid temperature changes in the peripheral nervous system and modulate neuron firing rates. This effect could represent a new form of biofeedback not in any way related to 'thermal' biofeedback.

On a molecular level, microarray and proteomics technologies, applied to peripheral biomarkers, may be useful in giving an insight into the effects of RF exposure. Biofeedback systems that incorporate DNA-chip type technologies are being developed and the possibility of a bioelectromagnetic/DNA-chip technology may be soon realisable and offer a molecular-level insight and possibility of feedback. DNA conformation and bioelectromagnetics is also a potential avenue of investigation. The EEG is a type of 'ultradian clock' and it is thought that clocks on different timescales may represent a therapeutic target, and there is some evidence of modulation of these systems in lower organisms.

Theoretical findings support the possibility that the anomalous biological effects of RF exposure could relate to special states not fully understood.[7] The mode of action of millimetre-waves has not been resolved and initial expectations are that they cannot couple directly with brain activity, due to attenuation of intervening tissues. Whether it is mediated by direct coupling, or intermediary biochemical signalling originating in the skin or skin nervous system, the mode of action has not been fully elucidated.

Conclusion

Because of the potential scope of the technology, and the attractive characteristics that it may confer, even if there is low probability of it being effective in clinical practice, further investigation is still merited. A cautious approach is required that encompasses all the possible characteristics of low intensity RF radiation-biological system interaction. Research should also be conducted in a quantitative and rigorous way to prevent pseudoscientific claims and therapies emerging.

Conflict of interest: None declared.

