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FİZYOLOJİ ALANINDA ARAŞTIRMALAR VE DEĞERLENDİRMELER

Researches and Evaluations in Physiology

EDİTÖR

Doç. Dr. Sadettin DEMİREL

gece kitaplığı

İÇİNDEKİLER / CONTENTS

BÖLÜM 1

MAKİNE ÖĞRENMESİNİN TIPTA KULLANIM ALANLARI

Bora REŞİTOĞLU *7*

CHAPTER 2

CALCİUM SİGNALİNG AND NEUROPLASTİCİTY: THE BRAİN'S SELF-RENEWAL MECHANİSMS

Cagatay Han TURKSEVEN *19*

CHAPTER 3

MAINTAINING BRAIN FUNCTIONS AND HOMEOSTASIS

Ebru BARDAŞ ÖZKAN *37*

BÖLÜM 1

MAKİNE ÖĞRENMESİNİN TIPTA KULLANIM ALANLARI

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1. Makine Öğrenmesi

Yapay zeka, tıbbı geliştirme iddiasını 30 yılı aşkın bir süredir taşımaktadır ve son yıllarda bu vaadi gerçeğe dönüştürme potansiyeline sahip teknolojik ilerlemeler kaydedilmiştir. Bu ilerlemeler arasında, bilgi işleme gücündeki hızlı artışlar, büyük veri işleme teknolojileri, elektronik sağlık kayıtlarının kullanımıyla büyük klinik veri setlerine erişim ve makine öğrenimi (ML) bulunmaktadır (Handelman; 2018).

Makine öğrenimi terimi, ilk olarak 1959'da o dönemin önde gelen bilgisayar bilimcilerinden Arthur Samuel tarafından ortaya atılmıştır. Yapay zeka ve makine öğrenimi terimleri genellikle birbirleriyle eşanlamlı olarak kullanılır; yapay zeka, "düşünen makine" veya otomatik karar verme gibi geniş bir kavramı ifade ederken, makine öğrenimini "bilgisayarlara açıkça programlanmadan öğrenme yeteneği" olarak tanımlamıştır. Makine öğreniminin temel prensibi, bilgisayar analizi uygulayarak girdi verilerini alan, çıktı değerlerini tahmin etmek üzere önceki deneyimlerden öğrenen algoritmaları tanıtmaktır. Makine öğrenimi, bilgisayarların daha fazla analiz için kural tabanlı veya korelasyon varsayımları tasarlamak amacıyla insan operatörlere dayanan geleneksel istatistiksel yöntemlerle ulaşılması zor olan kalıpları ve sonuçları aydınlatmaya yönelik olarak ortaya çıkmıştır (Mitchell; 1997).

ML ile süreç yarı otomatiktir; bilgisayara veriler sağlanır ve tahmin doğruluğunu artırmak ve optimize etmek için öğrenme çerçevelerine dayalı karmaşık analitik modeller oluşturulur. Ancak bu, ML'nin geleneksel istatistiklerden doğal olarak farklı olduğu anlamına gelmez, çünkü birçok yönden istatistiksel temellere dayanır veya bunları benimser. İşlem gücü, bellek, depolama ve benzeri görülmemiş veri zenginliğindeki ilerlemelerden güç alan bilgisayarlar, karmaşık öğrenme görevlerini yerine getirme konusunda giderek daha fazla rol almaktadırlar ve çoğu zaman kayda değer başarılar elde etmektedirler. Veri depolama daha büyük, daha ucuz ve bağlantılı hale geldikten sonra, veri madenciliği ve büyük veri analitiğinin paradigmaya entegrasyonu, makine öğreniminin kapsamını ve potansiyelini artırmıştır (Breiman; 2001).

Makine öğrenimi, bilgisayarların verilerden nasıl bilgi edindiğine odaklanan bilimsel bir alandır. Verilerden örüntüleri ayırt etmeyi amaçlayan istatistik ile verimli hesaplama algoritmalarını vurgulayan bilgisayar biliminin kesiştiği noktada ortaya çıkar. Matematik ve bilgisayar bilimlerinin bu birleşimi, milyarlarca hatta trilyonlarca veri noktasını kapsayan devasa veri kümelerinden istatistiksel modeller oluşturmanın getirdiği kendine özgü hesaplama zorluklarından kaynaklanmaktadır. (Deo; 2015).

Öğrenme teknikleri, değişkenler arasındaki ilişkileri tanımlayan matematiksel prosedürler kümesi olan algoritmalara dayanır. Algoritmalar

türlerine bağlı olarak farklı şekilde işlese de, geliştirilmelerinde önemli ortak noktalar vardır. Makine öğrenimi (ML) algoritmalarının görünüşte ezoterik doğasına rağmen, genellikle geleneksel istatistiksel analizlerle ince bir benzerlikten daha fazlasını paylaşırlar. İstatistiksel ve makine öğrenimi teknikleri arasındaki ortak noktalara rağmen, ikisi arasındaki sınır bulanık veya kötü tanımlanmış görünebilir. İstatistiksel yöntemler çıkarım yapmayı, popülasyonlar hakkında sonuçlar çıkarmayı veya temsili bir örneklemden toplanan verilerden bilimsel öngörüler elde etmeyi amaçlar. Doğrusal ve lojistik regresyon gibi birçok istatistiksel teknik yeni verileri tahmin edebilirken, istatistiksel bir metodoloji olarak kullanımları öncelikle değişkenler arasındaki ilişkiler hakkında çıkarımlar yapmak için motive edilir. Örneğin, organ nakli ameliyatını takiben klinik değişkenler ve ölüm arasındaki ilişkinin modellenmesinde, düşük ve yüksek ölüm riskini birbirinden ayıran faktörlerin anlaşılması, sonuçları iyileştirmeye yönelik müdahalelerin geliştirilmesi için çok önemlidir. İstatistiksel çıkarımda amaç, değişkenler arasındaki ilişkileri anlamaktır. Bunun tersine, makine öğreniminde birincil kaygı doğru tahmindir 'nasıl'dan ziyade 'ne'. Örneğin, görüntü tanımada, tahmin doğruysa, bireysel özellikler ile sonuç arasındaki ilişki çok az önem taşır. Bu, makine öğrenimi tekniklerinde, özellikle de görüntü veya videolardaki pikseller ve coğrafi konum gibi girdiler arasındaki karmaşık ve genellikle doğrusal olmayan ilişkilerle uğraşırken çok önemlidir. Bu ilişkileri tutarlı bir şekilde tanımlamak, özellikle doğrusal olmayan ilişkiler ve her biri modele küçük bir bireysel katkı sağlayan çok sayıda tahminciyle uğraşırken son derece zor hale gelir. Neyse ki tıp alanında, vücut kitle indeksi ile diyabet riski veya tütün kullanımı ile akciğer kanseri arasındaki ilişkiler gibi birçok ilgi çekici ilişki oldukça basittir. Sonuç olarak, etkileşimleri genellikle nispeten basit modeller kullanılarak makul ölçüde iyi açıklanabilir (Sidey-Gibbons; 2019).

Bir makine öğrenimi sürecinin temel bir açıklaması, histopatolojik slaytlardan kanseri tespit etmek için bir bilgisayarın eğitilmesi örneği göz önünde bulundurularak elde edilebilir. Açıklamalı bir bilgi tabanı kullanarak, bilgisayarı, bir bazal membranı yoluyla hastalığın invazyonunu temsil eden renk ve çizgi kombinasyonlarını tespit etmek için bir kural tabanı kullanacak şekilde programlamaya çalışabilir ve daha sonra yeni bir slaytla sunulduğunda, bilgisayar programı bir güven puanı veya malignite olasılığı sağlayabilir. Alternatif olarak, bilgisayar programının iki kategori arasında en iyi ayrımı nasıl yapacağını belirlemesi için malign ve malign olmayan örneklerden oluşan bir görüntü veritabanı sunulabilir ve ardından doğruluğunu teyit etmek için yeni slaytlar sunularak programın başarısı değerlendirilebilir. Eğer başarılı olursa, bilgisayarın sonuçlara ulaşma süreci, nihai sonucu tahmin etmede mevcut bilgi ve kural tabanlı sistemimizden daha iyiyse daha az önem taşır (Mangasarian; 1995)

2. Makine Öğrenmesinin Tıpta Kullanımı

Yapay zekanın tıbba uygulanmasının 1970'lere kadar uzanan uzun geçmişine rağmen, birçok tıp uzmanı ML kavramını, potansiyel uygulamalarını veya kendi uzmanlık alanlarında ML ile ilgili kapsamlı literatürü bilmemektedir. Şimdiye kadar tamamlanan çalışmalar, makine öğreniminin benimsenmesi ve uygulanması yoluyla araştırmada tahmin ve görselleştirme kalitesini artırma potansiyeline işaret etmektedir. Birçok çalışma, makine öğrenen araçların veri bilimi ve istatistik temellerini detaylı bir şekilde açıklamıştır. Ancak, değerlendirme ve uygulama üzerine odaklanan çalışmalar oldukça sınırlıdır. (Antoniou; 2021)

Makine öğrenimi sağlık alanında çeşitli uygulamalara sahiptir. Bu uygulamalar zaman alıcı ve karmaşık görevleri kolaylaştırabilir. Makine öğrenimi, daha hızlı işlemcilerin tasarlanması ve dijital sağlık verilerine erişim alanındaki ilerlemelerle birlikte sağlık hizmetleri sürecini iyileştirecek fırsatlar sunmaktadır. Bu teknolojiler maliyetleri düşürürken, ilaç keşfini hızlandırabilir ve tedavi sonuçlarını iyileştirebilir. Makine öğrenimi, tıp alanındaki uygulamaları üç kategoriye ayırabiliriz: mevcut tıbbi yapıların iyileştirilmesi, tıbbi yapıların kişiselleştirilmesi ve bağımsız tıbbi yapılar. Bu uygulamalar, medikal alanda mevcut yapıların performansını iyileştirir, tıbbi tedavileri kişiselleştirir ve bağımsız olarak kararlar alabilirler. Bu nedenle, gelecekteki sağlık hizmetlerinde robotların rolü önemli olacak gibi görünmektedir. Ancak bu yeni teknolojinin bazı zayıflıkları ve kusurları olduğu için hala geliştirilmeye devam edilmelidir. (Rahmani; 2021)

Makine öğrenmesi günümüzde sağlıkta birçok alanda aktif olarak çalışılmaktadır. Hastalıkların tanı ve teşhisi (Kanser, Influenza, Sepsis, Kronik Obstrüktif Akçiğer hastalığı vb.) tıbbi görüntülemede kullanımları ve diabet riski hesaplanması gibi çalışmalar bunların başlıcalarıdır. Bu başlıklarda bazılarına değinecek olursak.

2.1 Kanser

Kanser, birçok farklı alt tipten oluşan heterojen bir hastalık olarak nitelendirilmektedir. Bir kanser türünün erken teşhisi ve prognozu, hastaların daha sonraki klinik yönetimini kolaylaştırabileceğinden, kanser araştırmalarında bir gereklilik haline gelmiştir. Kanser hastalarını yüksek veya düşük riskli gruplar halinde sınıflandırmanın önemi, biyomedikal ve biyoinformatik alanından birçok araştırma ekibinin makine öğrenimi yöntemlerinin uygulanmasını incelemesine yol açmıştır. Bu nedenle, bu teknikler kanserli durumların ilerlemesini ve tedavisini modellemek amacıyla kullanılmıştır. Buna ek olarak, makine öğrenimi araçlarının karmaşık veri kümelerinden temel özellikleri tespit etme yeteneği de önemini ortaya koymaktadır. ML tekniklerinin birçoğu, kanser araştırmalarında öngörücü modellerin geliştirilmesi için yaygın olarak uygulanmış ve etkili ve doğru

karar verme ile sonuçlanmıştır. Makine öğrenimi yöntemlerinin kullanımının kanserin ilerleyişine ilişkin anlayışımızı geliştirebileceği açık olsa da, bu yöntemlerin günlük klinik uygulamada dikkate alınabilmesi için uygun bir doğrulama seviyesine ihtiyaç duyulmaktadır. Tıp alanında yeni teknolojilerin ortaya çıkmasıyla birlikte, büyük miktarda kanser verisi toplanmış ve tıbbi araştırma topluluğunun kullanımına sunulmuştur. Bununla birlikte, bir hastalığın sonucunun doğru bir şekilde tahmin edilmesi, hekimler için en ilginç ve zorlu görevlerden biridir. Sonuç olarak, makine öğrenimi yöntemleri tıp araştırmacıları için popüler bir araç haline gelmiştir. Bu teknikler, bir kanser türünün gelecekteki sonuçlarını etkili bir şekilde tahmin edebilirken, karmaşık veri kümelerinden kalıpları ve aralarındaki ilişkileri keşfedebilir ve tanımlayabilir. ML tekniklerinin uygulanmasıyla kanser tahmin sonuçlarının doğruluğu son yıllarda %15-%20 oranında önemli ölçüde artmıştır. Bir hastalığın prognozunun başarısı şüphesiz tıbbi teşhisin kalitesine bağlıdır; ancak prognostik bir tahmin basit bir teşhis kararından daha fazlasını dikkate almalıdır. (Kourou; 2015, Cruz; 2006)

Kanser prognozu/öngörüsü ile uğraşırken üç öngörü görevi söz konusudur:

1. Kansere yatkınlığın öngörülmesi (risk değerlendirmesi)
2. Kanser nüksünün/lokal kontrolün öngörülmesi
3. Kanserde sağkalımın öngörülmesi.

Geçmişte, hekimler tarafından kullanılan tipik bilgiler, kanser prognozuna ilişkin makul bir kararla sonuçlanmakta ve histolojik, klinik ve popülasyona dayalı verileri içermekteydi. Aile öyküsü, yaş, diyet, kilo, yüksek riskli alışkanlıklar ve çevresel kanserojenlere maruz kalma gibi özelliklerin entegrasyonu kanser gelişiminin öngörülmesinde kritik bir rol oynamaktadır. Bu tür makro ölçekli bilgiler, standart istatistiksel yöntemlerin tahmin amacıyla kullanılabilmesi için az sayıda değişkene atıfta bulunsa da, bu tür parametreler sağlam kararlar almak için yeterli bilgi sağlamamaktadır. Genomik, proteomik ve görüntüleme teknolojilerinin hızla gelişmesiyle birlikte yeni bir tür moleküler bilgi elde edilebilmektedir. Moleküler biyobelirteçler, hücresel parametreler ve belirli genlerin ifadesinin kanser tahmini için çok bilgilendirici göstergeler olduğu kanıtlanmıştır. Günümüzde bu tür Yüksek Verimli Teknolojilerin (HTT'ler) varlığı, toplanan ve tıbbi araştırma topluluğunun kullanımına sunulan çok büyük miktarlarda kanser verisi üretmiştir. Makine öğrenmesinin kullanıldığı kanser çalışmalarına örnek verecek olursak (Ayer; 2010, Bach; 2003, Ren; 2013, Listgarten; 2004, Tharwat; 2022, Kadir; 2018);

Göğüs Kanseri

Multipl Miyelom

Kolon Kanseri

Ağız Kanseri

Rahim Ağzı Kanseri

Akçiğer Kanseri

Kanser araştırmaları, oldukça fazla toplumsal etkileri olan önemli bir alandır. Kanser çalışmalarında makine öğrenimi kullanımı, kanser türlerinin sınıflandırılması ve tahmini, ilaç yanıtı ve tedavi stratejileri gibi kanserle ilgili sorunların kıyaslaması da dahil olmak üzere çeşitli yönlerden yüksek potansiyel göstermektedir. ML modelleri, belirli ilaçların klinik etkinliğini ve belirli hastalar için uygun tedavi tekniklerini tahmin etmek için de kullanılabilir. Buna göre, Menden ve arkadaşları, kanser hücre hatlarının IC50 değerleri boyunca ölçülen tıbbi tedaviye tepkisini hesaplamak için ML modelleri, geliştirmiştir. Tahmin süreci, söz konusu ilaçların kimyasal özelliklerine ve hücre hatlarının genomik özelliklerine dayanmaktadır. IC50 profilinin tahmin edilmesinde her bir hücrenin genomik arka planı dikkate alınmıştır. Çalışmalarına dayanarak, binlerce ilacın potansiyel etkinliği, oluşumlarına bağlı olarak anti-tümör ajanları olarak test edilebilir (Shehab; 2022, Menden; 2013).

2.2 Tıbbi Görüntüleme

Görüntüleme ve bilgisayar alanındaki ilerlemeler, yapay zekânın risk değerlendirmesi, tespit, tanı, prognoz ve tedavi yanıtı gibi çeşitli radyolojik görüntüleme görevlerinde potansiyel kullanımında hızlı bir artışa neden olmuştur. Hastalıkların etkili tanı ve tedavisi, klinik, moleküler, görüntüleme ve genomik veriler (yani çeşitli "-omik" veriler) içeren birden fazla hasta testinden gelen bilgilerin entegrasyonuna dayanır. Radyomik, CADx'in (Bilgisayar Destekli Tanı) bir genişlemesi olarak, görüntülerin madenlenebilir verilere dönüştürülmesi şeklinde tanımlanmıştır. Radyomik verilerin elde edilmesi, bir tümörün arka plandan bilgisayarla segmentasyonu ve ardından çeşitli tümör özelliklerinin bilgisayar tarafından çıkarılması işlemini içerebilir. Kantitatif radyomiğin nihai faydaları, hassas tıp için tahmine dayalı görüntü tabanlı hastalık fenotipleri veya keşif için diğer -omik verilerle veri madenciliği yapılabilecek kantitatif görüntü tabanlı fenotipler sağlamaktır. (Giger; 2018)

Makine öğreniminin (ML) kullanımı, tıbbi görüntüleme alanında hızla artmaktadır. Bu artış, bilgisayar destekli tespit (CADe) ve teşhis (CADx), radyomik ve tıbbi görüntü analizi gibi alanlarda dikkat çekicidir. Bunun

temel nedeni, tıbbi görüntülerdeki lezyonlar ve organlar gibi nesnelerin, basit bir denklem veya modelle doğru bir şekilde temsil edilmesi için genellikle çok karmaşık olmasıdır. Örneğin, bir akciğer nodülü genellikle katı bir küre olarak modellenir, ancak çeşitli şekillerde ve homojen olmayan yapıda nodüller, örneğin spiküler nodüller ve buzlu cam nodüller de mevcuttur. Benzer şekilde, bir kolon polibi genellikle yuvarlak bir nesne olarak modellenirken, düz şekilli kolorektal lezyonlar da vardır.

Makine öğrenimi (ML) ile özellik bazlı giriş (özellik tabanlı ML, yaygın sınıflandırıcılar) kullanılarak yapılan birçok çalışma, tıbbi görüntüleme alanındaki uygulamalara odaklanmıştır. Bu uygulamalar arasında akciğer nodüllerinin akciğer grafisinde (CXR) ve torasik BT'de tespiti, akciğer nodüllerinin CXR ve torasik BT görüntülerinde benign veya malign olarak sınıflandırılması, mamografide mikrokalsifikasyonların tespiti, kitlelerin tespiti ve benign veya malign olarak sınıflandırılması, BT kolonoskopisinde polip tespiti ve beyin MRG'sinde anevrizmaların tespiti gibi konular bulunmaktadır. Mamografi görüntülerinde öznel benzerlik ölçüsünün belirlenmesi gibi regresyon problemleri için ML uygulamaları da rapor edilmiştir (Suziki; 2017).

Makine öğrenmesinin Radyolojik uygulamalarına başlıklar halinde bakacak olursa;

1. Görüntü sınıflandırma: Radyologların temel görevlerinden biri, her hastanın tıbbi görüntüleri için uygun bir diferansiyel tanı koymaktır ve bu sınıflandırma görevi, bir hastalığın varlığını veya yokluğunu belirlemekten, malignite türünü tanımlamaya kadar geniş bir yelpazeyi kapsar. Son zamanlarda tanıtılan Derin Sinir Ağları (DNN), özellikle Evrişimli Sinir Ağları (CNN) gibi makine öğrenmeleri, tüberküloz, diyabetik retinopati ve cilt kanserleri teşhisi gibi çeşitli tıbbi uygulamalarda görüntü tabanlı sınıflandırma performansını artırmıştır.

2. Nesne tespiti: nesnelerin bulunması ve kategorize edilmesidir. Biyomedikal görüntülerde, tespit tekniği, hastanın lezyonlarının bulunduğu alanları kutu koordinatları olarak belirlemek için de kullanılır.