References

1. Ruff CC, Driver J, Bestmann S. Combining TMS and fMRI: from 'virtual lesions' to functional-network accounts of cognition. *Cortex* 2009; **45**:1043–9.
2. Belyaev IY, Shcheglov VS, Alipov ED, Ushalov VD. Nonthermal effects of extremely high-frequency microwaves on chromatin conformation in cells in vitro – dependence on physical, physiological, and genetic factors. *IEEE Trans Microwave Theory Techniques* 2000; **48**:2172–9.
3. Furia L, Hill DW, Gandhi OP. Effect of millimeter-wave irradiation on growth of Saccharomyces cerevisiae. *IEEE Trans Biomed Eng* 1986; **33**:993–9.
4. Gos P, Eicher B, Kohli J, Heyer WD. Extremely high frequency electromagnetic fields at low power density do not affect the division of exponential phase Saccharomyces cerevisiae cells. *Bioelectromagnetics* 1997; **18**:142–55.
5. Pakhomov AG, Akyel Y, Pakhomova ON, Stuck BE, Murphy MR. Current state and implications of research on biological effects of millimeter waves: a review of the literature. *Bioelectromagnetics* 1998; **19**:393–413.
6. Postow E, Swicord ML. In: Polk C, ed. *Handbook of Biological effects of Electromagnetic Fields*, 2nd edn. CRC Press, 1995:537–42.
7. Reimers JR, McKemmish LK, McKenzie RH, Mark AE, Hush NS. Weak, strong, and coherent regimes of Frohlich condensation and their applications to terahertz medicine and quantum consciousness. *Proc Natl Acad Sci USA* 2009; **106**:4219–24.
8. Lee YJ, Zhu YS, Xu YH, Shen MF, Zhang HX, Thakor NV. Detection of non-linearity in the EEG of schizophrenic patients. *Clin Neurophysiol* 2001; **112**:1288–94.
9. Paulus MP, Geyer MA, Braff DL. Use of methods from chaos theory to quantify a fundamental dysfunction in the behavioral organization of schizophrenic patients. *Am J Psychiatry* 1996; **153**:714–7.
10. Paulus MP, Braff DL. Chaos and schizophrenia: does the method fit the madness? *Biol Psychiatry* 2003; **53**:3–11.
11. Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N. Chaos and physiology: deterministic chaos in excitable cell assemblies. *Physiol Rev* 1994; **74**:1–47.
12. Rossler OE, Rossler R. Chaos in physiology. *Integr Physiol Behav Sci* 1994; **29**:328–33.
13. Skarda CA, Freeman WJ. Brains make chaos to make sense of the world. *Behav Br Sci* 1987; **10**:161–73.
14. Freeman WJ. The physiology of perception. *Sci Am* 1991; **264**:78–85.
15. Kaiser F. In: Walleczek J, ed. *External Signals and Internal Osciallation Dynamics: Principle Aspects and Responses Stimulated Rhythmic Processes.* Cambridge University Press, 2000:15–43.
16. Stam CJ. Brain dynamics in theta and alpha frequency bands and working memory performance in humans. *Neurosci Lett* 2000; **286**:115–8.
17. Meyer-Lindenberg A, Ziemann U, Hajak G, Cohen L, Berman KF. Transitions between dynamical states of differing stability in the human brain. *Proc Natl Acad Sci USA* 2002; **99**:10948–53.
18. Lloyd D. Oscillations, synchrony and deterministic chaos. In: Luttge U, Lüttge UE, Beyschlag W, Büdel B, Francis D (eds), *Progress in Botany 70.* Springer, 2009:69–91.
19. Stam CJ. Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. *Clin Neurophysiol* 2005; **116**: 2266–301.
20. Eckmann JP, Ruelle D. Ergodic-theory of chaos and strange attractors. *Rev Modern Phys* 1985; **57**:617–56.
21. Kim DJ, Jeong J, Chae JH, Park S, Yong KS, Jin GH, *et al.* An estimation of the first positive Lyapunov exponent of the EEG in patients with schizophrenia. *Psychiatry Res* 2000; **98**: 177–89.
22. Clark JW. The electroencephalogram. In: Webster JG, ed. *Medical Instrumentation Application and Design.*, 2nd edn. Orlando, USA, Houghton Mifflin Company, 1992:194–217.
23. Rapp PE, Zimmerman ID, Albano AM, Deguzman GC, Greenbaun NN. dynamics of spontaneous neural activity in the simian motor cortex – the dimension of chaotic neurons. *Phys Lett A* 1985; **110**:335–8.
24. Gautama T, Mandic DP, Van Hulle MM. Indications of nonlinear structures in brain electrical activity. *Phys Rev E Stat Nonlin Soft Matter Phys* 2003; **67**(4 Pt 2):046204.
25. Aftanas LI, Golocheikine SA. Non-linear dynamic complexity of the human EEG during meditation. *Neurosci Lett* 2002; **330**:143–6.
26. Roschke J, Aldenhoff JB. A nonlinear approach to brain function: deterministic chaos and sleep EEG. *Sleep* 1992; **15**:95–101.

27. De GL, Marzano C, Fratello F, Moroni F, Pellicciari MC, Ferlazzo F, *et al.* The electroencephalographic fingerprint of sleep is genetically determined: a twin study. *Ann Neurol* 2008; **64**:455–60.

28. Lehnertz K, Mormann F, Osterhage H, Muller A, Prusseit J, Chernihovskyi A, *et al.* State-of-the-art of seizure prediction. *J Clin Neurophysiol* 2007; **24**:147–53.

29. Tschacher W, Scheier C, Hashimoto Y. Dynamical analysis of schizophrenia courses. *Biol Psychiatry* 1997; **41**:428–37.

30. Pezard L, Nandrino JL. [Dynamic paradigm in psychopathology: ''chaos theory'', from physics to psychiatry]. *Encephale* 2001; **27**:260–8 (in French).

31. Roschke J, Mann K, Fell J. Nonlinear EEG dynamics during sleep in depression and schizophrenia. *Int J Neurosci* 1994; **75**:271–84.

32. Kotini A, Anninos P. Detection of non-linearity in schizophrenic patients using magnetoencephalography. *Brain Topogr* 2002; **15**:107–13.