3. Görüntü Segmentasyonu ve Kaydı: Tıbbi görüntüler çok miktarda bilgi sağladığından, çeşitli otomatik segmentasyon ve kaydetme algoritmaları klinik ortamlarda kullanılması için incelenmiş ve önerilmiştir. Son yıllarda, derin öğrenme teknolojisi tıbbi görüntüleri analiz etmek için çeşitli alanlarda kullanılmış ve segmentasyon ve kaydetme gibi uygulamalarda mükemmel bir performans sergilemiştir.

4. Görüntü Üretimi

5. Görüntü Dönüşümü

3. Makine Öğrenmesinin Tıpta Kullanımının Kısıtlamaları ve Etik Kaygılar

Gözlemlenmiştir ki, makine öğrenimi büyük ölçüde geleneksel, insan odaklı çözümleri daha verimli ve tutarlı bir şekilde taklit etme konusunda başarılı olmuştur. Ancak algoritmalar genellikle uzman görüşünü "doğru veri" olarak kullanarak eğitildiğinden, makine öğrenimi, problemlerin ya da doğruluk ölçütlerinin iyi tanımlanmadığı durumlarda sınırlı bir yarar sağlar. Sonuç olarak, makineler insan davranışını tekrarlama, otomatikleştirme ve standartlaştırma konularında mükemmel performans gösterebilse de, tanım, değerlendirme ve yargılama gibi kavramsal klinik zorluklar hâlâ insan zekâsı ve içgörüsü alanında kalmaktadır. Kullanılabilir veri setleri, belirli bir tıbbi durum için klinik durumu yalnızca kısmen yansıtarak veri seti yanlılığına yol açabilir. Örneğin, bir popülasyon çalışması kapsamında toplanan bir veri seti, hastanede tedavi gören kişilerden (hastalığın daha yüksek görülme oranı) farklı özellikler gösterebilir. Araştırmacının bu yanlılıktan haberdar olmaması, çalışmanın önemli eksikliklere sahip olmasına yol açabilir. Veri seti yanlılığı, karar modeli oluşturmak için kullanılan verilerin (eğitim verileri) dağılımının, uygulanacağı verilere (test verileri) kıyasla farklılık göstermesi durumunda ortaya çıkar. Klinik açıdan ilgili tahminleri değerlendirmek için test verileri, eğitim verilerinin rastgele bir alt kümesi yerine, gerçek hedef popülasyonu yansıtmalıdır. Bu uyumsuzluk, algoritmaların testlerde yüksek performans göstermesine rağmen gerçek dünyada kötü performans sergilemesine neden olabilir. Tıbbi görüntüleme alanında, veri seti yanlılığı göğüs röntgenlerinde, retinal görüntülemede, beyin görüntülemede, histopatolojide veya dermatolojide kendini göstermiştir. Bu tür yanlılıklar, farklı kaynaklardan gelen veri setleri üzerinde bir model eğitilip test edildiğinde ve kaynaklar arasında bir performans düşüşü gözlemlendiğinde ortaya çıkar. (Jarrett; 2019)

FDA (U.S. Food and Drug Administration) tarafından makine öğrenimi tabanlı, büyük veri kümelerinden öğrenebilen ve programlanmadan tahminler yapabilen otonom bir yapay zeka teşhis sisteminin onaylanmasıyla, ML sağlık uygulamaları, gelecekteki çekici bir olasılık olmaktan günümüz klinik gerçekliğine geçiş yaptı. Kesinlikle, ML sağlık süreçleri, kalite, maliyet ve erişim üzerinde büyük bir etki yaratacak ve bu süreçte sağlık bağlamında belirli ve belki de benzersiz etik düşünceler ve endişeler ortaya çıkacaktır. Makine öğrenmesinde karşılaşılabilecek etik endişelere örnek verecek olursak, ML'de kullanılan büyük veri kümelerinin nasıl satıldığı ve kullanıldığı, kişisel verilerin gizliliğinin ihlali ve Önyargılı eğitim verisi nedeniyle tahmin skorlarının başarısız olduğu durumlar verilebilir. ML çalışmalarında Irksal ayrımcılık yaşandığı görülmüştür. Örneğin, yargıçları ceza verilmesinde yönlendirmek amacıyla tasarlanan ML programları, ırksal ayrımcılık eğilimi göstermiştir (Char; 2020).

Tarihsel olarak, algoritmik adalet, korunan kimlikler arasında tıbbi koşullarda farklılıklara yol açan biyolojik, çevresel ve sosyal faktörler arasındaki karmaşık nedensel ilişkileri hesaba katmamıştır. Sağlığın sosyal belirleyicileri, özellikle risk modelleri için önemli bir rol oynamaktadır. Sosyal ve yapısal faktörler, kesişen birden fazla kimlikte sağlığı etkilemektedir, ancak sosyal belirleyicilerin sağlık sonuçlarını etkileme mekanizmaları her zaman iyi anlaşılamamaktadır. Farklılığın her zaman eşitsizliği beraberinde getirmediği gerçeğinden kaynaklanan ilave komplikasyonlar söz konusudur. Bazı durumlarda, kimlikler arasındaki farklılıkları dahil etmek uygundur çünkü makul bir nedensellik varsayımı vardır. Örneğin, cinsiyetler arasındaki biyolojik farklılıklar farmakolojik bileşiklerin etkinliğini etkileyebilir; bu farklılıkların reçete yazma uygulamalarına dahil edilmesi bu reçeteleri adaletsiz hale getirmez. Ancak, nedensel olmayan faktörlerin tavsiyelere dahil edilmesi, mevcut eşitsizlikleri yeniden tanımlayarak ve etkilerini şiddetlendirerek eşitsiz muameleyi yaygınlaştırabilir. Modellerin, sonuçla nedensel bir ilişkisi olmayan korunan kimliklere göre farklı bakım standartlarını teşvik etmesine izin vermemeliyiz. Bununla birlikte, birçok durumda farklılığı kabul etmek ile ayrımcılığı yaymak arasında ayrım yapmak zordur. (McCradden; 2020)

Makine öğrenimi algoritmaları en başından beri tıbbi veri kümelerini analiz etmek için tasarlanmış ve kullanılmıştır. Günümüzde makine öğrenimi, akıllı veri analizi için birçok vazgeçilmez araç sağlamaktadır. Özellikle son birkaç yılda dijital devrim, verilerin toplanması ve depolanması için nispeten ucuz ve kullanılabilir araçlar sağladı. Modern hastaneler izleme ve diğer veri toplama cihazlarıyla iyi bir şekilde donatılmıştır ve veriler büyük bilgi sistemlerinde toplanmakta ve paylaşılmaktadır. Makine öğrenimi teknolojisi şu anda tıbbi verileri analiz etmek için çok uygundur ve özellikle küçük özel teşhis problemlerinde tıbbi teşhis konusunda çok fazla çalışma yapılmaktadır. Makine öğrenimi sağlıkta gözetim, teşhis ve tedavi süreçlerini hızlandırıp kolaylaştırabilir. Bununla birlikte, makine öğrenimini tıbbi verilere uygulayan binlerce makaleye rağmen, çok azı klinik bakıma önemli katkılarda bulunmuştur. Bu etki eksikliği, makine öğreniminin diğer birçok sektördeki önemli önemi ile keskin bir tezat oluşturmaktadır.

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CHAPTER 2

CALCIUM SIGNALING AND NEUROPLASTICITY: THE BRAIN'S SELF-RENEWAL MECHANISMS

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Introduction

The concept of neuroplasticity was first introduced in the late 19th century by Italian neurologist Camillo Golgi and Spanish neurologist Santiago Ramón y Cajal (1). Considered a pioneer of modern neuroscience, Ramón y Cajal proposed the neuron doctrine, which posited that neurons are independent structures with a limited capacity for structural adaptation. However, Cajal believed that this adaptive capacity was particularly restricted in the adult brain (2). In the mid-20th century, the understanding of neuroplasticity made significant progress with the work of Donald Hebb. In his 1949 book The Organization of Behavior, Hebb proposed that learning and memory are associated with synaptic modifications (3). This idea is now widely known as Hebb's Rule: "Neurons that fire together, wire together." Hebb's approach laid the foundation for the modern understanding of neuroplasticity, suggesting that synaptic activity can lead to structural and functional changes in neural circuits. During the 1960s and 1970s, experimental evidence for neuroplasticity grew, with significant contributions from researchers such as Michael Merzenich and Paul Bach-y-Rita. Merzenich's pioneering studies on plasticity in the sensory cortex, in particular, demonstrated the brain's capacity for reorganization in response to environmental changes (4). During the same period, Paul Bach-y-Rita's work on sensory plasticity laid a crucial foundation for the clinical applications of neuroplasticity (5). These findings established the modern basis for neuroplasticity research, emphasizing the brain's lifelong ability to structurally and functionally adapt. Neuroplasticity is an extraordinary property that drives the brain's processes of adaptation, reorganization, and recovery in response to environmental changes. This dynamic nature supports fundamental cognitive functions such as learning, memory, and behavior, as well as functional recovery following injuries. However, neuroplasticity is a double-edged sword: while it enhances resilience, it also exposes the brain's vulnerability under adverse conditions. In particular, ischemic and traumatic brain injuries can lead to detrimental changes referred to as "negative neuroplasticity," which contribute to cognitive and neurological decline (6). Operating across multiple scales, from molecular and synaptic levels to cellular and network levels, neuroplasticity showcases the brain's remarkable capacity for reorganization. Mechanisms such as long-term potentiation (LTP) strengthen synaptic connections, forming the biological basis for learning and memory (7). However, these processes can lead to abnormal outcomes due to disruptions in signaling pathways or deficiencies in protein synthesis (8). Mitochondria and neurotrophins play central roles in these adaptive processes. Beyond energy production, mitochondria generate signaling molecules such as reactive oxygen species (ROS), proteins, and lipid mediators, which regulate synaptic remodeling

and neuronal differentiation (9). Mitochondrial dysfunction contributes to impaired neuroplasticity in various neurological disorders, including Alzheimer's disease, Parkinson's disease, psychiatric disorders, and stroke (10). Brain-derived neurotrophic factor (BDNF) plays a pivotal role in regulating synaptic plasticity and preventing neurodegenerative diseases (11). By modulating mRNA transport along dendrites and its translation at the synapse, BDNF contributes to long-term changes in the synaptic proteome (12). In addition, the effects of stress hormones on the hippocampus reflect the complex interplay between neuroplasticity and external factors. Stress hormones shape brain functions across a broad spectrum, from gene expression to synaptic transmission, thereby influencing learning and memory (13, 14). Glucocorticoid resistance is a significant link in stress-related mental illnesses, and its effects on neuroplasticity have also been examined (15). The science of connectomics enables us to understand the functionality of the brain's large-scale adaptive networks and allows for a higher-level analysis of how neuroplasticity impacts disease mechanisms (16). Over the past six decades, research on neuroplasticity mechanisms has made significant advancements. Innovations in biochemistry, molecular biology, and genetics have opened new horizons in understanding the adaptive and maladaptive forms of neuroplasticity (8). In the future, a deeper understanding of the fundamental principles of neuroplasticity will pave the way for innovative strategies in rehabilitation and the treatment of neurological disorders. Rehabilitation processes aim to reestablish connections between neurons—essentially rewiring the brain. This knowledge is critical not only for understanding brain functions but also for preventing and treating cognitive and neurological decline.

Electrobiophysical Basis of Synaptic Plasticity

The primary mechanism of neuroplasticity, synaptic plasticity, operates through changes in synaptic strength such as long-term potentiation (LTP) and long-term depression (LTD). These changes are driven by the synchronized activation of pre- and postsynaptic neurons, leading to structural modifications in synapses, dendritic spines, and axons (17, 18). In other words, synaptic plasticity refers to the nervous system's ability to adapt to environmental changes and experiences by altering the strength and structure of connections between neurons. This mechanism underpins learning, memory, and adaptation processes, encompassing both the structural and functional aspects of neuroplasticity. Processes such as synaptogenesis strengthen or remodel synaptic connections, maintaining the dynamic architecture of neuronal networks. Understanding these processes is critical for improving brain functions and developing treatments for neurological disorders (19-22).

Hebbian Plasticity: LTP and LTD

The mechanisms of synaptic plasticity can be explained through two primary processes: long-term potentiation (LTP) and long-term depression (LTD). LTP enhances the efficiency of communication between neurons by increasing synaptic strength. Bliss and Lomo (1973) described the LTP process by observing a sustained increase in synaptic strength following high-frequency stimulation in the dentate gyrus of the hippocampus (23). This process involves structural changes such as calcium-dependent activation of NMDA receptors, an increase in the size of postsynaptic dendritic spines, and an expansion of the postsynaptic density (PSD) area. These changes strengthen synaptic transmission and support learning and memory processes (24-26). In contrast, LTD reduces synaptic strength and decreases the efficiency of signal transmission. This process maintains synaptic homeostasis by weakening underused synapses. LTD represents a mechanism in which reduced synaptic activity leads to the shrinkage or elimination of dendritic spines (19, 22, 27, 28). Both LTP and LTD regulate synaptic strength within the framework of Hebbian plasticity principles. According to this principle, synapses that are active simultaneously are strengthened, while inactive synapses are weakened (29, 30).

Role of Glial Cells in Synaptic Plasticity

Synaptic plasticity encompasses not only the strengthening or weakening of neuronal connections but also the critical role of glial cells in these processes. Astrocytes and microglia interact continuously with neurons, regulating synaptic activity. The “tripartite synapse” model describes the influence of presynaptic, postsynaptic, and perisynaptic astrocytic processes on synaptic activity. Furthermore, as the role of microglia in synaptic regulation has become better understood, the “quad-partite synapse” model has been developed (31-33). Glial cells, with their capacity to rapidly respond to environmental changes, maintain synaptic homeostasis and support neuroplasticity (34, 35). Understanding the mechanisms of neuroplasticity offers promising opportunities for enhancing brain function and treating neurological disorders. While synaptic plasticity plays a central role in learning, memory, and adaptation, factors such as aging, injury, and neurodegenerative diseases can limit this capacity. Gaining deeper insights into these mechanisms can enable the development of therapeutic strategies to support the dynamic structure of the nervous system. In conclusion, synaptic plasticity and neuroplasticity are critical for understanding adaptive mechanisms in the brain and integrating this knowledge into clinical applications (21, 23, 24, 30).

Role of Calcium Signaling in Neural Adaptation

Calcium signaling is a critical component of the pathways that mediate neuroplasticity. It functions as a versatile regulator of neural adaptation, forming the foundation for numerous processes, including neurogenesis, synaptic plasticity, gene expression, and neurodegeneration. This mechanism not only guides complex cellular and molecular processes during neural development but also plays a crucial role in enabling functional adaptation in the adult brain.

Calcium Signaling in Neurodevelopment

The development of the nervous system occurs through a series of carefully choreographed steps, during which neural stem/progenitor cells (NSCs) proliferate, migrate significant distances from germinal centers to their targets, and ultimately differentiate into billions of neurons and glial cells that populate the brain. As these events unfold, rhythmic bursts of Ca^{2+} signaling in developing cells direct specific cellular Ca^{2+} responses that influence each step of the process. Cellular Ca^{2+} signals regulate nearly every aspect of neural development, including neurogenesis, proliferation, migration, and differentiation. A diverse array of Ca^{2+} signaling proteins expressed in the developing brain generates various Ca^{2+} signals to support these processes (36). In NSCs, sustained and oscillatory Ca^{2+} signals mediated by CRAC channels (Orai1 and STIM1—Stromal Interaction Molecule 1) promote gene expression and cell division (37-40). During this process, acetylcholine receptors (mAChRs—Muscarinic Acetylcholine Receptors and nAChRs—Nicotinic Acetylcholine Receptors) enhance Ca^{2+} influx, activating MAPK (Mitogen-Activated Protein Kinase) and ERK (Extracellular Signal-Regulated Kinase) signaling cascades to reinforce proliferation (41-47). Additionally, TRP (Transient Receptor Potential) channels and glutamatergic signaling play significant roles in the proliferation of neural progenitors (48, 49). Voltage-gated Ca^{2+} channels contribute to NSC development during later stages, supporting proliferation (50, 51). The regulation of calcium signaling occurs through various cell-surface receptors. Extracellular agonists (Ag) activate Ca^{2+} signaling pathways by binding to G protein-coupled receptors (GPCRs) such as mGluR (Metabotropic Glutamate Receptors), mAChR (Muscarinic Acetylcholine Receptors), and P2YR (Purinergic P2Y Receptors), as well as receptor tyrosine kinases (RTKs) such as Trk (Tropomyosin Receptor Kinase) and ErbB (Erythroblastic Leukemia Viral Oncogene Homolog B) receptors (36). GPCRs activate phospholipase C (PLC)-β, whereas RTKs activate PLC-γ. PLC generates inositol triphosphate (IP_3), which triggers Ca^{2+} release from endoplasmic reticulum (ER) stores through IP_3R (Inositol 1,4,5-Trisphosphate Receptors) channels (36). Upon depletion of these stores, STIM1 detects the loss of Ca^{2+} in the ER and facilitates extracellular Ca^{2+} entry via CRAC

(Calcium Release-Activated Calcium) channels (36). Additionally, other Ca^{2+}-permeable channels, such as voltage-gated Ca^{2+} channels (VOCCs), NMDA receptors (NMDARs), and nicotinic ACh receptors (nAChRs), regulate the influx of calcium signals into the cell (52-56). As seen, Ca^{2+} signaling functions in an integrated manner with both intracellular mechanisms and external environmental factors during these processes. Migration, another crucial step in neurodevelopment, involves the movement of NSCs to their target brain regions. Low-to-moderate levels of Ca^{2+} signals support migration, whereas high levels halt motility, enabling cells to anchor at their target sites (57). External factors such as purinergic agonists, growth factors (e.g., NRG1), and chemokines regulate directed migration by increasing intracellular Ca^{2+} levels (58). Specifically, NRG1/ErbB4 signaling promotes neuronal progenitor migration by activating Ca^{2+} release and CRAC channels (58). During migration, localized polarization of Ca^{2+} transients ensures proper directional guidance (59). Once NSCs reach their target regions, elevated Ca^{2+} signaling ceases mobility and initiates the differentiation process (57). Differentiation represents another critical stage in neurodevelopment driven by Ca^{2+} signaling. Spontaneous Ca^{2+} oscillations and activity-dependent Ca^{2+} influx through voltage-gated N- and L-type channels regulate processes such as axonal pathfinding, dendritic protrusion formation, and neurotransmitter specification (36). These Ca^{2+} signals support the expression of ion channels and neurotransmitter receptors, contributing to the determination of neuronal phenotype (60). For instance, GABAergic signaling and the activation of voltage-gated Ca^{2+} channels suppress proliferation while activating transcription factors such as NeuroD, thereby promoting neuronal differentiation (61). Additionally, activity-dependent Ca^{2+} signals shape the genetic programs of cells in response to environmental cues, optimizing brain development. These processes regulate gene expression pathways by activating transcription factors such as CREB, NFAT, NeuroD, and DREAM, which support the proliferation, migration, and differentiation of neural progenitor cells (62-68). During nervous system development, neural progenitors and epidermal progenitors are derived from the ectoderm, a process tightly regulated by calcium signaling during gastrulation. Calcium signals in dorsal ectoderm cells exhibit temporal and spatial characteristics that influence every stage of neural formation (69, 70). Studies in model organisms such as zebrafish and Xenopus have shown that calcium waves observed during gastrulation are associated with neural fate determination (71-75). In this process, the function of calcium channels, particularly DHP-Ca^{2+} channels, is critically important, and their expression is required for neural formation (74, 76). Inhibition of DHP-Ca^{2+} channels disrupts calcium transients and cellular Ca^{2+} levels, leading to reduced expression of early neural genes and abnormalities in brain structures (74, 75, 77). These findings highlight the regu-

latory role of calcium in vertebrate neurogenesis and demonstrate that this mechanism is evolutionarily conserved. The regulation of neural formation is driven not only by the direct effects of calcium but also by interactions between different signaling pathways. Evidence from Xenopus and mouse models indicates that mechanisms governing neural formation involve crosstalk, including the inhibition of the BMP signaling pathway, activation of the FGF/Erk pathway, and control of calcium homeostasis (78). In amphibians, intracellular Ca^{2+} increases during neural induction occur via voltage-operated Ca^{2+} channels (VOCCs) and TRPC channels, whereas in mouse embryonic stem cells (ESCs), this process is regulated by Ca^{2+} release from the endoplasmic reticulum and the SERCA2 pump (79). In both models, Ca^{2+} signals influence neural fate determination by inhibiting the BMP signaling pathway and modulating Erk phosphorylation. In amphibians, stimulants like caffeine enhance the expression of neural genes, whereas in mouse ESCs, Ca^{2+} signals are predominantly derived from internal stores (80, 81). These differences highlight the diversity of mechanisms between amphibians and mammals while underscoring the central role of calcium in neural induction across both models. These regulatory mechanisms continue to influence later stages of neural development. Neural development encompasses the proliferation, differentiation, and maturation of neural progenitors, all of which are tightly regulated by calcium signaling. During the proliferation of neural progenitors, Ca^{2+} waves mediated by ATP occur in radial glial cells within the ventricular zone, controlling the cell cycle. Calcium entry has been shown to be regulated through mechanisms involving TRPC1 channels and IP_3 receptors (82). In the differentiation of neural progenitors into neurons, calcium release channels such as RyR-2 play a critical role, along with contributions from GABA receptors and DHP-Ca^{2+} channels (83, 84). Additionally, extracellular calcium has been found to regulate neurite outgrowth and branching via the extracellular calcium-sensing receptor (CaSR) (85).