33. Saito N, Kuginuki T, Yagyu T, Kinoshita T, Koenig T, Pascual-Marqui RD, *et al.* Global, regional, and local measures of complexity of multichannel electroencephalography in acute, neuroleptic-naive, first-break schizophrenics. *Biol Psychiatry* 1998; **43**:794–802.

34. Keshavan MS, Cashmere JD, Miewald J, Yeragani VK. Decreased nonlinear complexity and chaos during sleep in first episode schizophrenia: a preliminary report. *Schizophrenia Res* 2004; **71**:263–72.

35. Bahrami B, Seyedsadjadi R, Babadi B, Noroozian M. Brain complexity increases in mania. *Neuroreport* 2005; **16**:187–91.

36. Fedorov VI, Popova SS, Pisarchik AN. Dynamic effects of submillimeter wave radiation on biological objects of various levels of organization. *Int J Infrared Millimeter Waves* 2003; **24**:1235–54.

37. Siegel PH. Terahertz technology in biology and medicine. *IEEE Trans Microwave Theory Techniques* 2004; **52**:2438–47.

38. Usanov DA, Krenitskiy AP, Mayborodin AV, Tupikin VD, Usanov AD, Rytik AP. Terahertz waves and perspectives of terahertz biomedical technologies development. *2008 Mikon Conference Proceedings, Vols 1 and 2*. NJ, USA, IEEE, 2008:825–34.

39. Santagada V, Frecentese F, Perissutti E, Fiorino F, Severino B, Caliendo G. Microwave assisted synthesis: a new technology in drug discovery. *Mini Rev Med Chem* 2009; **9**:340–58.

40. Alekseev SI, Radzievsky AA, Szabo I, Ziskin MC. Local heating of human skin by millimeter waves: effect of blood flow. *Bioelectromagnetics* 2005; **26**:489–501.

41. Alekseev SI, Ziskin MC. Effects of millimeter waves on ionic currents of Lymnaea neurons. *Bioelectromagnetics* 1999; **20**:24–33.

42. Alekseev SI, Ziskin MC. Local heating of human skin by millimeter waves: a kinetics study. *Bioelectromagnetics* 2003; **24**:571–81.

43. Rojavin MA, Ziskin MC. Medical application of millimetre waves. *QJM* 1998; **91**:57–66.

44. Polk C. Introduction. In: Polk C, Postow E, *Biological Effects of Electromagnetic Fields*, 2nd edn. Florida, USA, CRC Press, 1996:18–21.

45. Frohlich H. Coherence and long- range energy storage in biological systems. *Int J Quant Chem* 1968; **2**:641–9.

46. Frohlich H. Evidence for bose condensation-like excitation of coherent modes in biological-systems. *Phys Lett A* 1975; **51**:21–2.

47. Frohlich H. Long-range coherence in biological-systems. *Riv del Nuovo Cimento* 1977a; **7**:399–418.

48. Frohlich H. Possibilities of long- and short-range electric interactions of biological systems. *Neurosci Res Program Bull* 1977b; **15**:67–72.

49. Hinrikus H, Bachmann M, Lass J, Karai D, Tuulik V. Effect of low frequency modulated microwave exposure on human EEG: individual sensitivity. *Bioelectromagnetics* 2008; **29**:527–38.

50. Marinov BS, Chailakhian LM. [Regulation of superoxide dismutase activity by superhigh frequency radiation. The mechanism of SHF action]. *Dokl Akad Nauk* 1997; **356**:821–4 (in Russian).

51. Bawin SM, Gavalas-Medici RJ, Adey WR. Effects of modulated very high frequency fields on specific brain rhythms in cats. *Brain Res* 1973; **58**:365–84.

52. Reiser H, Dimpfel W, Schober F. The influence of electromagnetic fields on human brain activity. *Eur J Med Res* 1995; **1**:27–32.

53. Borbely AA, Huber R, Graf T, Fuchs B, Gallmann E, Achermann P. Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram. *Neurosci Lett* 1999; **275**:207–10.