Calcium Homeostasis in Glial and Neuronal Function

Following neurons, radial glial progenitors differentiate into glial cells, such as astrocytes and oligodendrocytes. During this process, calcium signaling regulates the balance between gliogenesis and neurogenesis. In astrocyte formation, proteins such as presenilins control Ca^{2+} homeostasis and influence gliogenesis by suppressing the transcription of genes like GFAP (Glial Fibrillary Acidic Protein) (86). Neurotrophic cytokines and molecules such as PACAP (Pituitary Adenylate Cyclase-Activating Polypeptide), a neuropeptide that regulates processes including nervous system development and cell differentiation, promote astrocyte differentiation. This is achieved via mechanisms like the JAK-STAT (Janus Kinase-Signal Transducer and Activator of Transcription) pathway, which plays a crucial

role in cell signaling and gene expression regulation mediated by Ca^{2+} signals (87, 88). In oligodendrocyte specification, calcium-sensing receptors (CaSR) and voltage-dependent Ca^{2+} channels are critical. Activation of these receptors supports progenitor cell proliferation and maturation (89, 90). Calcium acts as both an intracellular second messenger and an extracellular first messenger in these processes. In astrocytes, calcium signaling regulates mechanisms that support synaptic transmission and contribute to neuronal plasticity (91). Meanwhile, microglia maintain neural tissue homeostasis by regulating inflammatory responses (92). In addition to these processes, disruptions in calcium homeostasis are associated with neurodegenerative diseases and aging. In Alzheimer's disease, dysregulation of calcium homeostasis has been linked to amyloid-beta accumulation, increasing the risk of neuronal death (93). In Parkinson's disease, calcium-dependent dysfunctions in dopaminergic neurons contribute to neurodegeneration (94).

Conclusion

Calcium signaling functions as a versatile regulator across a wide spectrum of processes, ranging from the development of the nervous system to synaptic plasticity and neurodegeneration. Diverse calcium entry pathways, including CRAC channels, GPCR and RTK signaling pathways, and voltage-gated Ca^{2+} channels, emerge as fundamental mechanisms driving cellular responses. These pathways operate in integration with genetic programs and environmental signals, playing critical roles in both brain development and regeneration processes following brain injury.

Processes such as long-term potentiation (LTP) and long-term depression (LTD), which form the biological basis of synaptic plasticity, lie at the core of mechanisms underlying learning, memory, and adaptation. The influence of calcium signaling on these mechanisms is of paramount importance for maintaining normal brain functions and understanding disruptions that occur in pathological conditions, such as neurodegenerative diseases. Disruptions in calcium homeostasis have been shown to contribute to the progression of neurological disorders like Alzheimer's and Parkinson's diseases.

In summary, calcium signaling holds a central role in neurodevelopment, synaptic remodeling, and neuroregeneration. A deeper understanding of these mechanisms can pave the way for innovative strategies in the treatment of neurological disorders and applications in regenerative medicine. Future research, by delving into the effects of calcium signaling on the nervous system, aims to enhance neurological health at both individual and societal levels.

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CHAPTER 3

MAINTAINING BRAIN FUNCTIONS AND HOMEOSTASIS

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INTRODUCTION

The mechanism of the nervous system, which fights for the balance within the body, is essential for the existence of an organism. When we talk about homeostasis, we are actually talking about the internal balance of an organism and it takes a lot of energy to maintain this balance. The nervous system and other organs have sufficient aerobic capacity to fulfil homeostatic requirements. However, sometimes the organs may need a little help. When this happens, they communicate their energy requirements to the 'higher' layers of the control hierarchy. Both 'local' (such as hunger and eating) and 'global' (such as the whole brain) systems that maintain energy balance work in an 'interactive' and 'at least mostly cooperative' manner to keep the internal state of the organism in balance. In this context, according to Ross (2019), resonance is a reality that optimises the transfer of energy and information by vibrating in harmony with the natural frequencies of systems. Defined as the amplification of vibrations in a system in response to a specific frequency, resonance is extremely important for signal transmission and energy optimisation in biological systems. According to Levin and Dunn-Meynell (1999), it is very important for signal transmission, energy optimisation and control of system dynamics in biological systems.

The aim of this study is to investigate the functional mechanisms of resonance in the nervous system and its effect on homeostasis, which is considered as a fundamental element that increases the information processing capacity of neural networks, provides energy efficiency and maintains homeostatic balance. Accordingly, in order to better understand how resonance affects biological systems and thus open the door to new developments in biotechnological and medical applications, this study will discuss how brain resonance supports energy efficiency and controls neural network communication (Chen & Zhang, 2021).

NERVOUS SYSTEM EFFECTS OF RESONANCE

Periodic electrical fluctuations, called neuronal oscillations, enable the timing and coordination of brain activity. Resonance enables the amplification and control of nervous system oscillations, which are necessary for information processing, synaptic connections and overall system coordination (Buzsáki, 2006; Fries, 2005). Thus, resonance provides a fundamental mechanism for coordinating, amplifying and maximising neuronal oscillations in the neurological system (Tort et al., 2010). However, dysregulated resonance and oscillatory patterns have also been associated with a number of neurological diseases, such as epilepsy and Alzheimer's disease, in which disturbances in these oscillatory patterns are observed (Staba et al., 2004; Iaccarino et al., 2016).

NEURONAL RESONANCE AND SYNAPTIC CONDUCTANCE

It is known that the brain relies heavily on neuronal oscillations, especially at the γ (gamma) frequency (~30-80 Hz), to process information. These oscillations increase synaptic efficiency and control cognitive processes such as memory and attention during resonance (Buzsáki & Draguhn, 2004). Resonance enables more efficient information processing by coordinating neuronal oscillations at certain frequencies in the brain system. Neurons therefore interact by sending electrical and chemical signals. Since the energy efficiency of the neuronal system affects the metabolic balance in general, this connection between brain activity and energy systems is very important. The complex biocybernetics in homeostatic systems tries to maintain metabolic and neurological balance by controlling this functioning (Goldstein & Kopin, 2017). Therefore, in order for brain networks to function harmoniously, resonance is of great importance during neuron-to-neuron transmission. According to Siegel et al. (2012), high-frequency oscillations, especially gamma waves, are crucial for memory, learning and attention-related activities. Thanks to recent advances in optogenetics, these oscillatory activities can now be controlled, which can provide important information about their function in cognition and their therapeutic use (Boyden et al., 2005). On the other hand, it has been shown that hyper-synchronisation of neuronal oscillations, i.e. amplification of gamma oscillations in focal areas, may also promote seizure development in epilepsy (Staba et al., 2004).

NATURAL FREQUENCIES AND RESONANCE

Each neuronal network and brain region has a specific frequency value. For example, research on the hippocampus and cortex has shown that these two regions resonate at specific frequencies (Tort et al., 2010).

Hippocampus and Thalamus: The resonance between these two structures contributes to the regulation of wakefulness and sleep cycles (Fries, 2005).

Cerebral Cortex: The resonance between alpha and beta waves in response to external perceptions enables more efficient control of cognitive processes and motor movements (Siegel et al., 2012). In addition, changes in cortical oscillation patterns, such as altered alpha rhythms, have been identified as biomarkers for cognitive impairments in Alzheimer's disease (Smith et al., 2020).

ENERGY AND HOMEOSTASIS IN NEURAL SYSTEMS

The role of resonance in the brain is closely related to energy efficiency. Neurons require significant amounts of energy to maintain their electrochemical gradient. This energy is optimised when resonance increases

the synchronisation of oscillatory patterns. The metabolic processes that regulate the efficiency of these energy exchanges are critical for maintaining homeostasis, as the balance between energy supply and demand must be constantly regulated. Furthermore, calcium signalling, which plays a central role in synaptic transmission and plasticity, is closely linked to both energy metabolism and resonance events (Clapham, 2007; Hille, 2001). Disruptions in these mechanisms not only lead to metabolic inefficiencies, but can also cause degenerative diseases such as Alzheimer's disease and epilepsy. In recent years, machine learning techniques have been used to detect early biomarkers of these conditions by analysing oscillatory patterns (He et al., 2018).

NATURAL STRUCTURE OF NEURONAL OSCILLATIONS

The coherent rhythmic activities of each neuron and the neuronal network are recognised as neuronal oscillations. The main characteristics of these oscillations are given below:

Frequency: It is the number of oscillations per second. Certain frequencies are associated with different brain activities (Buzsáki, 2006).

Amplitude: The strength or intensity of oscillations (Fries, 2005).

Phase: It is the specificity of a moment in the oscillation cycle (Tort et al., 2010).

All these features can increase the functionality of oscillations by interacting with external stimuli during resonance (Siegel et al., 2012). For example, it has been shown that altered beta oscillations lead to impairments in motor control in Parkinson's patients. Therefore, deep brain stimulation has been shown to be effective in modulating these oscillations (Brown et al., 2001; Kühn et al., 2008).

BASIC MECHANISMS OF NEURONAL OSCILLATIONS AND FREQUENCY WAVES

Different regions in the brain coordinate brain functions by oscillating at different frequencies. These oscillations occur at different levels, from the activity of individual nerve cells to large networks of nerve cells. Thus, the brain optimises its functions such as information processing, storage and transmission by using different oscillation frequencies (Buzsáki, 2006). Therefore, it is also necessary to study the basic mechanisms of neuronal oscillations in terms of biophysical principles, functional organisation and properties of frequency waves. Thus, each frequency wave regulates the dynamic interaction between neuronal networks by serving specific functional processes in the brain (Wang, 2010). Resonance helps us understand how these oscillations are amplified and regulated by spe-

cific external stimuli or internal neuronal activities. Neuronal oscillations, each corresponding to a specific physiological or cognitive function, are classified in different frequency ranges (Fries, 2005):

Delta Waves (0.5-4 Hz)

Function: Deep sleep is associated with regeneration and unconscious processes (Brown, 2018).

Source: Cortex and thalamus.

Theta Waves (4-8 Hz)

Function: It plays a role in learning, memory consolidation and spatial navigation (Colgin, 2013).

Source: Especially the hippocampus and limbic system.

Alpha Waves (8-12 Hz)

Function: Rest is associated with mild concentration, with meditation (Bazanova & Vernon, 2014).

Source: Cortex, especially occipital and parietal regions.

Beta Waves (12-30 Hz)

Function: It is related to active thinking, problem solving and motor coordination (Engel & Fries, 2010).

Source: Motor cortical areas and frontal lobe.

Gamma Waves (30-80 Hz)

Function: It is associated with the formation of awareness, the realisation of perception and higher cognitive functions (Buzsáki & Wang, 2012).

Resources: Extensive networks that coordinate between different regions of the brain.

HIERARCHICAL ORGANISATION OF OSCILLATIONS

The human brain has a complex network structure regulated by neuronal oscillations organised at different scales. These oscillations consist of both local and large-scale neural networks and operate in a hierarchical order to increase the functional efficiency of the brain (Brown, 2018). The hierarchical organisation of neuronal oscillations is called the system form in which they operate simultaneously at different frequencies and these activities are integrated (Garcia et al., 2021):

Local Oscillations (Micro-Level): These are oscillations that occur within a neuron or a small group of neurons. These oscillations play an important role in local information processing (Jones & Taylor, 2019).

Regional Oscillations (Meso-level): These are oscillations that cover neuronal networks in specific brain regions.

Large-Scale Oscillations (Macro-Level): Large-scale oscillations that facilitate communication between different regions of the brain.

Cross Frequency Interactions: These are processes in which oscillations at different frequencies interact with each other (Canolty & Knight, 2010).

LOCAL OSCILLATIONS (MICRO LEVEL)

Local oscillations produced by individual neurons or small groups of neurons regulate local information processing and play a crucial role in understanding brain function and in medical research. These oscillations are particularly important when studying the electrical activities of the brain at the micro-level and their effects on health. Local oscillations refer to electrical vibrations between individual neurons or small neuronal groups. These oscillations form the basic building blocks that shape the behaviour of larger neuronal networks. Local oscillations are extremely important for information processing, signal integration, and communication at the micro-level (Jones & Taylor, 2019).

LINKING LOCAL OSCILLATIONS TO NEURONAL OSCILLATIONS

Local oscillations form the foundation for larger-scale neuronal oscillations. This relationship can be summarized as follows (Garcia et al., 2021):

Micro to Macro Transition: Local oscillations between individual neurons synchronize through synaptic communication to form larger, macro-level oscillations (e.g., those measured by EEG). Synchronization of local oscillations in a cortical region enables communication between different brain regions. Buzsáki (2006) explored how local oscillations synchronize with larger neuronal networks, emphasizing the role of synaptic plasticity in this process. It was shown that macro-level oscillations measured by EEG arise from the synchronization of local oscillations, and these play a key role in learning processes.

Functional Dependence: Synaptic plasticity and neuronal connections: Local oscillations support synaptic plasticity (learning) and the strengthening of neuronal connections. For larger-scale neuronal oscillations to function correctly, local oscillations must remain stable and coher-

ent. Fries (2005) found that synchronized gamma oscillations (30-80 Hz) support learning and attention processes.

Dynamic interactions: The stabilization and strengthening of synaptic connections enhances the contribution of local oscillations to the larger-scale dynamics of the brain (Jones & Taylor, 2019).

PATHOLOGICAL CONDITIONS

Epilepsy and Hyper-Synchronization: Disturbances in local oscillations can lead to neurological disorders such as epilepsy, Alzheimer's, and Parkinson's disease. Staba et al. (2004) demonstrated that abnormal gamma oscillations in focal regions of the brain can be used to predict the onset of seizures.

Neurodegenerative Diseases: Iaccarino et al. (2016) showed that optogenetic enhancement of gamma oscillations in Alzheimer's patients accelerates the clearance of amyloid beta plaques.

Depression and Alpha Oscillations: Levitt et al. (2020) discovered that Transcranial Magnetic Stimulation (TMS) could alleviate symptoms of depression by modulating alpha oscillations.

Parkinson's Disease and Beta Oscillations: Brown et al. (2001) found that Deep Brain Stimulation (DBS) improves motor symptoms in Parkinson's patients by reducing abnormal beta oscillations.

MEDICAL IMPORTANCE

The study of local oscillations is crucial for understanding brain diseases and developing treatment strategies. EEG and Local Field Potential (LFP) measurements can be used to detect abnormalities by analyzing local and neuronal oscillations (Smith et al., 2020). Disturbances in beta and gamma oscillations are recognized as biomarkers for the early diagnosis of Alzheimer's disease (Kühn et al., 2008).

TREATMENT AND INTERVENTION

DBS and Parkinson's Disease: DBS improves motor symptoms by regulating abnormal beta oscillations in subcortical structures (Kühn et al., 2008).

TMS and Depression: TMS alleviates symptoms of depression by modulating alpha oscillations (Levitt et al., 2020).

Optogenetics and Gamma Oscillations: Enhancing gamma oscillations through optogenetic methods shows promise for treating Alzheimer's disease (Iaccarino et al., 2016).

Photobiomodulation Therapy: This therapy regulates synaptic activities by enhancing neuronal energy production (Hamblin, 2017).

RESEARCH AND FUTURE PERSPECTIVES

Local oscillations play a crucial role in understanding the micro-level functionality of the brain, as well as in the diagnosis and treatment of neurological disorders. These oscillations provide insights into brain function across a broad spectrum, from synaptic communication to system-level interactions within neuronal networks. A better understanding of local oscillations is key to developing new approaches for treating neurological diseases and improving clinical interventions (Wilson, 2022).

Optogenetics and local oscillations: Optogenetics explores how local oscillations are generated and propagated across larger networks using light-controlled neurons. Boyden et al. (2005) proposed that optogenetic technology could be used to manipulate neuronal oscillations in a controlled manner and treat neurological diseases. This technique allows researchers to investigate how local oscillations strengthen synaptic connections and increase coordination between neural networks (Jones & Taylor, 2019).

Machine learning and early diagnosis: By analyzing data from local oscillations using machine learning algorithms, early diagnoses of neurological diseases can be made. He et al. (2018) developed a model capable of detecting synaptic changes in the early stages of Alzheimer's disease using EEG and local oscillation data. This approach offers significant opportunities for treating the disease before it progresses.

Individualized Treatment Methods: By analyzing individual patterns of local oscillations, personalized treatment strategies can be developed. Schneider et al. (2016) emphasized that understanding individual neuronal oscillation patterns can lead to more tailored treatment plans. In particular, modulating individual oscillations has shown potential for improving treatment outcomes in diseases such as depression and Parkinson's disease.

Innovative Technologies and Future Perspectives: Future research will deepen our understanding of local oscillations through the integration of technologies such as optogenetics, neuroscience, and artificial intelligence. Miller et al. (2017) noted that the use of AI to analyze local oscillation data could accelerate the diagnosis of neurological diseases and enhance personalized treatment approaches. Combining these technologies has the potential to greatly improve patient care.

RELATIONSHIP OF LOCAL OSCILLATIONS WITH NEURONAL MEMBRANES AND IONIC MECHANISMS

NEURONAL MEMBRANES AND ION CHANNELS

The neuronal membrane is a lipid bilayer structure that regulates the ionic balance between the inside and outside of the cell.

The main components that contribute to electrical oscillations are as follows: Membrane potential and ion balance: The neuronal membrane creates a potential difference across its inner and outer surfaces, which is mainly due to the selective permeability of ions and the differences in ionic concentrations inside and outside the cell. The resting potential is typically around -70 mV and is largely influenced by potassium (K^+) ion distribution (Jones & Taylor, 2019).

Ionic pumps and channels: The sodium-potassium pump (Na^+/K^+-ATPase) maintains the resting potential by regulating ion balance. Voltage-sensitive ion channels (such as Na^+, K^+, and Ca^{2+} channels) are fundamental for generating action potentials and local oscillations. Ligand-gated channels are essential for synaptic communication (Hille, 2001).

Ion currents and electrical activity: Ion movement across the membrane generates electrical currents, which are the basis of local oscillations (Hodgkin & Huxley, 1952).

IONIC MECHANISMS IN THE FORMATION OF LOCAL OSCILLATIONS

Ion Currents: The opening of voltage-sensitive Na^+ channels leads to Na^+ influx, causing membrane depolarization. Repolarization occurs when K^+ channels open, allowing K^+ ions to flow out (Hille, 2001). Calcium (Ca^{2+}) ions are crucial for synaptic vesicle release and synaptic communication. Ca^{2+} currents also play a role in long-term synaptic plasticity (Clapham, 2007).

Role of Ion Channels in Oscillations: Fast oscillations (e.g., gamma frequency) are controlled by voltage-dependent Na^+ and K^+ channels (Fries, 2005). Slow oscillations are associated with ligand-gated Cl^- or K^+ channels (Buzsáki, 2006).

Role of Resistance and Capacity: The capacitive properties of the neuronal membrane influence ion movement. This capacitance affects the fluctuation rate of local electrical activity (Jones & Taylor, 2019).

LOCAL OSCILLATIONS AND NEURONAL MEMBRANE PROPERTIES

Membrane impedance: The membrane functions like a capacitor, storing electrical charges. This property allows the cell to generate both fast and slow oscillations (Hodgkin & Huxley, 1952).

Dendritic oscillations: Local oscillations occur not only in the cell body but also in the dendrites and axons. Voltage-dependent ion channels in the dendritic regions generate local oscillations in response to synaptic inputs (Stuart et al., 1997).

FUNCTIONAL ROLE OF LOCAL OSCILLATIONS

Information processing and synchronization: Local oscillations help neurons integrate various synaptic inputs. Oscillations in dendrites are crucial for signal processing (Magee, 2000).

Synaptic plasticity: Calcium-dependent mechanisms strengthen synaptic connections (Clapham, 2007).

Network synchronization: Local oscillations coordinate rhythmic activities across larger neuronal networks, providing synchronization between groups of neurons (Buzsáki, 2006).