54. Huber R, Treyer V, Borbely AA, Schuderer J, Gottselig JM, Landolt HP. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. *J Sleep Res* 2002; **11**:289–95.

55. Huber R, Treyer V, Schuderer J, Berthold T, Buck A, Kuster N, *et al.* Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow. *Eur J Neurosci* 2005; **21**:1000–6.

56. Mann K, Roschke J. Sleep under exposure to high-frequency electromagnetic fields. *Sleep Med Rev* 2004; **8**:95–107.

57. Wagner P, Roschke J, Mann K, Fell J, Hiller W, Frank C, *et al.* Human sleep EEG under the influence of pulsed radio frequency electromagnetic fields. Results from polysomnographies using submaximal high power flux densities. *Neuropsychobiology* 2000; **42**:207–12.

58. Wagner P, Roschke J, Mann K, Hiller W, Frank C. Human sleep under the influence of pulsed radiofrequency electromagnetic fields: a polysomnographic study using standardized conditions. *Bioelectromagnetics* 1998; **19**: 199–202.

59. Bachmann M, Kalda J, Lass J, Tuulik V, Sakki M, Hinrikus H. Non-linear analysis of the electroencephalogram for detecting effects of low-level electromagnetic fields. *Med Biol Eng Comput* 2005; **43**:142–9.

60. Hinrikus H, Bachmann M, Kalda J, Sakki M, Lass J, Tomson R. Methods of electroencephalographic signal analysis for detection of small hidden changes. *Nonlinear Biomed Phys* 2007; **1**:9.

61. Arendash GW, Sanchez-Ramos J, Mori T, Mamcarz M, Lin X, Runfeldt M, *et al.* Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. *J Alzheimers Dis* 2010; **19**:191–210.