LOCAL OSCILLATIONS IN PATHOLOGICAL CONDITIONS

Epilepsy: Local oscillations can grow and spread abnormally during epileptic seizures. Staba et al. (2004) attributed this to uncontrolled ion channel activity.

Parkinson's Disease: Increased beta oscillations in the basal ganglia are associated with motor symptoms. DBS improves motor functions by reducing these abnormal oscillations (Brown et al., 2001).

MEDICAL AND RESEARCH PERSPECTIVES

Drugs: Na^+ channel blockers for epilepsy and K^+ channel activators for Parkinson's disease are used to stabilize local oscillations (Kandel et al., 2013).

Optogenetic methods: Local oscillations can be modulated by controlling specific ion channels using light (Boyden et al., 2005).

Brain-computer interfaces: The interaction of local oscillations with ionic mechanisms can enhance the sensitivity of signal processing (He et al., 2018).

INTERCELLULAR CONNECTIONS AND LOCAL OSCILLATIONS

Intercellular connections are essential for the emergence, synchronization, and integration of local oscillations into large-scale neuronal oscillations (Jones & Taylor, 2019). These connections include:

Chemical Synapses: Chemical synapses enable communication between neurons. Presynaptic neurons release neurotransmitters, and postsynaptic neurons receive these signals. This communication initiates local oscillations by generating excitatory postsynaptic potentials (EPSPs) or inhibitory postsynaptic potentials (IPSPs). Activation of glutamate receptors (AMPA and NMDA) increases local excitatory oscillations through EPSPs (Brown, 2018).

Electrical Synapses (Gap Junctions): Electrical synapses allow direct ion flow between cells, enabling local oscillations to propagate rapidly and synchronously. These are especially common among interneurons and play a key role in coordinating gamma oscillations (30-100 Hz) (Garcia et al., 2021).

Neurotransmitters and Neuromodulators: Neurotransmitters and neuromodulators can propagate beyond the synaptic gap to affect surrounding regions, allowing local oscillations to spread across larger areas (Wilson, 2022).

CHARACTERISTICS OF LOCAL OSCILLATIONS IN INTERCELLULAR CONNECTIONS

Intercellular connections help synchronize local oscillations between neurons, contributing to larger-scale neuronal oscillations (e.g., alpha and beta waves observed in EEG). This synchronization creates timing and phase coherence between brain regions. The balance between excitatory (glutamatergic) and inhibitory (GABAergic) signals through chemical synapses determines the frequency and amplitude of local oscillations. Excitatory inputs accelerate oscillations (e.g., gamma frequency), while inhibitory inputs result in slower oscillations (e.g., delta frequency). The electrical activity resulting from synaptic inputs can be recorded as local field potentials (LFPs), which measure the effect of intercellular connections on local oscillations (Brown, 2018).

EFFECTS OF LOCAL OSCILLATIONS ON INTERCELLULAR CONNECTIONS

Local oscillations not only shape intercellular connections but also influence their structure and function (Wilson, 2022).

Synaptic Plasticity: High-frequency local oscillations (>30 Hz) favor synaptic strengthening, a process known as long-term potentiation (LTP). In contrast, low-frequency oscillations (1-5 Hz) trigger synaptic weakening, known as long-term depression (LTD). These mechanisms form the biological basis for learning and memory (Jones & Taylor, 2019).

Phase Synchronization: Intercellular connections help synchronize the phases of oscillations, improving the efficiency of synaptic transmission. For example, the likelihood of synaptic strengthening increases when presynaptic and postsynaptic neurons are in the same phase (Garcia et al., 2021).

Dynamic Modulation: Local oscillations modulate synaptic activity based on timing. Spike-Timing-Dependent Plasticity (STDP) refers to synaptic strengthening or weakening depending on the timing of presynaptic and postsynaptic activities (Smith et al., 2020).

LOCAL AND NEURONAL OSCILLATIONS: FROM MICRO TO MACRO

Intercellular connections make local oscillations part of larger neuronal networks. In cortical regions, local oscillations are organized into small neuronal networks (microcircuits), which contribute to large-scale neuronal oscillations. Connections between different brain regions (e.g., thalamocortical pathways) integrate local oscillations with global oscillations. For example, thalamocortical connections are crucial for regulating delta oscillations during sleep (Wilson, 2022).

ABNORMALITIES IN INTERCELLULAR CONNECTIONS AND LOCAL OSCILLATIONS

Disruptions in intercellular connections can lead to dysregulation of local oscillations, affecting neuronal functions. Abnormal intercellular connections can cause hyper-synchronized local oscillations, leading to epileptic seizures. In schizophrenia, disrupted synchronization of gamma oscillations is caused by defects in intercellular connections. In Alzheimer's disease, synaptic losses cause disruptions in local oscillations and neuronal synchronization, significantly impacting memory and cognitive function. In Parkinson's disease, abnormal beta oscillations (13-30 Hz) in the basal ganglia are associated with disruptions in intercellular connections (Jones & Taylor, 2019).

MEDICAL AND RESEARCH PERSPECTIVES

Deep Brain Stimulation (DBS): Electrical stimulation techniques regulate local oscillations by modulating abnormal intercellular connections.

Transcranial Magnetic Stimulation (TMS): This technique is used

therapeutically to investigate how local oscillations affect intercellular connections.

Optogenetic Techniques: These allow precise control of local oscillations in intercellular connections.

The relationship between local oscillations and intercellular connections forms the foundation of the brain's information processing capacity. This dynamic relationship is vital for understanding neurological diseases as well as cognitive processes like learning, memory, and perception (Garcia et al., 2021).

REGIONAL OSCILLATIONS (MESO LEVEL) AND NEURONAL OSCILLATIONS

At the micro level, neuronal oscillations are rhythmic electrical activities of individual neurons or small groups of neurons. These activities are caused by events such as action potentials and postsynaptic potentials. Regional oscillations at the meso level are the synchronized electrical activity of cortical columns or groups of neurons in a specific brain region (Jones & Taylor, 2019).

SOURCE OF REGIONAL OSCILLATIONS

Regional oscillations are formed by the coordinated action of individual neuronal oscillations. The basic components of these structures are:

Local Neuronal Networks: Interneurons and pyramidal cells form the basis of regional oscillations.

Interneurons: Especially GABAergic interneurons shape gamma (30-100 Hz) oscillations (Buzsáki, 2006).

Pyramidal Cells: These cells play a role in regulating alpha and beta oscillations through excitatory inputs.

REGIONAL CONNECTIONS

Connections such as cortical columns and thalamocortical circuits organize groups of neurons to produce regional oscillations. Thalamocortical connections are especially important for the formation of delta waves (1-4 Hz) during sleep (Wilson, 2022).

IONIC AND SYNAPTIC MECHANISMS

Fast Oscillations: These are supported by Na^+ and K^+ currents.

Slow Oscillations: Ca^{2+} waves play an important role in these mechanisms (Clapham, 2007).

RELATIONSHIP BETWEEN REGIONAL AND NEURONAL OSCILLATIONS

Regional oscillations arise from the synchronization of individual neuronal oscillations.

Phase-Locking: Neuronal oscillations adjust to a specific phase of regional oscillations. For example, fast gamma oscillations are locked to specific phases of slower theta waves (4-8 Hz) (Fries, 2005).

Lower and Upper Frequencies: Lower frequencies (e.g., delta, theta) regulate broader regional oscillations and provide overall synchronization, while higher frequencies (e.g., gamma) are used for more localized information processing tasks.

Information Processing and Transmission: Regional oscillations support communication between different brain regions. For example, theta oscillations establish communication between the prefrontal cortex and the hippocampus (Smith et al., 2020).

THE ROLE OF REGIONAL OSCILLATIONS IN COGNITIVE FUNCTIONS

Sensory Processing: Gamma frequency neuronal oscillations synchronize with beta and alpha oscillations, facilitating efficient processing of sensory inputs (Brown, 2018).

LEARNING AND MEMORY

Theta Frequency in the Hippocampus: Theta waves are crucial for learning and memory processes. High-frequency gamma oscillations, when synchronized with the phase of theta oscillations, help strengthen memory processes (Buzsáki, 2006).

Attention and Decision Making: In the prefrontal cortex, the interaction between beta and gamma oscillations plays a key role in attention and decision-making processes (Fries, 2005).

REGIONAL AND NEURONAL OSCILLATION RELATIONSHIP IN PATHOLOGICAL CONDITIONS

Epilepsy: In epilepsy, hyper-synchronized neuronal oscillations lead to abnormal growth of regional oscillations.

Schizophrenia: In schizophrenia, the disruption of gamma oscillations is linked to disconnection at both the neuronal and regional levels (Garcia et al., 2021).

Alzheimer's Disease: In Alzheimer's, decreased theta oscillations and disrupted gamma oscillations cause dysfunction in hippocampal and corti-

cal networks, which impairs cognitive function (Smith et al., 2020).

Parkinson's Disease: In Parkinson's disease, increased beta oscillations disrupt motor networks and affect the normal pattern of neuronal oscillations (Wilson, 2022).

RESEARCH AND APPLICATIONS

Deep Brain Stimulation (DBS): DBS is used to alleviate symptoms of conditions such as Parkinson's disease and epilepsy (Kühn et al., 2008).

Transcranial Magnetic Stimulation (TMS): TMS can regulate regional and low-level neuronal oscillations, offering therapeutic benefits (Smith et al., 2020).

Brain-Computer Interfaces: Regional oscillations are utilized to read and control neurological signals, aiding in the development of brain-computer interfaces.

Artificial Neural Networks: Regional and neuronal oscillations are modeled to improve the efficiency of artificial neural networks (Miller et al., 2017).

CROSS-FREQUENCY COUPLING (CFC)

CFC refers to the coupling of oscillations in different frequency bands, where the activities of one frequency band are dependent on another. Several mechanisms facilitate this coupling:

Phase-Amplitude Coupling (PAC): The phase of a low-frequency oscillation modulates the amplitude of a high-frequency oscillation. For instance, the phase of hippocampal theta waves (4-8 Hz) can modulate the amplitude of gamma oscillations (30-100 Hz).

Frequency-Frequency Coupling: Oscillations at two different frequencies are directly dependent on each other.

Amplitude-Amplitude Coupling: The amplitudes of oscillations at different frequencies become related.

Phase-Phase Coupling: There is a consistent relationship between the phases of different frequency bands.

RELATIONSHIP BETWEEN CROSS-FREQUENCY COUPLING AND NEURONAL OSCILLATIONS

Neuronal oscillations represent rhythmic electrical activity in different brain regions, operating in various frequency bands. CFC allows these frequencies to coordinate with each other, fulfilling several key functions:

Combining Different Time Scales: Low-frequency oscillations (e.g., delta, theta) operate over broader time scales, while high-frequency oscillations (e.g., gamma) work on faster time scales. By combining these different time scales, CFC facilitates both short-term and long-term processing in the brain.

Integrating Local and Global Processing: Low-frequency oscillations help regulate global synchronization between large brain regions, while high-frequency oscillations support more localized information processing. CFC integrates these two levels to coordinate both large-scale and local processing.

Neuronal Coding: Neuronal populations use phase-based coding through CFC. For example, different phases of low-frequency theta oscillations may represent different types of information, while gamma oscillations may encode specific details.

Long and Short Range Connections: CFC supports long-distance communication between different brain regions. For instance, theta-gamma coupling between the prefrontal cortex and hippocampus helps coordinate learning and memory processes.

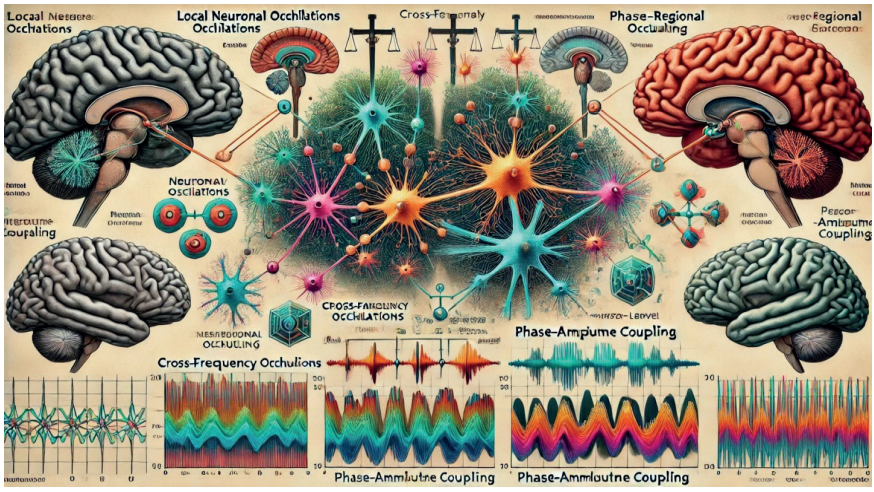

Figure 1: Synchronized oscillations between neurons, connections at the micro and meso levels, interactions of different frequency waves (e.g., theta, gamma), and pathways between brain regions.

THE ROLE OF CROSS-FREQUENCY COUPLING IN COGNITIVE FUNCTIONS

Cross-frequency coupling (CFC) plays a crucial role in various cognitive functions of the brain. The hippocampus, for example, is key to learning and memory processes. Theta-gamma coupling enables the creation and recall of memory traces. Different phases of low-frequency theta waves carry distinct information, while the amplitude of gamma oscillations modulates this information. For instance, when recalling a list of words in working memory, each word is encoded in a different phase of the theta cycle. Alpha-gamma coupling, on the other hand, is prominent in attention processes. Alpha waves (8-12 Hz) help regulate attention by selectively focusing on specific regions, ensuring gamma oscillations are directed where needed. The prefrontal cortex also shows coupling between different frequency bands, particularly beta-gamma coupling, which is important for motor preparation and decision-making. During sleep, delta-gamma coupling supports the brain's ability to process information and consolidate learning. For example, in deep sleep, delta waves regulate synaptic plasticity and integrate with sleep spindles to support memory consolidation.

NEURAL MECHANISMS OF CROSS-FREQUENCY COUPLING

Several mechanisms explain the neural basis of CFC:

Phase-Amplitude Modulation: Neuronal groups are sensitive to the phase of low-frequency oscillations. These groups exhibit high-frequency activity aligned with the phase of the low-frequency oscillations. For example, neuronal activity may peak during the maximum phase of the theta cycle.

Neuromodulatory Systems: Neurotransmitters such as dopamine, serotonin, and acetylcholine regulate the activity and dynamics of different frequency bands, influencing CFC.

Synaptic Plasticity: CFC also affects the processes of synaptic strengthening or weakening, depending on the timing of presynaptic and postsynaptic activities.

ABNORMALITIES IN CROSS FREQUENCY COUPLING

Disruptions in CFC are linked to various neurological and psychiatric disorders. In epilepsy, abnormal CFC leads to hyper-synchronization of neuronal groups, which facilitates the spread of seizures. In schizophrenia, reduced theta-gamma coupling between the prefrontal cortex and hippocampus is associated with disturbances in perception and memory. In Parkinson's disease, abnormal beta-gamma coupling contributes to motor symptoms. In Alzheimer's disease, reduced theta-gamma coupling leads to impaired memory and cognitive decline.

RESEARCH AND APPLICATIONS

Deep brain stimulation (DBS) is used in clinical practice to regulate CFC. Neurofeedback allows individuals to improve CFC dynamics by monitoring their own brain activity. Brain-Computer Interfaces (BCI), information about coupling between different frequency bands is used in signal processing and control mechanisms. Cross-frequency coupling (CFC) is a critical mechanism that enables synchronisation and coordination between neuronal oscillations. This process combines the information processing capacities of the brain at different scales and plays a central role in cognitive processes such as perception, learning and memory. The association of disturbances in CFC with neurological and psychiatric disorders further increases the importance of this mechanism in medical research and therapies.

FUNCTIONAL HIERARCHICAL ORGANISATION

Deep Brain Stimulation (DBS) is used in clinical settings to regulate CFC, offering benefits for conditions like Parkinson's disease. Neurofeedback also allows individuals to improve their own CFC dynamics by monitoring their brain activity. Brain-Computer Interfaces (BCIs) leverage information about CFC to process and control signals between the brain and external devices. The study of CFC is vital because it helps synchronize and coordinate neuronal oscillations, facilitating the brain's information processing at different scales. This coordination is central to cognitive processes like perception, learning, and memory. The association between CFC disturbances and neurological disorders underscores its importance in medical research and therapeutic applications.

DISRUPTION OF HIERARCHICAL ORGANISATION

Disruption of the brain's hierarchical oscillation structure can lead to cognitive and motor impairments. For example, excessive synchronization in epilepsy can disrupt large-scale oscillations, while disturbances in gamma oscillations in schizophrenia can affect cognitive processes. Understanding this hierarchical organization is crucial for both basic science

and clinical neuroscience.

EVOLUTIONARY DIMENSION OF RESONANCE

Resonance in neuronal oscillations has likely been advantageous in the evolutionary process, helping to increase energy efficiency. This energy management has enabled humans to adapt more quickly to environmental changes. In cognitive evolution, resonance mechanisms in the brain may have paved the way for higher cognitive functions such as language, problem-solving, and creative thinking (Garcia et al., 2021).

RESONANCE AND ENVIRONMENTAL INTERACTIONS

Both natural and artificial electromagnetic fields can influence the resonance of biological systems. For example, the effects of new technologies like 5G on neural resonance are currently being studied. Low-frequency sound vibrations, such as those used in sound therapy, can help reduce stress, manage pain, and support psychological healing by increasing resonance. Additionally, certain wavelengths of light (e.g., red and near-infrared) have been shown to improve mitochondrial function by enhancing resonance at the cellular level, a technique used in photobiomodulation therapy (Smith et al., 2020).

FUTURE RESEARCH DIRECTIONS

Collaborative research across fields like physics, biology, neurology, and engineering will help unravel the complex nature of resonance in the brain. Artificial intelligence (AI) and deep learning algorithms can also be employed to model the role of resonance in neural and metabolic systems, allowing for personalized treatments. Developing biomarkers to measure individual differences in resonance could pave the way for more precise, personalized medical interventions (Brown, 2018).

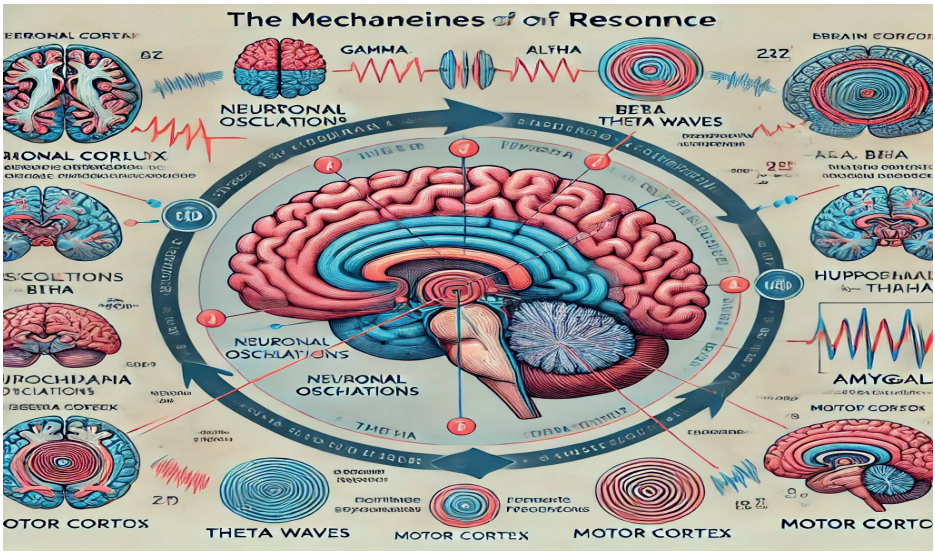

Figure 2. This diagram illustrates the mechanisms of resonance in the brain, highlighting the interaction between key areas such as the prefrontal cortex, hippocampus, amygdala, and motor cortex. It shows how resonance affects memory, emotion, and motor control, as well as the role of neuronal oscillations (Gamma, Beta, Alpha, Theta, Delta waves) in synchronizing signals for optimal brain function.

CONCLUSION

The complex interplay between resonance in neuronal oscillations, energy optimization, and homeostasis is essential for proper brain function. Resonance not only enhances the efficiency of information processing but also contributes to the metabolic balance needed to sustain cognitive and neural activities. Maintaining energy homeostasis in neural systems is a critical area of research in both neuroscience and biomedical sciences. Emerging therapies like photobiomodulation are showing promise in restoring normal oscillatory activity in neural disorders. Understanding the hierarchical organization of neuronal oscillations and the role of resonance could significantly improve how we enhance brain function and treat neurological and psychiatric conditions. As research progresses, new discoveries in this field will open up innovative approaches to optimizing neural function and treating pathological conditions.

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