62. Webb S, Dodds D. Inhibition of bacterial cell growth 136 GHz microwave. *Nature* 1968; **218**:374–5.
63. Alekseev SI, Radzievsky AA, Logani MK, Ziskin MC. Millimeter wave dosimetry of human skin. *Bioelectromagnetics* 2008; **29**:65–70.
64. Gandhi OP. Some basic properties of biological tissues for potential biomedical applications of millimeter waves. *J Microw Power* 1983; **18**:295–304.
65. Belyaev IY, Alipov YD, Shcheglov VS, Lystsov VN. Resonance effect of microwaves on the genome conformational state of E. coli cells. *Z Naturforsch [C]* 1992; **47**:621–7.
66. Grundler W, Keilmann F. Nonthermal effects of millimeter microwaves on yeast growth. *Z Naturforsch [C]* 1978; **33**:15–22.
67. Khizhnyak EP, Ziskin MC. Heating patterns in biological tissue phantoms caused by millimeter wave electromagnetic irradiation. *IEEE Trans Biomed Eng* 1994; **41**:865–73.
68. Pakhomov AG, Murphy MR. Low-intensity millimeter waves as a novel therapeutic modality. *Ieee Transact Plasma Sci* 2000; **28**:34–40.
69. Logani MK, Bhanushali A, Anga A, Majmundar A, Szabo I, Ziskin MC. Combined millimeter wave and cyclophosphamide therapy of an experimental murine melanoma. *Bioelectromagnetics* 2004; **25**:516–23.
70. Logani MK, Szabo I, Makar V, Bhanushali A, Alekseev S, Ziskin MC. Effect of millimeter wave irradiation on tumor metastasis. *Bioelectromagnetics* 2006; **27**:258–64.
71. Radzievsky AA, Rojavin MA, Cowan A, Ziskin MC. Suppression of pain sensation caused by millimeter waves: a double- blinded, cross-over, prospective human volunteer study. *Anesth Analg* 1999; **88**:836–40.
72. Radzievsky AA, Rojavin MA, Cowan A, Alekseev SI, Ziskin MC. Hypoalgesic effect of millimeter waves in mice: dependence on the site of exposure. *Life Sci* 2000; **66**:2101–11.
73. Rojavin MA, Ziskin MC. Electromagnetic millimeter waves increase the duration of anaesthesia caused by ketamine and chloral hydrate in mice. *Int J Radiat Biol* 1997; **72**:475–80.
74. Szabo I, Rojavin MA, Rogers TJ, Ziskin MC. Reactions of keratinocytes to in vitro millimeter wave exposure. *Bioelectromagnetics* 2001; **22**:358–64.
75. Belyaev IY, Shcheglov VS, Alipov YD, Polunin VA. Resonance effect of millimeter waves in the power range from 10(-19) to 3 x 10(-3) W/cm2 on Escherichia coli cells at different concentrations. *Bioelectromagnetics* 1996; **17**:312–21.
76. Radzievsky AA, Rojavin MA, Cowan A, Alekseev SI, Radzievsky AA Jr, Ziskin MC. Peripheral neural system involvement in hypoalgesic effect of electromagnetic millimeter waves. *Life Sci* 2001; **68**:1143–51.
77. Radzievsky AA, Gordiienko OV, Alekseev S, Szabo I, Cowan A, Ziskin MC. Electromagnetic millimeter wave induced hypoalgesia: frequency dependence and involvement of endogenous opioids. *Bioelectromagnetics* 2008; **29**:284–95.
78. Pongrac J, Middleton FA, Lewis DA, Levitt P, Mirnics K. Gene expression profiling with DNA microarrays: advancing our understanding of psychiatric disorders. *Neurochem Res* 2002; **27**:1049–63.
79. Mirnics K, Middleton FA, Lewis DA, Levitt P. The human genome: gene expression profiling and schizophrenia. *Am J Psychiatry* 2001; **158**:1384.
80. Atz M, Walsh D, Cartagena P, Li J, Evans S, Choudary P, *et al.* Methodological considerations for gene expression profiling of human brain. *J Neurosci Methods* 2007; **163**:295–309.
81. Drolet M. Growth inhibition mediated by excess negative supercoiling: the interplay between transcription elongation, R-loop formation and DNA topology. *Mol Microbiol* 2006; **59**:723–30.
82. Pooley D, Gibson C, Stewart W, Magee J, Ellison B, Lloyd D. Biological effects of millimeter-wave radiation: a high-throughput screening system. *Rev Scientific Instr* 2003; **74**:1296–302.
83. Ho PS, Ellison MJ, Quigley GJ, Rich A. A computer aided thermodynamic approach for predicting the formation of Z-DNA in naturally occurring sequences. *EMBO J* 1986; **5**:2737–44.
84. Gueron M, Demaret J, Filoche M. A unified theory of the B-Z transition of DNA in high and low concentrations of multivalent ions. *Biophys J* 2000; **78**:1070–83.
85. Kim YG, Kim PS, Herbert A, Rich A. Construction of a Z-DNA-specific restriction endonuclease. *Proc Natl Acad Sci USA* 1997; **94**:12875–9.
86. Lloyd D. Respiratory oscillations in yeasts. *Adv Exp Med Biol* 2008; **641**:118–40.
87. Aon MA, Cortassa S, O'Rourke B. The fundamental organization of cardiac mitochondria as a network of coupled oscillators. *Biophys J* 2006; **91**:4317–27.
88. Golant MB, Kuznetsov AP, Bozhanova TP. [The mechanism of synchronizing yeast cell cultures with EHF-radiation]. *Biofizika* 1994; **39**:490–5 (in Russian).
89. Adey WR. Potential therapeutic applications of nonthermal electromagnetic fields: ensemble organization of cells in tissues as a factor in biological field sensing. In: Markov MS, ed. *Bioelectromagnetic Medicine*. New York, Marcel Decker, 2004:1–16.
90. Belyaev I. Nonthermal biological effects of microwaves: current knowledge, further perspective, and urgent needs. *Electromagn Biol Med* 2005; **24**: 375–403.